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Uranium*

Guideline

The interim maximum acceptable concentration (IMAC) for uranium in drinking water is 0.02 mg/L (20 µg/L).

Identity, Use and Sources in the Environment

Uranium occurs naturally in the +2, +3, +4, +5 or +6 valence states, but most commonly in the hexavalent form. In nature, hexavalent uranium is commonly associated with oxygen as the uranyl ion, UO_2^{2+}. Naturally occurring uranium (^{nat}U) is a mixture of three radionuclides (^{234}U, ^{235}U and ^{238}U), all of which decay by both alpha and gamma emissions.[1,2] The alpha energies are all clustered around 4.5 MeV. Natural uranium consists almost entirely of the ^{238}U isotope, with the ^{235}U and ^{234}U isotopes constituting about 0.71% and 0.0057%, respectively[3]; 1 µg of natural uranium has an activity of 0.025 Bq.[1] Uranium is widespread in nature, occurring in granites and various other mineral deposits.[2,4]

The United States, Canada and South Africa produce approximately 80% of the uranium in the western world.[3] It is estimated that more than 13 million kilograms were produced in Canada in 1987.[5] Uranium is used mainly as fuel in nuclear energy plants.

Uranium is present in water supplies as a result of leaching from natural deposits, its release in mill tailings, emissions from the nuclear industry and the combustion of coal and other fuels.[1,6–8] Phosphate fertilizers, which may contain uranium at concentrations as high as 150 mg/kg, may also contribute to the uranium content of groundwater.[9]

Analytical Methods and Treatment Technology

Uranium in water is most commonly measured by solid fluorimetry with either laser excitation or ultraviolet light following fusion of the sample with a pellet of carbonate and sodium fluoride (detection limit 0.1 µg/L).[10] Sample preparation for this method is tedious, however, and there is interference from other metals. Uranium can also be determined by inductively coupled plasma mass spectrometry, which has the same detection limit (0.1 µg/L) and a between-run precision of less than 6%.[11] Alpha spectrometry has been used for the determination of uranium in bottled waters[12] and environmental media,[13] although the recovery is often highly variable owing to the low specific activity of natural uranium.[13] Kinetic phosphorescence analysis shows promise as a sensitive and selective method for the analysis of uranium and other lanthanides in drinking water and other media.[14]

The effectiveness of water treatment processes for uranium removal has not been well documented in full-scale treatment plants. Laboratory studies and pilot plant tests have shown that conventional anion exchange resins are capable of removing uranium from drinking water supplies to concentrations as low as 0.1 µg/L (99.9% removal). Gamma radiation buildup in the uranium removal system does not appear to be a health concern.[15] However, because uranium is highly preferred by anion resins, regeneration may be difficult.[16] A number of other treatment methods, including conventional coagulation, lime softening, activated alumina and reverse osmosis, have also been found to reduce uranium concentrations to 1–5 µg/L (>90% removal) in laboratory and pilot plant studies.[17–20] Uranium complexes that occur in natural water have been removed experimentally by nanofiltration at efficiencies in the range of 90–98%, depending on the type of nanofiltration membrane employed.[21] Although cation exchange and granular activated carbon can remove uranium effectively at controlled pHs and for limited duration, they are not considered practical methods for drinking water

* This review addresses only the chemical aspects of uranium toxicity. Information pertinent to the derivation of a guideline based on radiological effects is discussed separately in a Criteria Summary on radiological characteristics.

treatment.[16] Feed water matrix effects (e.g., presence of ions other than uranium) influence the uranium removal efficiency, especially with ion exchange and, to a limited extent, reverse osmosis technologies.[22]

In areas with high natural uranium levels, it may be difficult to achieve low final uranium concentrations (i.e., <5 µg/L) with the treatment technology available.[23] Using ion exchange, for example, uranium removal efficiency is reduced when the uranium concentration in the feed water is high (e.g., >100–500 µg/L), and the uranium level in the treated water will be around 10 µg/L.[22]

Exposure

Uranium concentrations of up to 700 µg/L have been found in private groundwater supplies in Canada.[24,25] In a 1980–81 survey of 13 selected sites in south-central British Columbia, the mean uranium concentration (n = 519) in surface water and groundwater (some treated) supplies was 4.06 µg/L.[26] The mean and median levels of naturally derived uranium in groundwaters of 287 wells sampled in southeastern Manitoba (1982–84) were 58.3 µg/L and 10 µg/L, respectively; the maximum value was 2020 µg/L.[27] Uranium levels were highest in Precambrian rock aquifers (average 115.6 µg/L) and lowest in Paleozoic sedimentary rock aquifers (average 3.5 µg/L). In a radionuclide survey (n = 154) carried out by the Radiation Protection Bureau, Health Canada, in Manitoba in 1984 and 1987, levels of uranium ranged from less than the detection limit (5 µg/L) to 96 µg/L, and the mean concentration for samples with levels greater than the detection limit (45% of samples) was 16.1 µg/L.[28] In another survey conducted by Health Canada between 1975 and 1986, uranium was not found at concentrations above the detection limit (5 µg/L) in raw and treated water samples from Alberta, British Columbia, New Brunswick, Newfoundland, Nova Scotia, Quebec and the Yukon. Uranium levels above 5 µg/L were detected in water samples from Saskatchewan (80/243 samples; range 5–51 µg/L), Manitoba (7/88 samples; range 6.1–26 µg/L), Ontario (7/629 samples; range 5.2–39 µg/L) and the Northwest Territories (9/12 samples; range 19–2500 µg/L).[29] In a 1990–95 survey of 130 sites (approximately 3700 samples) in Ontario, the mean of the average uranium concentrations (range <0.05–4.21 µg/L; detection limit 0.05 µg/L) in treated drinking water was 0.40 µg/L.[30] In Quebec, uranium was detected (detection limit <5 µg/L) in only 1.7% of samples (n = 2809) taken between 1993 and 1996 (range <5–20 µg/L)[31]; the survey encompassed more than 5.9 million individuals. In a 1994–95 survey of 322 wells in the Kitigan Zibi First Nation community in Quebec, uranium was detected (n = 525) at levels ranging from 0.01 to 1481 µg/L, with mean and median levels of 5.1 µg/L and 5.2 µg/L, respectively; levels in surface water (n = 11) were less than 1.1 µg/L.[32] Multiple sampling in some of the wells revealed wide fluctuations in uranium levels within individual wells. For example, the concentration in one well was approximately 400 µg/L on July 14, 1994, >1400 µg/L on September 1, 1994, and just over 200 µg/L on February 6, 1995. No correlations were found between the uranium concentrations and pH, redox, total dissolved solids, hardness, anions, well depth or temperature.[32] In New Brunswick, the mean uranium concentration from 1382 samples taken between 1994 and 1997 was 1.83 µg/L.[33] In a 1981 survey of 72 municipally treated systems in Nova Scotia, 98.6% of the samples tested were found to have uranium levels below 10 µg/L.[34]

A mean uranium concentration of 2.55 µg/L was reported in drinking water from 978 sites in the United States in the 1980s.[35,36] The mean concentration of uranium in drinking water in New York City ranged from 0.03 to 0.08 µg/L.[37] In five Japanese cities, the mean uranium level in potable water supplies was 0.9 ng/L.[38] Uranium may leach into water from uranium-bearing glass items (maximum of 30 µg/L) or from ceramic-glazed items in which uranium is used as a colouring agent (approximately 300 mg/L).[39]

On the basis of the results of the survey from Ontario,[30] the daily intake of uranium from drinking water for an adult consuming 1.5 L/d is estimated to be 0.6 µg.

Uranium has been detected in a variety of foodstuffs, with the highest concentrations being found in shellfish. The concentrations of uranium in muscle (dry weight) from fish caught in a Canadian lake receiving uranium mill effluents were 7–11 times higher than those from fish caught in uncontaminated lakes.[40] Other dietary components that contribute to the daily intake of uranium are fresh vegetables and cereals. The predominant uranium isotope in food is ^{238}U.[41] Levels of ^{234}U and ^{238}U ranging from <1 to 220 mBq/L and from <2 to 740 mBq/L (0.2–60 µg/L), respectively, were reported in bottled waters in the Federal Republic of Germany.[12] In a study by Cheng *et al*.,[42] the mean uranium concentration in nine different beverages was 0.98 µg/L (range 0.26–1.65 µg/L), and the mean concentration of uranium in mineral water was 9.2 µg/L.

The average daily per capita intake of uranium in food has been reported to be 1.3 µg[41] and 2–3 µg[43] in the United States and 1.5 µg in Japan.[38] In a review of naturally occurring sources of radioactive contamination in food, dietary intakes of ^{238}U were found to range from 1.0 to 3.6 µg/d (12–45 mBq/d) in several European countries, from 0.9 to 4.8 µg/d (11–60 mBq/d) in Japan (the higher values were found in uranium mining areas) and from 1.2 to 1.4 µg/d (15–17 mBq/d) in the United States. The average daily dietary intake was of the order of 20 mBq, or about 1.6 µg. It was often difficult to

determine whether these dietary intakes included that from drinking water, and it was emphasized that the latter has sometimes been found to be equal to that from the diet.[44]

Mean levels of uranium in ambient air have been reported to be 0.02 ng/m^3 in Tokyo (based on a 1979–81 survey)[45] and 0.076 ng/m^3 in New York (based on two samples, each a composite of two weekly air filter collections, from 1985 and 1986).[41] Tracy and Prantl[46] found the average concentration of uranium in air in a southern Ontario rural environment to be 0.1 ng/m^3, based on measurements of ^{226}Ra in dust and an assumption of equilibrium between ^{238}U and ^{226}Ra. Assuming a daily respiratory volume of 20 m^3 and a mean urban airborne level of 0.05 ng/m^3, the daily intake of uranium from air would be about 1.0 ng. Tobacco smoke (from two packages of cigarettes per day) contributes less than 0.05 µg of inhaled uranium per day.[47]

The daily intake of uranium from each source for adults is thus estimated to be: air, 0.001 µg; food, 2.0 µg; water, 0.6 µg. Thus, the total daily intake is approximately 2.6 µg, or 0.037 µg/kg bw for a 70-kg adult; the majority (77%) originates from food, whereas drinking water contributes most of the remainder. This is in general agreement with a review of available data for the U.S. Environmental Protection Agency, which suggested that the mean contribution of uranium from drinking water to total intake is 31.1%.[35,36] The potential for uranium exposure will be greater for individuals who consume foods grown in areas with elevated concentrations of uranium in the soil and for individuals who consume drinking water containing elevated concentrations of uranium.[48] In a Canadian study, Limson Zamora *et al*.[49] found that water contributed between 31 and 98% of total daily uranium intake from food and water for individuals whose drinking water contained uranium at concentrations ranging from 2 to 780 µg/L; in contrast, intake from water was only 1–9% of total uranium intake for individuals whose municipal drinking water supply contained uranium at a concentration of 0.02 ± 0.004 µg/L.

Health Effects

Absorption, Distribution and Excretion

Although ubiquitous in the environment, uranium has no known metabolic function in animals and is currently regarded as non-essential.[3]

Absorption of uranium from the gastrointestinal tract depends upon the solubility of the uranium compound,[3] previous food consumption,[50,51] dose[51] and the concomitant administration of oxidizing agents, such as the iron(III) ion and quinhydrone.[50] The average gastrointestinal absorption of uranium in an adult human is 1–2%,[52–54] but uptake may be less than 0.1% or as high as 5–6% under some conditions.[55] Tracy and Limson Zamora,[56] in a study of 60 volunteers, reported a geometric mean gastrointestinal uptake of 1%, with a variation from 0.1 to 4%. Only 0.06% of ingested uranium was absorbed in Sprague-Dawley rats and New Zealand white rabbits fed *ad libitum* and provided free access to drinking water containing uranyl nitrate hexahydrate at concentrations up to 600 mg/L for periods up to 91 days.[57]

Following ingestion, uranium rapidly appears in the bloodstream,[51] where it is associated primarily with the red cells[58]; in the plasma, a non-diffusible uranyl–albumin complex is formed in equilibrium with a diffusible ionic uranyl hydrogen carbonate complex ($UO_2HCO_3^+$).[25] Because of their high affinity for phosphate, carboxyl and hydroxyl groups, uranyl compounds readily combine with proteins and nucleotides to form stable complexes.[25] Clearance from the bloodstream is also rapid, and the uranium subsequently accumulates in the kidneys and the skeleton; little is found in the liver.[51] In the skeleton, which is the major site of uranium accumulation,[52] the uranyl ion replaces calcium in the hydroxyapatite complex of bone crystals.[25]

Based on the results of studies in experimental animals, it appears that the amount of soluble uranium accumulated internally is proportional to the intake from ingestion or inhalation.[52] It has been estimated that the total body burden of uranium in humans is 40 µg.[52,59]

Once equilibrium is attained in the skeleton, uranium is excreted in the urine and faeces. Urinary excretion in humans has been found to account for approximately 1% of total excretion, averaging 4.4 µg/d,[43] the rate depending in part on the pH of tubular urine.[3] Under alkaline conditions, most of the uranyl hydrogen carbonate complex is stable and is excreted in the urine. If the pH is low, the complex dissociates to a variable degree, and the uranyl ion may then bind to cellular proteins in the tubular wall. This results in reduced uranyl ion excretion, and the protein binding can impair tubular function.

The half-life of uranium in the rat kidney has been estimated to be approximately 15 days. Clearance from the skeleton is considerably slower; half-lives of 300 and 5000 days have been estimated, based on a two-compartment model.[52] Overall half-lives for the clearance of uranium from the rat kidney and skeleton of 5–11 and 93–165 days, respectively, were determined in another study, based on a 10-compartment model.[60] The overall elimination half-life of uranium under conditions of normal daily intake has been estimated to be between 180 and 360 days.[3] For rabbits, Tracy *et al*.[57] found uranium half-lives of 14 days in kidney and greater than 200 days in bone. Fourteen percent of absorbed uranium was deposited in bone, and 3% in kidney.

Effects in Humans

Nephritis is the primary chemically induced effect of uranium in animals and humans.[61]

Little information is available on the chronic health effects of exposure to environmental uranium in humans. In Nova Scotia, clinical studies were performed upon 324 persons exposed to variable amounts of naturally occurring uranium in their drinking water (uranium concentrations up to 0.7 mg/L), which was supplied from private wells. No relationship was found between overt renal disease or any other symptomatic complaint and exposure to uranium. However, a trend towards increasing excretion of urinary β_2-microglobulin with increasing concentration of uranium in well water was observed; this raises the possibility that an early tubular defect was present and suggests that this parameter might be useful as an index of subclinical toxicity. The group with the highest uranium concentration in well water failed to follow this trend, but this was attributed to the fact that most of the individuals in this group had significantly reduced their consumption of well water by the time the measurements were made, leading to the conclusion that the suspected tubular defect might well be rapidly reversible.[24,25]

In a study to determine renal effects induced by the chronic ingestion of uranium in drinking water, Limson Zamora *et al*.[49] divided residents from two communities (Nova Scotia and Ontario) into two groups: the high-exposure group (n = 30) consumed drinking water that came from private wells and contained uranium concentrations of 2–781 µg/L, whereas the low-exposure group (n = 20) drank water that was supplied through the municipal distribution system and contained uranium at levels of ≤1 µg/L. Total uranium intake from both water and food over a 3-day period was used as the indicator for establishing a correlation between uranium exposure and different biomarkers. Two types of biomarkers were used: indicators of kidney function (i.e., creatinine, glucose, total protein and β_2-microglobulin) and markers for cell toxicity (e.g., alkaline phosphatase, γ-glutamyl transferase and lactate dehydrogenase). Glucose excretion increased with increasing daily uranium intake, but creatinine and protein excretion did not; as well, alkaline phosphatase and β_2-microglobulin were positively correlated with uranium intake for pooled male and female data. Taken together, these results suggest that, at the levels of uranium intake observed in this study, the segment of the nephron most at risk to injury is the proximal tubule, rather than the glomerulus.

In a pilot study conducted in 1993 in three communities in Saskatchewan, there was a statistically significant association ($p = 0.03$) between increasing but normal levels of urine albumin (measured as mg/mmol creatinine) and the uranium cumulative index. According to the authors, microalbuminuria has been shown to be a sensitive indicator of early renal disease. The cumulative index was calculated for each study participant as the product of the uranium concentration in drinking water, the number of cups of water consumed per day and the number of years lived at the current residence.[62] The study was conducted with 100 participants in three different areas with mean uranium levels ranging from 0.71 (control) to 19.6 µg/L. Urine albumin levels ranged from 0.165 to 16.1 mg/mmol creatinine, with eight participants having "elevated" urine albumin concentrations (>3.0 mg/mmol creatinine). Three participants had serum creatinine concentrations of >120 µmol/L (range 50–170 µmol/L), which is indicative of prevalent renal damage. There is no reason to believe that these elevated creatinine values are due to uranium ingestion. It should be noted, however, that diabetics were not excluded from the study, although diabetic status and age, known risk factors for renal dysfunction, were factored into the statistical analysis of the results. A follow-up study is currently in progress.

Toxicological Studies

Reported oral LD_{50}s of uranyl acetate for rats and mice are 204 mg/kg bw and 242 mg/kg bw, respectively.[63] Among the most common signs of acute toxicity are piloerection, significant weight loss and haemorrhages in the eyes, legs and nose.

The most common renal injury caused by uranium in experimental animals is damage to the proximal convoluted tubules, predominantly in the distal two-thirds[3,64,65]; the rate at which the effects occur varies with dosage level.[66] It has recently been shown that uranyl inhibits both Na^+ transport-dependent and Na^+ transport-independent ATP utilization as well as mitochondrial oxidative phosphorylation in the renal proximal tubule.[65,66] At doses not high enough to destroy a critical mass of kidney cells, the effect appears to be reversible, as some of the cells are replaced; however, the new epithelial lining differs morphologically, and possibly functionally, from normal epithelium.[3,52] Histopathologically, the regenerated cells are simple flattened cells with no microvilli on luminal surfaces and with reduced numbers of mitochondria.[66]

There is some evidence that tolerance may develop following repeated exposure to uranium.[67–69] This tolerance does not, however, prevent chronic damage to the kidney, as the regenerated cells are quite different; although histopathologically it may appear that the repair process is well advanced, the urinary biochemical changes return to normal only slowly.[66] Alterations causing thickening of the glomerular basement membrane of the kidney, which results from the storage of uranium in the kidney, can be prolonged and severe enough to cause permanent damage.[70] Persistent ultrastructural changes in the proximal tubules of rabbits have also been reported to be associated with the kidney's ability to store uranium.[71] Cell damage in the

proximal tubules was significantly more severe in animals allowed up to a 91-day recovery period than in animals killed at the end of the exposure period. Acquired tolerance should therefore not be considered as a practical method of protection against uranium intoxication.

Forty male Sprague-Dawley rats given uranyl ethanoate dihydrate at 0, 2, 4, 8 or 16 mg/kg bw per day (equivalent to uranium doses of 0, 1.1, 2.2, 4.5 or 9.0 mg/kg bw per day) in drinking water for 4 weeks exhibited a variety of biochemical effects, including increases in blood glucose levels at ≥4 mg uranyl ethanoate dihydrate/kg bw per day, decreases in aspartate aminotransferase and alanine aminotransferase levels at ≥8 mg uranyl ethanoate dihydrate/kg bw per day, increases in several other haematological parameters at 16 mg uranyl ethanoate dihydrate/kg bw per day and increases in total protein levels in all treated groups.[72] The authors considered the no-observed-adverse-effect level (NOAEL) to be 2 mg uranyl ethanoate dihydrate/kg bw per day (1.1 mg U/kg bw per day).

Groups of 15 male and 15 female weanling Sprague-Dawley rats consumed water containing uranyl nitrate hexahydrate at <0.001 (control), 0.96, 4.8, 24, 120 or 600 mg/L (equivalent to uranium doses of <0.0001, 0.06, 0.31, 1.52, 7.54 and 36.73 mg/kg bw per day in males and <0.0001, 0.09, 0.42, 2.01, 9.98 and 53.56 mg/kg bw per day in females) for 91 days.[73] Histopathological changes were observed mainly in the liver, thyroid and kidney. In the liver, treatment-related lesions were seen in both sexes at all doses and were generally non-specific nuclear and cytoplasmic changes. The thyroid lesions were not considered specific to the uranium treatment. The kidney was the most affected tissue. In males, statistically significant treatment-related kidney lesions (reported at all doses) included nuclear vesiculation, cytoplasmic vacuolation and tubular dilation. Other statistically significant lesions in males (≥4.8 mg uranyl nitrate hexahydrate/L) included glomerular adhesions, apical displacement of the proximal tubular epithelial nuclei and cytoplasmic degranulation. In females, statistically significant changes in the kidney included nuclear vesiculation of the tubular epithelial nuclei (all doses) and anisokaryosis (all doses except 4.8 mg uranyl nitrate hexahydrate/L). However, the most important changes in the female were the capsular sclerosis of glomeruli and reticulin sclerosis of the interstitial membranes; these changes occurred in all dose groups and are considered to be "nonreparable lesions." The lowest-observed-adverse-effect level (LOAEL) for adverse effects on the kidney of male and female rats, based on the frequency of degree of degenerative lesions in the renal proximal convoluted tubule, was considered to be 0.96 mg uranyl nitrate hexahydrate/L (equivalent to 0.09 mg U/kg bw per day in females and 0.06 mg U/kg bw per day in males). The reason for the difference in sensitivity between males and females is not clear, but it did not appear to be due to differences in pharmacokinetics, as accumulation of uranium in renal tissue did not differ significantly between the two sexes at all doses and females received a larger time-weighted average dose than males.

In a similar study, groups of 10 male New Zealand white rabbits were given uranyl nitrate hexahydrate in drinking water at concentrations of <0.001 (controls), 0.96, 4.8, 24, 120 or 600 mg/L (determined to be equivalent to doses of 0, 0.05, 0.2, 0.88, 4.82 and 28.7 mg U/kg bw per day) for 91 days.[74] These rabbits were not *Pasteurella*-free, and four of them contracted a *Pasteurella* infection during the course of the study. In the same study, 10 *Pasteurella*-free female rabbits were exposed to drinking water containing <0.001 (controls), 4.8, 24 or 600 mg uranyl nitrate hexahydrate/L (equivalent to doses of 0, 0.49, 1.32 and 43.02 mg U/kg bw per day) for 91 days. In both sexes, histopathological changes were observed in the kidney tubule, liver, thyroid and aorta. In male rabbits, histopathological findings were observed in the kidney tubules at doses above 0.96 mg uranyl nitrate hexahydrate/L. When compared with controls, significant treatment-related changes included cytoplasmic vacuolation, anisokaryosis, nuclear pyknosis and nuclear vesiculation; the incidence of nuclear vesiculation and anisokaryosis appeared to be dose-related, with nuclear vesiculation having the higher frequency and severity. Other treatment-related changes included tubular dilation, hyperchromicity, tubular atrophy, changes in the interstitium collagen and reticulin sclerosis. In total, 10 different morphological indicators of tubular injury were observed in the highest exposure group. The LOAEL, based on the nuclear changes in the kidney, was considered to be 0.96 mg uranyl nitrate hexahydrate/L (equivalent to 0.05 mg U/kg bw per day). In *Pasteurella*-free female rabbits, dose-related and treatment-related nuclear changes in the kidney tubule included anisokaryosis and vesiculation, which were significantly different from effects observed in controls at all doses. Other treatment-related changes in the kidney included cytoplasmic vacuolation, tubular atrophy and nuclear pyknosis. In general, histopathological changes in the kidney in females were generally less marked than in males. The LOAEL was considered to be 4.8 mg uranyl nitrate hexahydrate/L (equivalent to 0.49 mg U/kg bw per day). In both sexes, histopathological changes in the liver, thyroid and aorta were similar. In the liver, changes may have been treatment-related, although very mildly affected animals were seen in all groups, and changes in the thyroid were mild. Changes in the aorta were not dose-dependent. It should be noted that no similar aortic changes were observed in the 91-day uranyl nitrate hexahydrate studies in rats.[73] It is interesting to note, however, that even though the female rabbits consumed on average 65% more water than

the males and their average uranium intake was approximately 50% greater on a mg/kg bw per day basis, their average tissue levels were not similarly raised. The average kidney uranium level in females was 20% of that in males, whereas the average bone uranium level in females was 76% of that in males. The differences between the males and females, both qualitative and quantitative, suggest pharmacokinetic parameter differences, which contrasts with the findings in the rat study by the same authors.[73]

In an additional study to observe the reversibility of renal injury in *Pasteurella*-free male New Zealand white rabbits, groups of 5–8 animals were given <0.001 (control), 24 or 600 mg uranyl nitrate hexahydrate/L (equivalent to 0, 1.36 and 40.98 mg U/kg bw per day) in drinking water for 91 days, with a recovery period of up to 91 days.[75] Minor histopathological lesions were seen in the liver, thyroid and aorta. In the kidney, tubular injury with degenerative nuclear changes, cytoplasmic vacuolation and tubular dilation was observed in the high-dose group, which did not exhibit consistent resolution even after a 91-day recovery period. Although the severity of the histopathological changes at 600 mg uranyl nitrate hexahydrate/L did not increase between the 45-day and 91-day recovery groups, the continued prevalence of histopathological changes during this time suggests a self-sustaining injury. Also, the presence of sclerotic changes in the tubular basement membranes and renal interstitium persisted during the recovery period and most likely represents a permanent injury.[70,71,75] In general, the male rabbits did not respond as dramatically as those in the earlier study,[74] although the histopathological changes observed in this study were similar to those noted in the female rabbits of the previous study. Animals in this study consumed approximately 33% more uranium per day than the males in the previous study,[74] yet uranium residues in kidney tissue were 30% less, which would appear to indicate that *Pasteurella*-free rabbits are less sensitive than the non-*Pasteurella*-free strain to the effects of the uranyl ion in drinking water. Based on the histopathological data in the kidney, a LOAEL for the male New Zealand rabbits in this study is estimated to lie at or below 24 mg uranyl nitrate hexahydrate/L.

In an early series of experiments, very high doses (up to 20% in the diet) of a variety of uranium compounds were fed to rats, dogs and rabbits for periods ranging from 30 days to 2 years.[76] On the basis of very limited histopathological investigations, renal damage was reported in each species.

Adverse reproductive effects, in terms of total number of litters and average number of young per litter, were reported in rats given 2% uranyl nitrate hexahydrate for 7 months.[76] More recent studies have examined the teratogenic/embryotoxic effects and reproductive outcomes of uranyl acetate dihydrate administration to mice. Domingo *et al*.[77] evaluated the developmental toxicity of uranium by treating groups of 20 pregnant Swiss mice by gavage to doses of 0, 5, 10, 25 or 50 mg uranyl acetate dihydrate/kg bw per day (equivalent to 0, 2.8, 5.6, 14 and 28 mg U/kg bw per day) on days 6–15 of gestation; the animals were sacrificed on day 18. Although all dams survived, there was a dose-related reduction in maternal weight gain, a significant decrease in daily feed intake and a significant increase in liver weights. Exposure-related foetotoxicity, including reduced foetal body weights and length, increased incidence of stunted foetuses per litter, increased incidence of both external and internal malformations and increased incidence of developmental variations, was observed in the foetuses of mice at all doses. At doses of ≥14 mg U/kg bw per day, specific malformations included cleft palate and bipartite sternebrae, and developmental variations included reduced ossification and unossified skeletal variations. There was no evidence of embryolethality at any dose. Based on both the maternal and foetotoxic effects, a LOAEL of 2.8 mg U/kg bw per day could be considered.

A second study by Domingo *et al*.[78] evaluated the effect of uranium on late foetal development, parturition, lactation and postnatal viability. Groups of 20 female mice were treated by gavage from day 13 of pregnancy until day 21 of lactation to doses of 0, 0.05, 0.5, 5 or 50 mg uranyl acetate dihydrate/kg bw per day (equivalent to 0, 0.028, 0.28, 2.8 and 28 mg U/kg bw per day). Maternal deaths (2/20 and 3/20 at the two highest doses, respectively) were attributed to the treatment; however, maternal toxicity was not evident from changes in body weight or food consumption, although relative liver weight was significantly reduced in all treatment groups. Decreases in pup viability, as indicated by significant decreases in litter size on day 21 of lactation, and significant decreases in the viability and lactation indexes were observed in the highest dose group. Based on developmental effects in pups, the authors established a no-observed-effect level (NOEL) of 2.8 mg U/kg bw per day.

Paternain *et al*.[79] studied the effects of uranium on reproduction, gestation and postnatal survival in mice. Groups of 25 mature male Swiss mice were administered intragastric doses of 0, 5, 10 or 25 mg uranyl acetate dihydrate/kg bw per day (equivalent to 0, 2.8, 5.6 and 14 mg U/kg bw per day) for 60 days prior to mating with mature females (25 per group). Females were exposed for 14 days prior to mating (males and females were mated according to their respective dose levels), and exposure continued through mating, gestation, parturition and nursing of litters; half the treated dams were sacrificed on day 13 of gestation. No treatment-related effects on mating or fertility were observed. Embryolethality (number of late resorptions and dead foetuses) was significantly increased and the number of live

foetuses was decreased in the highest dose group. Lethality in pups (at birth and at day 4 of lactation) was significantly increased at ≥5.6 mg U/kg bw per day, and pup growth (decreases in weight and length) and development of offspring, from birth and during the entire lactation period, were significantly affected in the high-dose group. The NOEL was 5 mg uranyl acetate dihydrate/kg bw per day, equivalent to 2.8 mg U/kg bw per day.

Unspecified degenerative changes in the testes of rats have also been reported following chronic administration of uranyl nitrate hexahydrate and uranyl fluoride in the diet.[76,80,81] In a more recent study, male Swiss mice were exposed for 64 days to uranyl acetate dihydrate in drinking water at doses of 0, 10, 20, 40 or 80 mg/kg bw per day (equivalent to 0, 5.6, 11.2, 22.4 and 44.8 mg U/kg bw per day) prior to mating with untreated females for 4 days.[82] With the exception of interstitial alterations and vacuolization of Leydig cells at the highest dose, no effects were observed in testicular function/spermatogenesis. There was, however, a significant, non-dose-related decrease in the pregnancy rate of these animals.

Although bone cancer has been induced in experimental animals by injection or inhalation of soluble compounds of high-specific-activity uranium isotopes or mixtures of uranium isotopes, no carcinogenic effects have been reported in animals ingesting soluble or insoluble uranium compounds.[52]

Mutagenicity

Uranyl nitrate was cytotoxic and genotoxic in Chinese hamster ovary cells at concentrations ranging from 0.01 to 0.3 mmol/L. There was a dose-related decrease in the viability of the cells, a decrease in cell cycle kinetics and increased frequencies of micronuclei, sister chromatid exchanges and chromosomal aberrations.[83] The authors suggest that the data provide a possible mechanism for the teratogenic effects observed in the studies by Domingo *et al*.[77] The genotoxic effects in this study were thought to occur through the binding of the uranyl nitrate to the phosphate groups of DNA. Chromosomal aberrations have also been induced in male mouse germ cells exposed to enriched uranyl fluoride; however, these aberrations may have been produced by the radioactivity of the test compound.[84]

Other Special Studies

A number of studies have reported that the toxic effects of uranium can be prevented, or possibly alleviated, by the administration of chelating agents.[65] Three chelating agents have been found to be effective at enhancing faecal excretion of uranium and reducing levels of uranium in bone and kidney in mice — sodium 4,5-dihydroxybenzene-1,3-disulfonate (Tiron), desferrioxamine (DFOA) and 1,2-dimethyl-3-hydroxypyrid-4-one (L1); Tiron was the most effective agent of the compounds studied. However, administration of these agents 24 hours or more after uranium exposure was not effective.

Classification and Assessment

Although the potential exists for radiological toxicity of orally administered ^{nat}U, this has not been observed in humans or animals, presumably because of the relatively low specific activity of this mixture of uranium radionuclides. Experimental evidence of the carcinogenicity of uranium is restricted to highly insoluble or enriched uranium compounds delivered by inhalation or injection. Although these observations do not seem relevant to the ingestion of ^{nat}U in drinking water,[52] the associated risk for induction of bone cancer has been inferred from the known risk due to ^{226}Ra exposure. The estimated excess risk of induction of bone sarcoma is considered to be insignificant compared with the normal background lifetime risk.[52] The chemical toxicity of ^{nat}U has been observed in both humans and animals. Because the chemical data reviewed to date suggest a more stringent recommendation than those based upon available radiological criteria, it is recommended that the assessment of uranium toxicity in drinking water be based upon chemical criteria. Uranium has, therefore, been included in Group V (inadequate data for evaluation of carcinogenicity).

For compounds classified in Group V, the maximum acceptable concentration (MAC) is derived on the basis of the division of the NOAEL or LOAEL for the critical response (i.e., nephrotoxicity for uranium) in humans or an animal species by an appropriate uncertainty factor. As no adequate chronic study was identified, the tolerable daily intake (TDI) has been derived based on the results of the most extensive subchronic studies, in the most sensitive sex and species, conducted to date in which uranium was administered in drinking water.[73] In the 91-day study in rats, the LOAEL for degenerative lesions in the proximal convoluted tubule of the kidney in males was considered to be 0.96 mg uranyl nitrate hexahydrate/L, which is equivalent to 0.06 mg U/kg bw per day (or 60 µg/kg bw per day). The TDI is derived as follows:

$$\text{TDI} = \frac{60\ \mu\text{g/kg bw per day}}{100} = 0.6\ \mu\text{g/kg bw per day}$$

where:

- 60 µg/kg bw per day is the LOAEL for adverse effects on the kidney in male rats (the most sensitive sex and species) in a subchronic study[73] (male rabbits were also more sensitive to the renal effects of uranium than females), and

- 100 is the uncertainty factor (×10 for intraspecies variation and ×10 for interspecies variation).*

Rationale

Based on the above TDI, a health-based guideline value (GV) may be determined as follows:

$$GV = \frac{0.6\ \mu g/kg\ bw\ per\ day \times 70\ kg\ bw \times 0.35}{1.5\ L/d} \approx 10\ \mu g/L$$

where:

- 0.6 µg/kg bw per day is the TDI, as derived above,
- 70 kg bw is the average weight of an adult,
- 0.35 is the proportion of daily intake of uranium allocated to drinking water; this allocation factor was determined, from data in the "Exposure" section, to best describe intake for the general population, which is generally exposed to drinking water containing uranium at concentrations below 10 µg/L,
- 1.5 L/d is the average daily consumption of drinking water by an adult.

After due consideration of both the treatment costs associated with achieving uranium concentrations in drinking water at or below the health-based guideline value and the health risks associated with concentrations of uranium in drinking water above the guideline value, the Committee on Drinking Water has concluded that an interim maximum acceptable concentration (IMAC) of 20 µg/L should be adopted. This value is considered to be an interim guideline value because it is the result of a risk management decision and exceeds the health-based guideline value.

This IMAC is supported by a probabilistic analysis using Monte Carlo simulation in which a distribution of body weights and consumption rates for five different age categories was used to generate a distribution of guideline values. In this analysis, it was assumed that food is the only other significant source of exposure to uranium aside from drinking water. Food intake data from a duplicate diet study in a Nova Scotia community that had high levels of uranium in the drinking water were used. A guideline value of 20 µg/L was shown to be suitably protective of the bulk of the population, especially if one considers that the TDI is already conservative, since it is based on a sensitive outcome in a sensitive species, with large uncertainty factors applied.

The IMAC will be reviewed periodically in light of developments in treatment technology and additional data on health risks associated with exposure to uranium in drinking water.

* There is no need to apply an additional uncertainty factor to account for the use of a LOAEL instead of a NOAEL because of the minimal degree of severity of the lesions being reported. Also, an additional uncertainty factor for the length of the study (91 days) is not required because the estimated half-life of uranium in the kidney is 15 days.

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