PUBLIC HEALTH GOALS FOR CHEMICALS IN DRINKING WATER

URANIUM

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Public Health Goal for URANIUM In Drinking Water

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PREFACE

Drinking Water Public Health Goals

Pesticide and Environmental Toxicology Section

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365), amended 1999, requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and publish PHGs for contaminants in drinking water based exclusively on public health considerations. Section 116365 specifies that the PHG is to be based exclusively on public health considerations without regard to cost impacts. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based upon currently available data and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs published by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs published by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA Web site at www.oehha.ca.gov.

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PUBLIC HEALTH GOAL FOR URANIUM IN DRINKING WATER

SUMMARY

A Public Health Goal (PHG) has been developed for uranium in drinking water based on its radioactivity. All isotopes of uranium are radioactive, and the total radioactivity depends on the ratio of isotopes. The ionizing radiation from uranium is considered to be inherently carcinogenic. The PHG for uranium is based on the U.S. Environmental Protection Agency's latest cancer risk calculations for uranium exposure (U.S. EPA, 1999), and recent data on ratio of uranium isotopes in California drinking water (Wong *et al*., 1999), from which is calculated the uranium specific activity of 0.79 pCi/μg (radioactivity output per mass unit). The resulting PHG of 0.5 ppb (0.43 pCi/L) developed for natural uranium in drinking water is based on a *de minimis* 10^{-6} lifetime cancer risk for exposure to ionizing radiation. This PHG level is supported by a study showing changes in indicators of kidney function (increased β2-microglobulin and γ-glutamyl transferase levels in the urine) in a human population, associated with a no-observed-effect-level (NOEL) of 6 μg/day. OEHHA considers cancer risks below the *de minimis* one in a million theoretical risk to be negligible.

Uranium is a naturally occurring radioactive element that is ubiquitous in the earth's crust. Uranium is found in ground and surface waters due to its natural occurrence in geological formations. The average uranium concentrations in surface, ground, and domestic water are 1, 3, and 2 pCi/L, respectively. The uranium intake from water is about equal to the total from other dietary components. Natural uranium contains 99.27 percent ^{238}U, 0.72 percent ^{235}U and 0.006 percent ^{234}U by weight. The primary noncarcinogenic toxic effect of uranium is on the kidneys. Recently published studies in rats, rabbits, and humans show effects of chronic uranium exposure at low levels in drinking water. Effects seen in rats, at the lowest average dose of 0.06 mg U/kg-day, including histopathological lesions of the kidney tubules, glomeruli and interstitium are considered clearly adverse effects albeit not severe. Histopathological effects were also seen at the same exposure level in the liver including nuclear anisokaryosis and vesiculation. Effects on biochemical indicators of kidney function were seen in urine of humans exposed to low levels of uranium in drinking water for periods up to 33 years. These effects, such as increased urinary glucose, β2-microglobulin, and γ-glutamyl transferase, are indicative of potential kidney injury rather than toxicity per se. Uranium is an emitter of ionizing radiation, and ionizing radiation is carcinogenic, mutagenic and teratogenic. A level of 0.5 ppb (0.43 pCi/L) is considered protective for both carcinogenicity and kidney toxicity and is therefore established as the PHG for natural uranium in California drinking water.

The U.S. Environmental Protection Agency (U.S. EPA) has established a maximum contaminant level (MCL) for natural uranium of 30 μg/L (ppb), based on a cost-benefit analysis (U.S. EPA, 2000). The U.S. EPA maximum contaminant level goal (MCLG) is zero. The State of California has an MCL for uranium of 20 pCi/L based on earlier studies of toxicity to the kidney in rabbits.

INTRODUCTION

Uranium occurs as a trace element in many types of rocks. Because its abundance in geological formations varies from place to place, uranium is a highly variable source of contamination in drinking water.

Other agencies have developed health protective levels for uranium (see page 23), these differ from each other and provide equivocal guidance for setting a PHG for natural uranium. The purpose of this document is to review the evidence on toxicity of natural uranium and to derive an appropriate PHG for natural uranium in drinking water.

CHEMICAL PROFILE

Uranium is a radioactive metallic element (atomic number 92). Naturally occurring uranium contains 99.27 percent ^{238}U, 0.72 percent ^{235}U and 0.006 percent ^{234}U. One microgram (μg) of natural uranium has an activity of 0.67 pCi (Cothern and Lappenbusch, 1983). This is the equilibrium specific activity for natural uranium. Natural uranium in geological formations usually has this specific activity. Natural uranium in drinking water may not be in equilibrium, and therefore its specific activity may vary, as discussed below.

U.S. EPA proposed a definition of the term "natural uranium" as uranium with a varying composition, but typically with the composition given above (Fed. Reg. 51: 34836, September 30, 1986). On an equal weight basis the radioactivity of ^{234}U is 17,000-fold and that of ^{235}U is six-fold greater than that of ^{238}U (NRC, 1983). Uranium may be found in valence states of +2, +3, +4, +5 or +6, but +6 is the most stable form and exists as the oxygen-containing uranyl cation (UO_2^{+2}) (Cothern and Lappenbusch, 1983).

The best known use of uranium is as a source of fuel for nuclear reactors and nuclear bombs. The fissionable form of uranium is the isotope ^{235}U. This isotope is only a small fraction of naturally occurring uranium. Several complex minerals are of commercial importance, including carnotite, pitchblende and tobernite (Stokinger, 1981).

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

U.S. EPA measured ambient air levels of uranium in 51 urban and rural areas of the United States (U.S.) (U.S. EPA, 1986). The measured concentrations ranged from 0.011 fCi/m^3 to 0.3 fCi/m^3. Ambient air is unlikely to be a significant source of exposure to uranium outside of mining and occupational settings.

Soil

Uranium is present in soils and rocks in concentrations generally varying between 0.5 and 5 ppm (NRC, 1983). It is found in granites, metamorphic rocks, lignite, monazite sands, and phosphate deposits as well as in minerals (Cothern and Lappenbusch, 1983). Uranium enters other media (air, water, and food) from the rocks and soil.

Water

The naturally occurring uranium concentration in drinking water sources depends on factors such as the uranium concentration in the host aquifer rock, the partial pressure of CO_2, the presence of O_2 and complexing agents in the aquifer, the pH and the nature of the contact between the uranium minerals and water (Hess *et al.*, 1985). Uranium in water is derived from phosphate deposits and mine tailings, as well as from run-off of phosphate fertilizers from agricultural land. Greater than 99 percent of uranium transported by runoff from land to fresh water systems is in suspended particles and remains in the sediment (Cothern and Lappenbusch, 1983). Environmental pH also influences both the type and relative amount of chemical complexing agents present in solution, which are known to facilitate uranium solubility and mobility.

The average amount of uranium in drinking water in the U.S. is 2 pCi/L. Of 59,812 community drinking water supplies in the U.S., 25 to 650 exceeded a uranium concentration of 20 pCi/L; 100 to 2,000 exceeded 10 pCi/L; and 2,500 to 5,000 exceeded 5 pCi/L (Cothern and Lappenbusch, 1983. Assuming a 0.9 p Ci/μg conversion factor, the number of community water systems predicted to have concentrations greater than 20 μg/L is 790 (U.S. EPA, 2000).

Some water supplies contain more activity from ^{234}U than from ^{238}U, resulting in a $^{234}U/^{238}U$ activity ratio greater than one. It has been observed that the largest disequilibrium ratio occurs in slightly oxidizing environments. The activity ratio is seldom less than one and rarely exceeds two (Cothern and Lappenbusch, 1983). The radioactivity calculated for ^{234}U and ^{238}U, determined by chemical uranium analysis, and using the equilibrium factor of 0.67 pCi/μg, will be in error if the two isotopes are not in equilibrium. The actual factor can range from 0.33 pCi/μg (no ^{234}U) to at least 7 pCi/μg ($^{234}U/^{238}U = 20$) (Blanchard *et al.*, 1985). U.S. EPA has estimated a specific activity of 1.3 pCi/μg for uranium in drinking water sources based on the results of a nationwide survey (Fed. Reg. 56: 33050-33127, July 18, 1991). The relative abundance of isotopes in a drinking water source depends on physical and chemical factors (such as an oxidizing environment, and the rate of removal of uranium compounds from rocks or soil) and varies greatly from place to place (Cothern and Lappenbusch, 1983). For this reason U.S. EPA's estimate does not necessarily apply to California drinking water sources. Fluorimetric methods for uranium determination have the necessary sensitivity and accuracy for estimating water concentrations to 10 pCi/L (Blanchard, *et al.*, 1985).

In 1984 California Department of Health Services (DHS) conducted an extensive investigation of radioactivity in ground water in the community of Glen Avon. Four samples had levels greater than 40 pCi/L. Forty-eight samples had uranium activity between 10 and 40 pCi/L. Eight samples had less than 10 pCi/L. Apparently acidic ground water is responsible for mobilizing naturally occurring uranium in the soil (DHS, 1985).

Wong, *et al.* (1999) studied the isotopic abundance ratios of natural uranium in selected California groundwater. Representative samples from 102 groundwater locations throughout the state were analysed for gross alpha by internal proportional counting, total uranium by laser phosphorimetry and total uranium by inductively coupled plasma-mass spectrometry (ICPMS). Selected samples (43) were analysed for isotopic abundances of ^{234}U, ^{235}U, and ^{238}U. The average $^{234}U/^{238}U$ activity ratio for the study was 1.32 ± 0.30 SD. The average activity to mass conversion factor (specific activity) was 0.79 pCi/μg with a standard deviation of 0.10. The latter data set from Wong *et al.* (1999) was analyzed using Microsoft Excel (Version 4) Crystal Ball (Version 4, Decisioneering, Inc) and the normal distribution was found to best fit the data.

Food

Because uranium is present in many soils and in some water supplies, it also occurs in many foods. The use of phosphate fertilizers increases the uranium level in foods. The National Council on Radiation Protection and Measurements (NCRPM) has estimated that humans take in approximately the same amount of uranium in food as they do in drinking water (NCRPM, 1984). This would suggest a relative source contribution (RSC) in the range of 40 to 60 percent for use in calculating a PHG based on experiments in which total uranium exposure is measured.

METABOLISM AND PHARMACOKINETICS

Absorption

Inhalation is a minor route of entry for uranium into humans in the general population. The use of water that contains uranium could expose an individual to uranium by dermal contact or ingestion. Human skin absorption data are not available. Percutaneous absorption has been reported as an effective route of penetration for soluble uranium compounds after application to rat skin (De Rey *et al.*, 1983). Single or daily applications were performed with uranium compounds mixed with emulsion composed of Vaseline® and water (De Rey *et al.*, 1983). The lowest administered dose (0.5 g/kg body weight) was orders of magnitude greater than could result from exposure to the highest levels of uranium found in potential California drinking water sources. Electron microscopy showed that the uranium penetrated into the intercellular space between the horny and granular layers of the epidermis. Adverse effects such as purulence and detachment of the horny layer were observed (De Rey *et al.*, 1983).

Gastrointestinal absorption studies of uranium include single oral administration experiments of soluble uranium compounds to rats, dogs, hamsters, baboons, and neonatal swine. Gastrointestinal absorption is consistently lower in rats (less than 0.5 percent) than in other species studied (Wrenn *et al.*, 1985). Fractional absorption in two-day old rats given uranyl nitrate orally was estimated as 0.01 to 0.07 (ICRP, 1995). In feeding studies, it was found that absorption was doubled in fasted rats, and increased 3.4 fold in iron-deficient rats (ATSDR, 1997).

Average absorption was reported to be 1.55 percent (0.83 to 2.3 percent) for seven dogs (Fish *et al.*, 1960). Gastrointestinal absorption for adult Syrian hamsters was calculated to be 0.77 percent (Harrison and Stather, 1981). $UO_2(NO_3)_2$ given by gavage to one-day old miniature swine at a dose of 1.5 to 2.0 mg uranium/kg showed absorption of at least 34.5 percent (Sullivan and Gorham, 1982).

There is limited published information on gastrointestinal absorption of uranium in humans. Hursh *et al.* (1969) studied oral uranium absorption in four male hospital patients (ages 56 to 78 years). $UO_2(NO_3)_2$ (10.8 mg) dissolved in 100 mL Coca Cola® was ingested by each subject after an overnight fast. Urine and fecal samples were collected and analyzed for uranium. The four subjects showed uranium absorption of 0.3, 0.7, 1.1, and 3.3 percent. The authors suggest that the data support an approximate 1 percent value for gastrointestinal absorption of uranium in humans. Unabsorbed uranium passes into the feces. Daily excretion of uranium in urine approximates the

uranium absorbed from food and drink. Hursch and Spoor (1973) cited data indicating that between 12 and 30 percent of uranium ingested in the normal diet is absorbed from the gastrointestinal tract. The levels of natural uranium in food and water are lower than those used experimentally.

In general, the smaller the amount of uranium ingested, the greater the fraction absorbed (Wrenn *et al.*, 1985). On the basis of a U.S. survey (Welford and Baird, 1967), it was estimated that the intake of uranium from the normal diet is 1.75 μg/day, and that the extent of gastrointestinal absorption was 7.7 percent (Wrenn *et al.*, 1985). Fisher *et al.* (1983) reported that uranium absorption for three controls was 0.6 to 1 percent and for three retired uranium workers it was 0.55 to 1.6 percent. Wrenn *et al.* (1985) using data from three human studies and six animal experiments, gave a best estimate of gastrointestinal absorption of uranium for adult humans at environmental levels of uranium intake of 1.4 percent. From all the data sets available, Wrenn *et al.* found a range of mean values of 0.3-7.8 percent of ingested uranium absorbed, with a grand mean of 1.8 percent. No values for human neonates were given. Gastrointestinal absorption of ^{238}Pu (plutonium) was about 100 times higher in neonatal rodents than in adult rodents and this difference was 10 to 20 times greater in swine (Sullivan, 1980a,b). Absorption of uranium by neonatal swine is higher than absorption of Pu from the gastrointestinal tract (Sullivan and Gorham, 1982).

Enhanced permeability of the intestine of the neonate facilitates passage from the nursing mother's milk to the neonate of macromolecules that are essential to immunity (Sullivan and Gorham, 1982). Uranium may be associated with proteins during passage across the intestinal mucosa. Absorption of iron and other heavy metals increases during lactation (Batey and Gallagher, 1977; Bhattacharrya *et al.*, 1981 and 1982; Kostial and Momcilovic, 1972). Given these facts it is reasonable to assume that nursing infants and lactating mothers may have higher gastrointestinal absorption of uranium than normal healthy adults. In its review of the literature, U.S. EPA found values for gastrointestinal absorption of uranium in humans ranging from 1 to 30 percent (U.S. EPA, 1991a, b). For purposes of calculating the cancer risk of natural uranium in drinking water, U.S. EPA chose 20 percent as the "best estimate" acknowledging that there is "substantial uncertainty" associated with this number (U.S. EPA, 1991a, b).

The latest guidance from U.S. EPA on gastrointestinal absorption of uranium is found in Federal Guidance 13 (U.S. EPA, 1999). This document gives gastrointestinal absorption fractions (F1 values) for uranium of 2 percent for children aged 1 to 15 years, and 2 percent for adults. The value listed for infants is 4 percent. U.S. EPA took these data from the International Commission on Radiological Protection (ICRP, 1995).

Distribution and Excretion

Bicarbonate complexes are the chief form in which uranium is absorbed and transported within the human body (Hodge, 1973). $UO_2(HCO_3)_2$ in plasma is taken up by bone and filtered by the glomeruli into the urine (Durbin and Wrenn, 1975). Most of the studies involving distribution and excretion of uranium have been based on administration by intravenous or intraperitoneal injection, feeding or inhalation to animals. Stevens *et al.* (1980) measured the distribution, retention and excretion of ^{233}U in seven beagles injected intravenously with 2.8 μCi ^{233}U per kg body weight, and sacrificed at times ranging from 1 to 726 days post injection. Twenty-two percent of the injected uranium was found in the kidney at one day post injection with high concentrations localized in the proximal tubules and 7.7 percent of the uranium was found in the skeleton. In a study with female mice exposed orally to uranyl nitrate hexahydrate at a dose of 462 mg/kg-day for 36 to 44 weeks, average uranium accumulation was 6 μg per pair of kidneys,

46 μg/mg bone, and 0 to 0.5 μg/mg whole liver (Tannenbaum *et al.*, 1951). Autoradiographic studies in Sprague-Dawley rats showed that, in bone, uranium accumulates mainly in the cancellous portion (trabeculae) and endosteum; whereas accumulation in the kidney occurs in the cortex and in the corticomedullary junction (Tannenbaum *et al.*, 1951).

The kidneys and bones are the principal sites of accumulation and toxic action of uranium (Yuile, 1973; Stevens *et al.*, 1980; Morrow *et al.*, 1982). Following uranium administration, 80 percent is excreted in urine and feces, 10 percent is deposited in the kidneys and the remaining 10 percent is deposited in the skeleton with negligible concentrations appearing in other tissues (NRC, 1983). The skeleton is the major site of long-term storage of uranium (Wrenn and Singh, 1982).

Several studies have reported the amount of uranium in the skeleton of persons with no known occupational exposure to uranium. The average values ranged from 2.3 to 61.6 μg with a mean value of 24.9 ± 22 μg uranium in 5,000 grams of bone, or 5.0 ± 4.4 μg/kg of bone (Wrenn *et al.*, 1985).

Kathren *et al.* (1989) reported uranium concentrations in tissues collected at autopsy from an individual who worked as a "chemical operator" in a uranium processing plant for 20 years. Deposition of uranium followed the pattern: skeleton > liver > kidney, with ratios of 63:2.8:1. The rank order of uranium content was in agreement with the observations by Fisenne and Welford (1986) for New York City residents but in disagreement with the data reported for the ICRP Reference Man (ICRP, 1975). The uranium order content in the Reference Man is skeleton > kidney > lung > liver or 59, 7, 1, 0.45 μg, respectively. Recently, uranium in all tissues of two whole bodies were measured and reported by the U.S. Transuranium and Uranium Registries (USTUR) (Kathrin, 1998). The data showed lung > kidney > liver in one case and kidney > lung > liver in the other. In both cases, pulmonary lymph nodes were an order of magnitude higher in uranium concentration than other soft tissues. Such differences may be due to sampling error or real differences in exposure history and individual variability.

In humans, most of the uranium (approximately 90 percent) is excreted in the feces; the remainder is excreted in the urine (Wrenn *et al.*, 1985). In rats, most of the absorbed dose leaves the body within a few days in the urine (ATSDR, 1997); half is excreted in two to six days (Durbin and Wrenn, 1975), and 98 percent is excreted within seven days (Sullivan *et al.*, 1986).

There is a fast and a slow phase of uranium excretion in humans and animals. The retention half lives of uranium in bone and kidney are of most relevance. For bone, half-lives of 883 days (Stevens *et al.*, 1980), 180 and 360 days (Hursh and Spoor, 1973) and 800 days (Bernard, 1958) have been reported. Retention half-lives for uranium in human kidney have been reported as 30 days (Bernard, 1958) and more recently as 6 days and 1,500 days for the fast and slow components, respectively (ICRP, 1979). Wrenn *et al.* (1985) utilized a 15-day half-life (Hursh and Spoor, 1973) and this value was incorporated into the uranium pharmacokinetic model.

Biokinetic Models

Biokinetic models mathematically characterize the movement, translocation, fate, deposition, and excretion of a substance (e.g., uranium) in a living system. Such models predict where substances go in the body, and how long they remain, which permits the calculation of internal doses and risks to specific tissues and organs as well as the whole body (Kathrin, 1998). Such models may be generally descriptive of the retention of radionuclides in the body with virtual compartments or physiological where model compartments represent actual body organs and tissues. In the dose-computation scheme of the ICRP, information on the biological behavior of

radionuclides is contained in three main types of biokinetic model: a respiratory model, a gastrointestinal (GI) model, and an element-specific systemic model.

The GI model is used to describe the movement of swallowed or endogenously secreted material through the stomach and intestines. Element-specific GI absorption fractions (F1 values) describe the rate and extent of absorption from the small intestine to blood (U.S. EPA, 1999). The GI model developed by U.S. EPA (1999) has been used by ICRP for many years. The model divides the GI tract into four compartments: stomach (St); small intestine (SI); upper large intestine (ULI); and lower large intestine (LLI), and assumes first-order transfer of material from one compartment to the next. Absorption of ingested material to blood is assumed to occur only in SI in terms of a fraction F1. The fraction (F1) of ingested material moves from SI to BLOOD and the fraction 1-F1 moves from SI to ULI and eventually via excretion to FECES, in simple mass-balance and rate equations.

The source of the uranium systemic biokinetic model used by U.S. EPA (1999) is ICRP (1995). The ICRP's physiologically based models for bone-seeking elements were developed within two frameworks: one designed for the class of "calcium-like" or bone volume filling elements such as strontium, radium, and lead; and the other designed for the class of "plutonium-like" or bone-surface-seeking radionuclides such as thorium. The uranium model is of the calcium-like type. The model incorporates a central blood Plasma and RBC compartment connected to tissue compartments: Skeleton, Kidneys, Liver, and Other Soft Tissues, and to output compartments: GI Tract and Feces, Urinary Bladder and Urine. The tissue compartments are subdivided into sub-compartments of faster or slower turnover. The implementation of the model is described by Leggett *et al.* (1993). A simpler five compartment exponential model has been proposed by Fisher *et al.* (1991) based on an acute accidental occupational inhalation exposure of 31 workers to UF_6. In this model the fractional urinary excretion Y(t) is predicted as a function of time (in days) after exposure. The excretion constants of the five exponential compartments correspond to residence half-times of 0.25, 6, 26, 300, and 3,700 days in the lungs, kidneys, other soft tissues, and two bone compartments, respectively.

TOXICOLOGY

Toxicological Effects in Animals

Numerous animal studies of the toxicity of uranium have been undertaken, beginning with the Manhattan Project in the 1940s. These studies have been reviewed by Yuile (1973). More recently, the toxicology of uranium in animals has been reviewed by Durbin and Wrenn (1975) and by Wrenn *et al.* (1985).

Acute Toxicity

The acute oral toxicity of uranium compounds is low. There are large differences in sensitivity to uranium among the species tested. The LD_{50}s of intraperitoneal uranium nitrate ranged from 0.1 to 0.3 mg/kg in the rabbit and guinea pig to as much as 20 to 25 mg/kg in mice (Durbin and Wrenn, 1975). The approximate lethal doses of $UO_2(NO_3)_2$ administered intravenously to four species are given in Table 1.

Table 1. Median Lethal Doses (LD_{50}) of Uranium Administered Intravenously

Species	Median Lethal Dose (mg uranium/kg)	Dose Ratio
rabbit	0.1	1
guinea pig	0.3	3
rat	1.0	10
mouse	10 to 20	100 to 200

Nine days after a single intravenous injection of 2.8 μCi ^{233}U/kg or 2.8 μCi natural uranium/kg, a marked elevation of the blood urea nitrogen (BUN) was observed in all dogs tested (Stevens *et al.*, 1980). Two episodes of azotemia (retention in the blood of excessive amounts of nitrogenous compounds) were noted. The first increase in BUN was attributed to chemical toxicity rather than radiation-induced toxicity because a similar effect was observed in the dogs given natural uranium instead of ^{233}U. Nine weeks after injection, a secondary episode of azotemia occurred in the dogs injected with ^{233}U, but not in the dogs injected with natural uranium. The authors hypothesized that the secondary increase may have been radiation-induced. Stevens *et al.* (1980) commented that following prolonged exposure of beagle dogs to ^{232}U or ^{233}U, the skeleton and not the kidney may be the primary target organ and osteosarcoma may be the cause of death.

Braunlich and Fleck studied the effect of a single nephrotoxic dose (6 mg/kg) of uranyl nitrate in rats of different ages (1981). They found that alkaline phosphatase in the urine was a good indicator of nephrotoxicity (Braunlich and Fleck, 1981).

Subchronic and Chronic Toxicity

Noncarcinogenic Effects

In a study of 30 dogs administered $UO_2(NO_3)_2$ (Yuile, 1973) in the diet for one year at dose levels of 0.0002 to 10 g/kg, adverse effects on growth were noted only for those dogs receiving 0.2 g/kg of uranyl nitrate.

Morrow *et al.* (1982) published inhalation studies with uranium on dogs. They found that an absorbed dose of approximately 10 μg U^{6+}/kg body weight produced renal injury and proposed that a concentration of 0.3 μg/g kidney is the threshold concentration for renal injury in dogs. The mechanism of toxic action on the kidney postulated by Hodge (1973) and Nechay *et al.* (1980) was that UO_2^{++} may compete with Mg^{++} and Ca^{++} at ATP binding sites for these metals, thus disrupting active transport across the cell membrane.

Studies conducted from one day to five years showed that dogs, monkeys and rats could breathe a $UO_2(NO_3)_2$ aerosol at 5.8 mg/m^3 of air with little evidence of serious injury (Leach *et al.*, 1970). Following the five-year exposures, groups of animals were held for postexposure study as long as 6.5 years (Leach *et al.*, 1973). Pulmonary neoplasia developed in a high percentage of the dogs examined two to six years after exposure. Pulmonary and tracheobronchial lymph node fibrosis was more marked in monkeys than in dogs.

Novikov (1970) pointed out that acute and chronic uranium poisoning produces disturbances, not only in the kidney, but also in the cardiovascular system, the blood and hematopoietic system, the

immune system, the thyroid, adrenal gland and liver, and in basal metabolism. Novikov (1970) stated that the use of the uranium concentration in the kidney as the sole criterion of toxicity is untenable because of toxicity in other organ systems. Novikov and Yudina (1970) examined the effects of 0.02, 0.2 and 1.0 mg/kg of uranium administered orally for 12 months to rabbits. They observed no changes in serum urea, creatinine and chloride levels. A dose of 1.0 mg/kg inhibited nucleic acid metabolism in rabbit kidney and liver.

Gilman *et al.* (1998a) studied the toxic effects of uranium administered to rats in drinking water. Following a 28-day range finding study, five groups of 15 male and 15 female weanling Sprague-Dawley rats were exposed for 91 days to uranyl nitrate hexahydrate (UN) in drinking water at 0.96, 4.8, 24, 120, or 600 mg UN/L. A control group was given tap water with less than 0.001 mg U/L. No dose-related effects on hematological or biochemical parameters were seen. Histopathological lesions were observed in the kidney and liver, in both males and females, in all dose groups. Renal lesions of tubules (apical nuclear displacement and vesiculation, cytoplasmic vacuolation, and dilation), glomeruli (capsular sclerosis), and interstitium (reticulin sclerosis and lymphoid cuffing) were observed in the lowest exposure groups. However, these do not generally increase in the higher dose groups. The authors identified a study LOAEL of 0.96 mg UN/L drinking water, equivalent to average doses of 0.06 and 0.09 mg U/kg-d in male and female rats, respectively.

Gilman *et al.* (1998b) exposed male New Zealand White (NZW) rabbits for 91 days to 0.96, 4.8, 24, 120, or 600 mg UN/L in drinking water. Subsequently females were similarly exposed for 91 days to 4.8, 24, or 600 mg UN/L. No dose-related changes in hematological or biochemical parameters were observed. Dose dependent effects were seen primarily in the kidney, where changes in the renal tubules were characteristic of uranium toxicity. The authors identified a study a lowest-observed-adverse-effect-level (LOAEL) of 0.96 mg UN/L in drinking water, equivalent to an average dose in males of 0.05 mg U/kg-d. The reversibility of uranium kidney toxicity was also investigated by Gilman *et al.* (1998c). Specific-pathogen free (SPF) male NZW rabbits were exposed to 24 or 600 mg UN/L in drinking water for 91 days. Recovery periods were 0, 8, 14, 45, or 91 days. Renal tubular injury with degenerative nuclear changes, cytoplasmic vacuolation, and tubular dilation was seen in the high dose group, without consistent resolution even after 91 days recovery.

Reproductive and developmental effects have been studied in rodents by several groups of investigators. These studies are summarized in U.S. EPA's drinking water criteria document (U.S. EPA, 1991b). In general, uranium salts cause reproductive and developmental effects (e.g., embryolethality, malformations and testicular effects) only when administered at much higher doses than those that would cause nephrotoxicity.

Carcinogenic Effects

Sarcomas resulted in rats injected with metallic uranium in the femoral marrow and in the chest wall (Hueper *et al.*, 1952). The authors were unable to determine whether the local tumors induced by uranium were caused by metallocarcinogenic or radiocarcinogenic action. Alpha-emitting, bone-seeking radionuclides such as ^{232}U, ^{233}U and ^{226}Ra have been shown to induce bone tumors in rodents (U.S. EPA, 1991a, b). In general, ionizing radiation is regarded by U.S. EPA as carcinogenic, mutagenic and teratogenic in animals and humans (U.S. EPA, 1991a, b).

Toxicological Effects in Humans

Acute Toxicity

One case study reported two deaths of human beings accidentally exposed to uranium hexafluoride and its breakdown products (uranyl fluoride and hydrofluoric acid) by inhalation (ATSDR, 1997). The acute effects of this exposure were characteristic of hydrofluoric acid exposure. No studies were found of acute effects to humans resulting from oral exposure to uranium or uranium compounds. Levels of $UO_2(NO_3)_2$ below 70 μg/kg administered intravenously to six terminally ill patients (Hursh and Spoor, 1973) did not produce renal injury as evidenced by changes in urinary proteins and catalase.

Chronic Toxicity

Noncarcinogenic Effects

The human data on uranium toxicity have been summarized by Hursh and Spoor (1973), Adams and Spoor (1973) and by Boback (1975). Boback (1975) found no abnormal clinical chemistry parameter effects in urine from uranium workers involved in exposure incidents that produced urinary uranium concentrations up to 2.85 mg/L. Clarkson and Kench (1952) found low but significantly elevated levels of amino acids in the urine of 12 workers exposed to uranium hexafluoride.

Short-term follow-up studies in the 1940s and 50s of uranium workers exposed for several months or years to high levels of soluble uranium compounds showed only transient kidney damage (proteinuria) and no evidence of permanent effects (Hursh and Spoor, 1973).

Moss and McCurdy (1982) reported that increased β2-microglobulin (BMG) excretion in urine could be correlated with uranium in drinking water at concentrations up to 0.7 mg/L. Under normal conditions, only small amounts of protein are detected in the urine (Zamora, *et al.*, 1998). Excretion of low molecular weight proteins such as BMG may increase as a result of increased plasma concentration or decreased tubular absorption (Zamora, *et al.*, 1998). Even among those individuals who drank water with the highest uranium concentration, there were no overt signs of kidney dysfunction, nor histories of kidney ailments. No subtle changes in kidney function were revealed by clinical chemistry. Wrenn and Singh (1981) concluded that the skeleton is the major site of storage of uranium, but the kidney is the principal site of uranium injury after it once gains entrance to the circulation. More recently, Thun *et al.* (1985) found significantly higher urinary excretion of BMG and five amino acids in uranium workers than in a reference group. Increased renal excretion was associated with length of exposure to soluble uranium. These data were consistent with uranium-induced nephrotoxicity.

Uranium has a pronounced tissue toxicity quite apart from its potential toxicity to the skeleton. Chen *et al.* (1961) concluded that ^{238}U would not pose a radiological hazard in humans because the quantities necessary to deposit sufficient uranium in bone to cause radiation effects would be far in excess of the uranium doses causing lethal renal damage. More recent analyses of the potential carcinogenic effects of natural uranium due to ionizing radiation do not agree with this conclusion (U.S. EPA, 1991a, b).

Zamora *et al.* (1998) studied the effects of uranium exposure in 50 subjects in two Canadian communities. The first had private wells supplied from a groundwater source whose uranium content was well above the current Canadian drinking water guideline of 100 μg/L (Health and Welfare Canada, 1996). The second community had drinking water that contained less than 1 μgU/L. The indicators of kidney function measured included glucose, creatinine, protein, and BMG. The markers for cell toxicity were alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), lactate dehydrogenase (LDH), and *N*-acetyl-β-D-glucosaminidase (NAG). These appear in the urine as a result of cell toxicity (Zamora, *et al.*, 1998). Urinary glucose was found to be significantly different and positively correlated with uranium intake for males, females and pooled data. Increases in ALP and BMG were also observed to be correlated with uranium intake for pooled data. In contrast, the indicators for glomerular injury, creatinine and protein, were not significantly different in the two groups or correlated with uranium intake. The authors conclude that chronic uranium intakes of 0.004 μg/kg-day to 9 μg/kg-day via drinking water affect kidney function and that the proximal tubule is the site of action. The authors note that these effects may represent a manifestation of subclinical toxicity which may not necessarily lead to kidney failure or overt illness. It may, however be the first step in a process where chronic intake of elevated levels of uranium may lead to progressive or irreversible renal injury.

In another small study, Health Canada (1998) investigated kidney effects of exposure to uranium in people living in Kitigan Zibi, a town in Quebec. This town is supplied with drinking water from wells that have uranium concentrations ranging from 10 to 1,418 ppb. Exposure to uranium was estimated by measuring uranium excretion in the urine. Effects on kidney function were determined (as in the previous study) by analyzing urine samples for a variety of parameters and enzymes, including urine volume, urine specific gravity, GGT and BMG. In this study it was found that for the pooled male and female data there was a statistically significant positive correlation ($p<0.01$) between four parameters associated with tubule effects and uranium excretion (see Table 2, below). These four parameters were urine volume, specific gravity, GGT and BMG. Other parameters related to tubule effects (urinary glucose, ALP, LDH, and NAG) did not show a statistically significant correlation with uranium excretion. Two parameters related to glomerular effects (urinary creatinine and protein) were not correlated with uranium excretion in a statistically significant manner. The data from this study are discussed further in the Dose-Response section below.

Carcinogenicity

A mortality study was conducted on 2,731 males employed at a uranium refining and processing facility. Exposure and smoking habits were not analyzed. No deaths occurred from cancers of the bone or thyroid, but deaths from cancer of the esophagus showed a statistically significant increase (Dupree, 1980).

In uranium miners, an increased mortality from lung cancer has been recognized for many years (Pochin, 1985). Lung cancer has been related to the radiation dose to lung tissues. The dose to the lung in uranium mines comes essentially from the radioactive decay products of the radioactive gas radon, rather than from uranium itself. The atmosphere in mines is likely to contain materials such as arsenic and diesel fume polycyclic aromatic hydrocarbons, which have significant carcinogenic effects. These would have confounding effects on any study of the carcinogenicity of uranium itself.

Table 2. Uranium Excretion Correlation Coefficients for Volume Adjusted Data

Biomarkers	Kidney Site Affected	Volume Adjusted Data (pooled male and female)
Urine volume	Tubule	0.50 (0.0001)*
Specific gravity	Tubule	0.35 (0.0088)*
Glucose	Tubule	0.14 (0.31)
Creatinine	Glomerulus	0.24 (0.08)
Protein	Glomerulus	0.23 (0.09)
ALP	Tubule	0.15 (0.29)
LDH	Tubule	0.16 (0.26)
GGT	Tubule	0.37 (0.0064)*
NAG	Tubule	0.15 (0.29)
BMG	Tubule	0.49 (0.0047)*

Legend: * indicates statistically significant at 0.01 level. ALP=alkaline phosphatase, LDH=lactate dehydrogenase, GGT=gamma glutamyl transferase, NAG=N-acetyl glucosamine, BMG=beta microglobulin. Based on Table 7 of Health Canada, 1998.

The cigarette smoking habits of the miners also need to be determined and accounted for in the epidemiological risk assessment. It should be noted that other types of underground mining including iron, lead, and fluorspar have also been associated with radon gas-induced lung cancer (Zeise *et al.*, 1987). Therefore, at the present time inhalation of natural uranium has not been demonstrated to be carcinogenic for humans.

Polednak and Frome (1981) described mortality in a cohort of 18,869 white males who were employed between 1943 and 1947 at a uranium conversion and enrichment plant in Oak Ridge. Standardized mortality ratios (SMRs) for various sites, including lung cancer, bone cancer, leukemia, and disease of the respiratory and genitourinary system did not tend to be higher in workers exposed to the highest average levels of uranium dust. Workers in the "alpha chemical department" were exposed to the highest levels of airborne uranium dust. There were no deaths from bone cancer or leukemia, or from chronic nephritis. SMRs for lung cancer were analyzed by age at hire and job classification. The SMRs for lung cancer in these alpha chemistry workers hired at ≥ 45 years of age was high, based on small numbers. None of the seven lung cancer decedents worked for one year or longer in alpha chemistry.

There are no reports of experimental induction of bone cancer by ingested, injected or inhaled natural uranium in soluble form (Wrenn *et al.*, 1985). However, bone cancer has been induced in experimental animals by injection or inhalation of soluble compounds of high specific activity uranium isotopes, ^{232}U and ^{233}U (Finkel, 1953). Lung cancer was produced in rats and dogs, but not in monkeys following continuous inhalation of large amounts of highly soluble UO_2 for two to five years (Leach *et al.*, 1970; Leach *et al.*, 1973).

Wilkinson (1986) has reported that several counties in northern New Mexico displayed high rates of mortality from gastric cancer. Significant differences in sex-specific, age-adjusted, average annual stomach cancer mortality rates during 1970 to 1979 were found between counties with significant deposits of uranium compared to those without significant deposits (Wilkinson, 1986). The identification of uranium deposits is based on a qualitative survey designed to identify areas containing uranium deposits that might be of commercial value. Wilkinson (1986) advanced a working hypothesis that residents of counties with significant deposits of uranium are exposed

to higher levels of radionuclides such as radon and radon daughters than residents of counties lacking the uranium deposits.

Genotoxic and Cytotoxic Effects

Uranium miners have been found to have increased frequency of chromosomal aberrations in human lymphocytes, but these have been thought to be due to radon or its radioisotope daughters (Brandom *et al.*, 1978; ATSDR, 1997). Other genotoxic effects have not been adequately tested (ATSDR, 1997).

Blood lymphocyte cultures from two groups of workers exposed to uranium were examined for asymmetric chromosomal aberrations and sister-chromatid exchanges (SCEs). Significant increases were seen in both of these cytogenetic endpoints (Martin *et al.*, 1991). These investigators interpreted their results as evidence of clastogenic effects of uranium.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

The recently published studies of Gilman *et al.* (1998a-c) provide a basis for a dose response assessment of noncarcinogenic effects caused by chronic uranium intake via drinking water. In particular the 91-day study in Sprague-Dawley rats identifying a subchronic oral LOAEL of 0.06 mg/kg-d for renal and liver lesions in males appears to be a reliable basis. The histological changes that were observed at this lowest dose did not generally increase in number at the higher doses, so these data cannot be said to exhibit a dose-response relationship above the lowest dose tested. This observation diminishes the value of these data as an indication of the beginning of potentially pathological changes. A similar subchronic LOAEL of 0.05 mg/kg-d was observed in male New Zealand White rabbits although the study was compromised by a microbial infection in four animals.

Effects on human kidney function have been reported from quite low exposure levels of uranium in drinking water (0.004 μg/kg-d to 9 μg/kg-d) suggesting a very broad dose-response range, although the effects noted cannot be considered toxic as such (Zamora *et al.*, 1998). One could question the toxic significance of the histological lesions seen in the Gilman *et al.* studies and while it is often difficult to identify clearly adverse effects in such studies, for the purpose of determining a PHG, OEHHA considers such effects to be adverse albeit weak. Each human kidney contains about one million nephrons, and considerable loss of these is required to reduce kidney function or result in kidney disease. However, chronic subclinical kidney toxicity ought to be considered as a continuum where certain levels of injury may compromise the body's resistance to other environmental insults.

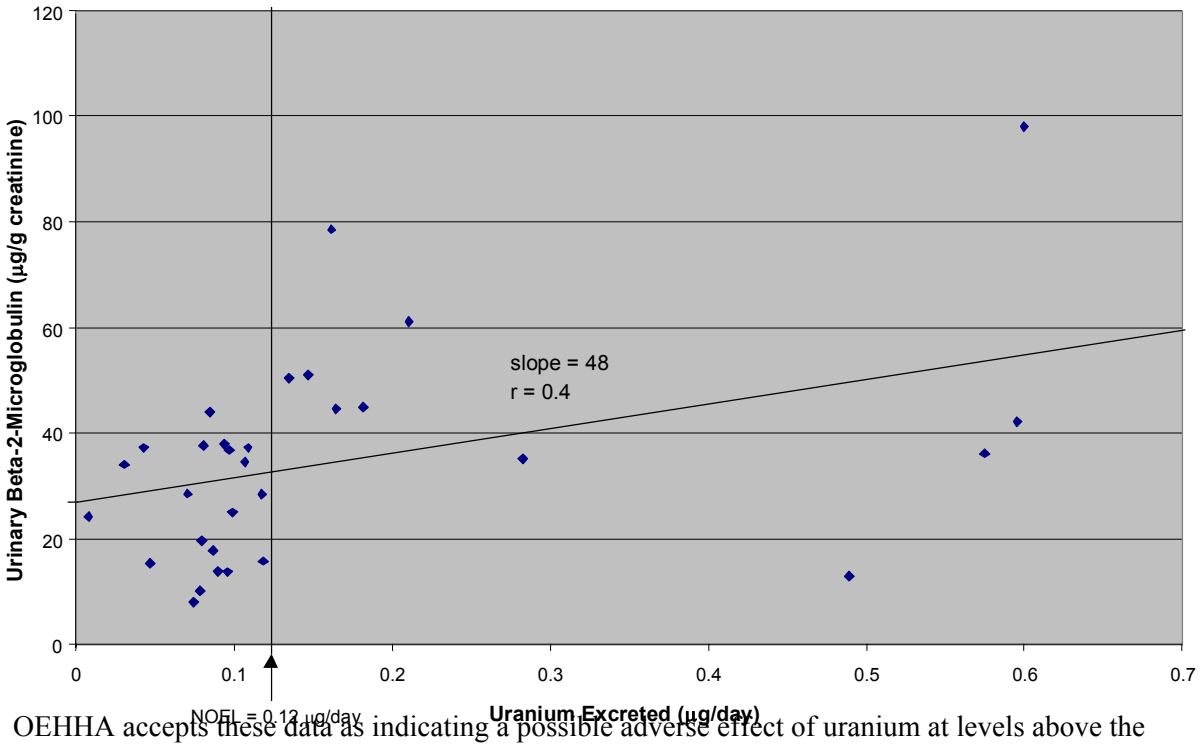
The Zamora *et al.* (1998) kidney function study compared two communities in Canada based on high and low uranium intake in drinking water. The authors reported that daily uranium intake in the high exposure group was associated with higher urinary glucose levels in males and females. They also reported a positive correlation between individual total uranium intake and individual urinary glucose levels for the high exposure group. Increases in ALP and BMG were also correlated with uranium intake for pooled (male and female) data. The range of daily intake associated with the "high exposure group" was from 0.004 to 9 μg/kg. The median

high exposure intake in this study was 58 µg/day. Thus, the daily intake was on the order of 1 µg/kg at the median dose level.

As discussed above (page 11), the Health Canada (1998) study found four parameters related to tubule effects to be positively correlated in a statistically significant manner with uranium excretion. These four parameters are urine volume, urine specific gravity, GGT, and BMG. Of these, the first two are of questionable specificity, i.e. they may or may not be related to effects of uranium on the kidney tubules. GGT and BMG are more reliable indicators of kidney tubule effects of uranium exposure. Both of these data sets were analyzed by OEHHA using linear regression statistics. Both data sets showed a high degree of correlation (r=0.4 for both data sets). The BMG and GGT data sets were chosen to use for determination of a no-observed-effect-level (NOEL) for kidney tubule effects caused by uranium in drinking water.

The BMG data set (Figure 1) exhibits a positive correlation between urinary BMG and uranium excreted (r = 0.40, p= 0.0026). At urinary excretion levels below 0.12 µg/day there is no correlation (r = 0.010, p = 0.97) even though there are enough data points below this level (n=20) to show a correlation if there had been one. This shows that exposures below those corresponding to excretion of 0.12 µg/day have no effect on urinary BMG levels, i.e. the variation in BMG levels below this level are essentially random. Since the data between 0 and 0.12 µg/day exhibit no effect, 0.12 µg/day can be considered an excretion level that corresponds to a NOEL for this endpoint. An effect on BMG begins to be observed at excretion levels of 0.14 µg/day and increases with increasing excretion levels. The GGT data set was analyzed, with similar results. For the GGT data set there was no correlation below the 0.12 µg/day excretion level (r=0.066, p=0.70) but a strong correlation for the whole data set (r=0.41, p=0.002). The 0.12 µg/day excretion level thus appears to be a NOEL for both data sets.

Figure 1. Correlation of Urinary BMG with Uranium Excretion (Health Canada, 1998)



OEHHA accepts these data as indicating a possible adverse effect of uranium at levels above the 0.12 ug/day excretion level, but concludes that the data are not strong enough to be the basis of a

PHG. These two small "ecological" studies demonstrate an association between several parameters of kidney function and population exposures to increased uranium in drinking water, but cannot demonstrate a cause and effect relationship. Nevertheless, the potential for kidney effects at these low levels of uranium in drinking water should be considered in derivation of a PHG.

Carcinogenic Effects

U.S. EPA has classified natural uranium as a Group A carcinogen ("human carcinogen based on sufficient evidence from epidemiological studies") because it is an emitter of ionizing radiation. U.S. EPA classifies all emitters of ionizing radiation as Group A carcinogens. U.S. EPA acknowledges that "studies using natural uranium do not provide direct evidence of carcinogenic potential." However, studies with radium and certain isotopes of uranium provide evidence for the carcinogenicity of ionizing radiation in humans (U.S. EPA, 1991a, b). U.S. EPA also considers agents emitting ionizing radiation to be mutagens and teratogens.

Mays *et al.* (1985) estimated the lifetime cancer risk of daily intake of uranium in drinking water based on data from induction of skeletal cancers by radium isotopes. They estimated that exposure of one million persons to 5.0 pCi per day from uranium isotopes in drinking water would be expected to result in 1.5 additional bone sarcomas. This is equivalent to a cancer risk for uranium in drinking water of 6.0×10^{-7} per pCi/L (assuming consumption of two liters of water per day). This is virtually identical to the U.S. EPA's 1991 estimate.

More recently, U.S. EPA developed carcinogenic potencies or risk coefficients for over 100 radionuclides including six uranium isotopes (U.S. EPA, 1994, 1999). The risk coefficients developed apply to an average member of the public in that estimates of risk are averaged over the age and gender distributions of a hypothetical closed population with an unchanging gender ratio whose survival functions and cancer mortality rates are based on the 1989-1991 U.S. decennial life table (NCHS, 1997) and U.S. cancer mortality data for the same period (NCHS, 1992, 1993a, b). For each radionuclide and exposure route both mortality and morbidity risk coefficients are provided. The five steps in computing the risk coefficients for internal exposure are as follows:

- Step 1 (Lifetime risk per unit absorbed dose at each age): Radiation risk models are used to calculate gender-specific lifetime risks per unit of absorbed dose for 14 cancer sites.
- Step 2 (Absorbed dose rates as a function of time post-acute intake at each age): Age-specific biokinetic models are used to calculate the time-dependent inventories of activity in various regions of the body following an acute intake of a unit of radionuclide activity. Six ages are used: 100 days and 1, 5, 10, 15, 20-25 years.
- Step 3 (Lifetime cancer risk per unit intake at each age): For each cancer site, the gender-specific values of lifetime risk per unit absorbed dose received at each age (from the first step) are used to convert the calculated absorbed dose rates to lifetime cancer risks for the case of acute intake of one unit of activity at each age x_i.
- Step 4 (Lifetime cancer risk for chronic intake): It is assumed that the concentration of the radionuclide in the environmental medium remains constant and that all persons in the population are exposed throughout their lifetimes.
- Step 5 (Average lifetime cancer risk per unit activity intake): Because a risk coefficient is an expression of the radiogenic cancer risk *per unit activity intake*, the calculated lifetime

cancer risk from chronic intake of the environmental medium must be divided by the expected lifetime intake.

A more detailed explanation of these five steps is presented in the most recent U.S. EPA report (U.S. EPA, 1999).

Analyses involving the risk coefficients should be limited to estimation of prospective risks in large existing populations, rather than being applied to specific individuals. Also the risk coefficients may not be suitable for assessing the risk to an average individual in an *age-specific* cohort. All computations of dose and risk were performed using DCAL, a comprehensive biokinetics-dose-risk computational system designed for radiation dosimetry (U.S. EPA, 1999). DCAL has been extensively tested and has been compared with several widely used solvers for biokinetic models and systems of differential equations. DCAL was used by a task group of the ICRP to derive or check the dose coefficients given in its series of documents on age-specific doses to members of the public from the intake of radionuclides (e.g., ICRP, 1996).

The two most common uranium isotopes in drinking water are ^{234}U and ^{238}U with lifetime mortality risk coefficients for exposure via tap water of 1.24×10^{-9} Bq^{-1} and 1.13×10^{-9} Bq^{-1}, respectively. Multiplying by 0.037 Bq/pCi converts these coefficients to lifetime risks of 4.6×10^{-11} and 4.2×10^{-11} per pCi. These risks from specific isotopes should be adjusted to net risk based on the isotope ratios actually found in drinking water, which can vary slightly from the crustal abundance. Recent calculations of the relative abundance of ^{234}U and ^{238}U in California groundwater (Wong et al., 1999) are based on sampling from 102 groundwater locations throughout California, and analyses of total uranium by laser phosphorimetry and inductively coupled plasma-mass spectrometry, plus gross alpha determinations by internal proportional counting. Selected samples were also analyzed for uranium isotopic abundance by alpha spectroscopy. There was good agreement among the different methods, yielding an average $^{234}U/^{238}U$ ratio of 1.32 ± 0.3 (SD) (Wong *et al.*, 1999). At this isotopic ratio, the combined risk coefficient for uranium in California water is 4.4×10^{-11} $(pCi)^{-1}$. Assuming a lifetime to be 25,550 days (70 years) and daily water consumption to be 2 L, a unit risk of 2.3×10^{-6} $(pCi/L)^{-1}$ can be calculated. The U.S. EPA risk coefficient incorporates a gastrointestinal uptake factor (F1) of 0.02 (2 percent).

CALCULATION OF PHG

Noncarcinogenic Effects

We will calculate public-health protective concentrations (C) for noncarcinogenic endpoints, using first the rat studies of Gilman *et al.* (1998a), then using the human data from Health Canada (1998).

Calculations Based on Data from Rat Studies

First, using the data from Gilman *et al.* (1998a), a public health-protective concentration (C) for uranium in drinking water (in mg/L) can be calculated following the general equation for noncarcinogenic endpoints:

$$C = \frac{\text{NOAEL or LOAEL x BW x RSC}}{\text{UF x W}}$$

where,

NOAEL or LOAEL	=	no-observed-adverse-effect-level or lowest-observed-adverse-effect-level (LOAEL of 0.06 mg/kg-d for toxicity in rats evidenced by a variety of kidney and liver histological lesions from Gilman *et al.*, 1998a);
BW	=	body weight default for an adult human (70 kg);
RSC	=	relative source contribution of 40 percent (0.4);
UF	=	uncertainty factor of 3000: This includes a factor of 3 for LOAEL to NOAEL assuming the histological lesions in the rat study are relatively mild adverse effects; a factor of 10 for interindividual differences in sensitivity to uranium toxicity; 10 for interspecies differences; and 10 for extrapolation from a 91 day study to lifetime exposure; and
W	=	daily water consumption default for an adult (2 L/day).

Therefore,

$$C = \frac{0.06 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.4}{3000 \times 2 \text{ L/day}} = 0.00028 \text{ mg/L} = 0.0003 \text{ mg/L} = 0.3 \text{ ppb (rounded)}$$

The C value of 0.0003 mg/L (0.3 μg/L) is equivalent to approximately 0.24 pCi/L (based on a specific activity of 0.79 pCi/μg).

Repeating the same calculation for a child:

$$C = \frac{NOAEL \times BW \times RSC}{UF \times W}$$

where,

NOAEL	=	same as for the adult calculation,
BW	=	an assumed default child's body weight (10 kg),
RSC	=	relative source contribution of 40 percent (0.4 as for the adult),
UF	=	uncertainty factor of 3000 (as for the adult), and
W	=	daily water consumption for a child (1 L/day).

Therefore,

$$C = \frac{0.06 \text{ mg/kg-day} \times 10 \text{ kg} \times 0.4}{3000 \times 1 \text{ L/day}} = 0.00008 \text{ mg/L} = 0.08 \text{ ppb.}$$

The health-protective concentration based on noncarcinogenic effects in children is 0.00008 mg/L, equivalent to 0.063 pCi/L. This calculation is based on rat data that exhibited an apparent LOAEL, but did not exhibit a positive dose-response relationship at doses above the LOAEL.

Calculations Based on Data from Human Studies

The human data from Health Canada (1998) can be used to calculate a health protective value as follows. The excretion NOEL of 0.12 μg/day from the Health Canada (1998) human study can be used to calculate a C value for natural uranium in drinking water. If we assume that the individuals are in equilibrium, the uranium excreted would equal the uranium intake multiplied by the percentage absorbed. In its review of the literature, U.S. EPA found values for gastrointestinal absorption of uranium in humans ranging from 1 to 30 percent (U.S. EPA, 1991a,b). As discussed above in the section on absorption (page 3) the value for absorption recommended by the U.S. EPA in Federal Guidance 13 (U.S. EPA, 1999) is 2 percent. Assuming 2 percent absorption, the NOEL would be 50 times the excretion NOEL of 0.12 μg/day, or 6.0 μg/day. This NOEL is expressed in μg/day, so body weight is not included in the equation.

$$C = \frac{\text{NOEL}}{\text{UF} \times 2 \text{ L/day}}$$

No RSC is included in the equation because the data are taken from an ecological human study that directly compares drinking water exposures. Since this is a NOEL based on human data, the only uncertainty factor needed is a factor of 10 for intra-human variability, i.e. to protect sensitive individuals including children and individuals with subclinical kidney impairment. At these low levels, only lifetime or very long exposures would be effective, so we can base the calculation on adult water consumption (2 L/day). The equation thus becomes:

$$C = \frac{6 \text{ μg/day}}{10 \times 2 \text{ L/day}} = 0.3 \text{ μg/L or } 0.3 \text{ ppb.}$$

Because it involves less uncertainty (no interspecies extrapolation or long-term exposure extrapolation), is specifically protective of the effects of concern in humans, and because the animal data did not show a clear dose-response, the 0.3 ppb based on human data is the preferable number to use for a health protective concentration based on noncarcinogenic effects to the kidney. However, the nature of these data (small changes in urinary parameters in a small ecologic study) would make this a relatively weak basis for determination of a PHG, compared to the better-known carcinogenic effects of ionizing radiation. OEHHA therefore chooses to establish the PHG for uranium based on its carcinogenic effects due to exposure to ionizing radiation.

Carcinogenic Effects.

As noted above under Dose/Response Assessment, the unit risk of uranium in California drinking water is 2.3×10^{-6} $(pCi/L)^{-1}$, based on default assumptions. Therefore the drinking water concentration corresponding to negligible risk would be given by:

$$C = \frac{\text{Risk}}{\text{Unit Risk}} = \frac{1 \times 10^{-6}}{2.3 \times 10^{-6}\ (pCi/L)^{-1}} = 0.43\ pCi/L.$$

This calculation and those above for noncarcinogenic health effects are based on point estimates rather than distributions (i.e., a deterministic approach). Probabilistic or stochastic methods can be used to predict a distribution of safe drinking water levels, thereby making use of the information available concerning the distributions of risk factors, and clarifying the uncertainty associated with the use of single point values. For example, an alternate probabilistic expression for health protective concentrations with distributions represented by bold face symbols is as follows:

$$C = \frac{\text{Risk} \times 0.02}{\text{RC} \times \text{L} \times \mathbf{F1} \times \mathbf{W}} = pCi/L.$$

where,

Risk	=	negligible lifetime individual risk of 10^{-6},
RC	=	risk coefficient of 4.4×10^{-11} $(pCi)^{-1}$ lifetime,
L	=	lifetime of 74 yr or 27,000 d/lifetime (rounded),
F1	=	intestinal absorption fraction lognormal distribution (Wrenn *et al.*, 1985), and
W	=	daily water intake in L/d lognormal distributions (Ershow and Cantor, 1989).

A variant of this relation employed separate distributions for body weight (BW) in kg and specific water intake (WI) in L/kg-d with an assumed correlation of 0.5 (data not shown). However, the simpler expression is preferred. The RC value was determined for F1 = 0.02 and the **F1** distribution adjusts this value based on the data of Wrenn *et al.* (1985) for variation in intestinal uptake of uranyl nitrate (p 4). Similarly the data of Ershow and Cantor (1989) was used to derive distributions of daily intake for total water and tap water. The distribution parameters used in the analyses are shown in Table 3. The distributions are empirical but similar to modeled distributions over the range of predicted distribution values, i.e., 10-90 percent (OEHHA, 1996).

Table 3. Parameters Used in Stochastic Calculations of Health Protective Concentrations of Uranium in Drinking Water

Variate	Distribution Type	Parameters Mean ± SD	Limits	Reference
BW	Lognormal	71.0 ± 15.9 kg	45.0,115.0 kg	Finley *et al.*, 1994
W (total)[1]	Lognormal	2.206 ± 0.886 L/d	1.0, 7.0 L/d	Ershow & Cantor, 1989
W (tap)[1]	Lognormal	1.263 ± 0.674 L/d	0.5, 3.5 L/d	Ershow & Cantor, 1989
F1	Lognormal	0.0186 ± 0.0216	0.003, 0.078	Wrenn *et al.*, 1985
Specific activity	Normal	0.79 ± 0.10 pCi/µg	0.45, 1.20 pCi/µg	Wong *et al.*, 1999

Note: (1) Western U.S. Regional data for all individuals. Tap water includes water used for drinking, making beverages, etc. Total water includes water used in food preparation, consumed in bottled drinks, etc.

Simulations were performed with Microsoft Excel v. 4.0 and Crystal Ball v. 4.0 (Decisioneering, Inc.) software employing 20,000 trials and Latin hypercube sampling. Selected percentiles of the predicted distributions of safe drinking water concentrations with negligible lifetime extra cancer risk from uranium's ionizing radiation are shown in Table 4, where the percentiles refer to the fraction of the population that would exceed a *de minimis* risk level under the two water exposure assumptions (tap water or total water exposures). As can be seen, the predicted safe values for all individuals range from 0.13 to 1.12 with a mean of 0.53 pCi/L based on total water intake (see also Figure 2). For consumers of tap water only, the values are about double those for total water, or about 0.2 to 2.25 with a mean of 1.0 pCi/L.

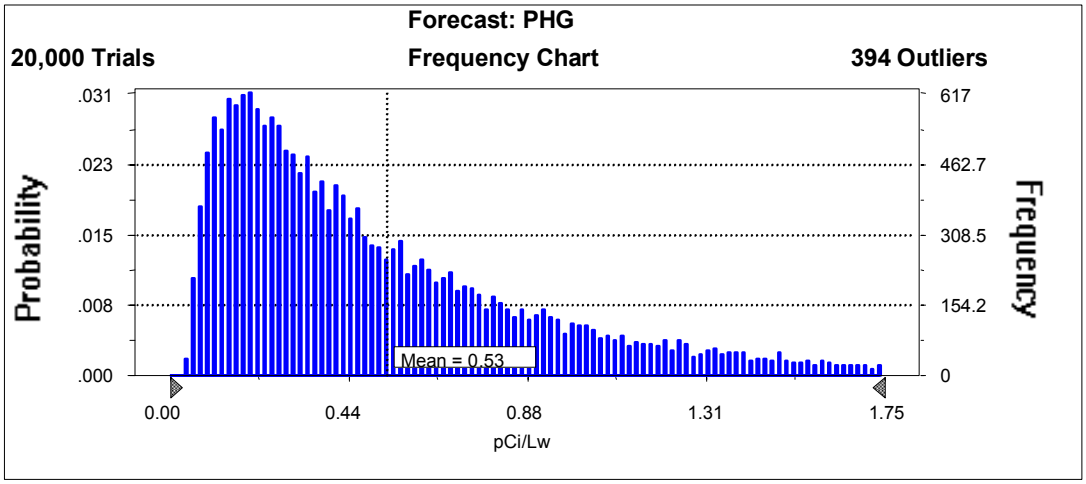
It is important to note that the accuracy of these predictions is based in part upon the assumption that the variation in absorption observed by Wrenn et al. (1985) in rats holds for humans despite obvious differences in the anatomy and physiology of the rodent and human gastrointestinal tracts. Also care should be taken in interpreting the values in Table 4 and Figure 2. In the latter, the predicted distribution for the concentration of uranium associated with negligible lifetime cancer risk for total daily water intake shows a long tail indicating a lognormal-like behavior. This graph has an inverse health protective character in that the more health protective values are in the direction of the 10th percentile rather than the 90th percentile. We have not conducted such analyses with other compounds and for this reason consider this evaluation most helpful for understanding the range of uncertainty around the deterministic value.

Table 4. Distributions of Health Protective Concentrations for Natural Uranium in California Drinking Water (pCi/L)*

Target Population, Water Exposure	10%	50%	Mean	90%
Western Regional Population, Total Water Exposure	0.13	0.40	0.53	1.12
Western Regional Population, Tap Water Exposure	0.22	0.74	1.04	2.26

*Note: Concentrations equivalent to 1×10^{-6} theoretical lifetime extra risk of cancer mortality

Figure 2. Distribution of Safe Drinking Water Concentrations of Natural Uranium based on distribution of total water intake from Ershow and Canter, 1989.



Based on considerations of theoretical radiation risk and exposure via drinking water, a health protective concentration for natural uranium in drinking water would be 0.43 pCi/L from the deterministic calculation, which is within the 10-90 percentile *de minimis* risk range for total water intake from the stochastic analysis. According to the deterministic analysis, a *de minimis* (10^{-6}) cancer risk level for the ionizing radiation effects of natural uranium in drinking water is approximately 0.43 pCi/L.

Based on the California specific activity of 0.79 pCi/µg (Wong et al., 1999), a public health protective level would be calculated as follows:

$$C = \frac{0.43 \text{ pCi/L}}{0.79 \text{ pCi/µg}} = 0.54 \text{ µg/L} = 0.5 \text{ ppb (rounded)}$$

A level of 0.5 ppb of total uranium in drinking water would be protective against cancer and is also low enough to protect against potential kidney toxicity. The PHG for natural uranium in California drinking water is therefore established as 0.5 ppb (0.43 pCi/L).

RISK CHARACTERIZATION

The PHG of 0.5 ppb (0.43 pCi/L) for natural uranium in drinking water is based on the latest U.S. EPA estimates of carcinogenic risk from uranium (U.S. EPA, 1999), recent data on specific activity of natural uranium in California water (Wong et al., 1999), and estimates of mean drinking water consumption (Ershow and Cantor, 1989). This recommended health protective level is supported by kidney toxicity data from a study of a human population (Health Canada, 1998) that examined measures of kidney function, urinary β2-microglobulin (BMG) and γ-glutamyl transferase (GGT), related to kidney tubule effects.

The 10^{-6} cancer risk level of 0.43 pCi/L has been calculated based on the carcinogenic effects of ionizing radiation. This level would correspond to a *de minimis* risk level for the carcinogenic effects of ionizing radiation from natural uranium in drinking water. A number of assumptions

were made in calculating this *de minimis* risk level. Each of these assumptions is a source of uncertainty. It was assumed that ionizing radiation (particularly alpha particles) emitted by natural uranium would be as carcinogenic as ionizing radiation emitted by more highly radioactive substances including man-made isotopes of uranium. This assumption and extrapolation is the source of some uncertainty. There are a number of studies indicating that the radiogenic dose response may be nonlinear or linear-quadratic or that tumors develop more slowly at low doses (e.g., Raabe *et al.*, 1980; Billen, 1990; Makinodan and James, 1990; Cohen, 1995, and Pollycove, 1998). U.S. EPA has characterized such effects in terms of a dose and dose rate effectiveness factor (DDREF): e.g., a DDREF of three means the risk per unit dose observed at high acute doses should be divided by three before being applied to low dose (dose rate) conditions (U.S. EPA, 1999). With the possible exception of lung cancer, current scientific data generally indicate DDREFs between one and three for human cancer induction. For uranium and radionuclides emitting high-LET alpha radiation, the radiobiological results generally support a linear nonthreshold dose response, except for a possible fall-off in effectiveness at high doses (U.S. EPA, 1999). At this point it appears that the linear paradigm of radiogenic risk dose response best satisfies the requirements of the PHG mandate with respect to waterborne natural uranium at low levels. Other extrapolation methods are possible. It is noteworthy that Mays *et al.* (1985) arrived at a similar estimate of the cancer potency of uranium, based on a different methodology.

The direct toxic effects of uranium on the kidney are well established from both human and animal studies. The recent Canadian studies help estimate a NOAEL for these effects in humans, especially the report from Health Canada (1998). A particular strength of this study is its correlations of urinary parameters with actual measurements of uranium excretion in urine. One of the sources of uncertainty in this calculation has to do with whether the observed urinary changes are truly an indicator of the beginning of an adverse effect, or whether this is just a transient effect not related to adverse kidney effects. We are regarding this effect as an indicator of an incipient change in kidney function that can lead ultimately to frankly adverse effects such as breakdown of tubular function, although the data are not clear enough to utilize these endpoints as the basis for the PHG. The BMG and GGT data are supported by the data for two other parameters (urine volume and specific gravity) related to tubule effects in the same study that also showed a positive correlation with uranium excretion. The kidney is a well-recognized target organ for uranium toxicity, and effects on tubule function were observed in an earlier human study (Zamora *et al.*, 1998) as well as the histological effects noted in several animal studies (Gilman *et al.*, 1998 a-c).

Our PHG for uranium differs somewhat in concept from the MCLG as developed by U.S. EPA. U.S. EPA uses the following procedure in promulgating MCLGs:

1. Group A and B carcinogens (i.e., strong evidence of carcinogenicity) MCLGs are set to zero,
2. Group C (i.e., limited evidence of carcinogenicity), either an RfD approach is used (as with a noncarcinogen) but an additional UF of one to ten (usually ten) is applied to account for the limited evidence of carcinogenicity, or a quantitative method (potency and low-dose extrapolation) is used and the MCLG is set in the 10^{-5} to 10^{-6} cancer risk range,
3. Group D (i.e., inadequate or no animal evidence) an RfD approach is used to promulgate the MCLG.

OEHHA has chosen to identify a *de minimis* risk level for Group A and B carcinogens in order to provide more guidance for risk management than with the arbitrary value of zero. This is particularly relevant for widespread natural contaminants like uranium for which decisions about tolerable levels in drinking water must be made.

An additional source of uncertainty in development of this PHG is intrahuman variability in susceptibility to kidney effects. Individuals with compromised kidney function will of course be more sensitive to the nephrotoxic effects of uranium. The humans studied by Zamora et al. are the native American inhabitants of a Canadian village. Considering the small number of individuals studied, their limited genetic diversity, and the lack of information on incidence of renal diseases in this subpopulation, the extent to which they may encompass the variability of the more diverse American population is unknown. In the calculation of a noncancer health-protective concentration, OEHHA has therefore used the standard default of ten to account for the total potential variability. With this added factor, the inferred health protective level for kidney toxicity would be half that for protection against effects due to radiation. However, we believe the establishment of this concentration is too uncertain to provide a basis for the PHG. Similarly, the animal data, as represented by the rat studies of Gilman et al. (1988a) would indicate a lower health protective level only with the inclusion of large uncertainty factors. While extrapolation of radiation risk to very low levels is also uncertain, OEHHA believes that a linear extrapolation is prudent in this case.

Gastrointestinal absorption of uranium for humans was assumed to be 2.0 percent. The range of values identified in the literature is 1 to 30 percent (U.S. EPA, 1991a, b). Actual gastrointestinal absorption may vary from individual to individual. In the stochastic analysis described above OEHHA used the range of values from Wrenn *et al.* (1985) assuming a lognormal distribution, specifically 1.86 ± 2.16 percent (range 0.3 to 7.8 percent).

Standard default assumptions used by both OEHHA and U.S. EPA include 70 kg body weight for adults and two liters per day drinking water consumption. Actual body weights and drinking water consumption vary over a wide range. In the stochastic analysis we incorporated a number of water consumption distributions from U.S. national and western regional data sets published by Ershow and Cantor (1989). The range of predicted safe concentrations (pCi/L) was approximately an order of magnitude from the 10^{th} to the 90^{th} percentiles. The PHG is close to the mean of the predicted distribution based on total water consumption. It should be noted that the stochastic analysis employed exposure variates only since OEHHA currently has no proposed methodology for addressing the uncertainty in dose response mentioned above. The use of "average" values for body weight and drinking water consumption can be justified under the assumption that with longer-term exposures, average daily doses tend to migrate toward the mean.

Ionizing radiation has been conclusively shown to be carcinogenic in humans, therefore U.S. EPA classifies all emitters of ionizing radiation as Class A carcinogens. U.S. EPA also considers agents emitting ionizing radiation to be mutagens and teratogens. OEHHA concurs with these conclusions. There can be little doubt that high levels of natural uranium in drinking water would present cancer and other risks to humans who consume such water over a long period of time. The estimated PHG of 0.5 ppb (0.43 pCi/L) is considered to provide a *de minimis* risk based on the ionizing radiation emitted by natural uranium. It should also protect the population, including sensitive groups, against all non-cancer effects of uranium.

OTHER STANDARDS AND REGULATORY LEVELS

U.S. EPA has promulgated a final rule for uranium that establishes an MCL of 30 ppb (or 30 pCi/L) (U.S. EPA, 2000). The MCLG of 0 ppb for uranium has been confirmed, based on their classification of it as a known human carcinogen (Carcinogen Group A) (U.S. EPA, 1991a). The calculation of the U.S. EPA MCL assumes a uranium specific activity of about 1 pCi/µg, based on a new survey (U.S. EPA, 2000). According to the U.S. EPA's evaluation, the MCL level

would " corresponds to a cancer risk greater than $1x10^{-5}$. Economic and technical feasibility were considered in arriving at this proposed MCL. U.S. EPA concludes that the feasible level is 20 µg/L to protect against kidney toxicity, but chose the higher level based on economic considerations, which they concluded would also be protective.

The State of California adopted an MCL of 20 pCi/L for natural uranium based on kidney toxicity to adults (Lam *et al.*, 1994; DHS, 1987). This State MCL was based on a risk assessment which identified Novikov and Yudina (1970) as the key study. However, the more recent studies (Gilman *et al.*, 1998a-c; Zamora *et al*., 1998; Health Canada, 1998) indicate that there is some potential for kidney effects at this level, in our opinion.

In the earlier review by the National Research Council (NRC, 1983), a suggested no-adverse-response-level (SNARL) in drinking water for chronic exposure of 35 ppb (23 pCi/L, based on the equilibrium specific activity of 0.67 pCi/µg), was based on non-carcinogenic effects (weight loss and kidney effects) in a one-year feeding study in dogs (Maynard and Hodge, 1949). The National Workshop on Radioactivity in Drinking Water recommended that the limiting concentration for natural uranium in drinking water should be 100 ppb (67 pCi/L) (Wrenn *et al.*, 1985).

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