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Uranium in Drinking-water

Background document for development of
WHO *Guidelines for Drinking-water Quality*

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Uranium in Drinking-water
Background document for development of WHO *Guidelines for Drinking-water Quality*

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Preface

One of the primary goals of the World Health Organization (WHO) and its Member States is that "all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water." A major WHO function to achieve such goals is the responsibility "to propose ... regulations, and to make recommendations with respect to international health matters ...."

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International Standards for Drinking-water*. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO *Guidelines for Drinking-water Quality* (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002. The third edition of the GDWQ was published in 2004, the first addendum to the third edition was published in 2006 and the second addendum to the third edition was published in 2008. The fourth edition was published in 2011.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared and updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants of potential health concern in drinking-water. In the first and second editions, these constituted Volume 2 of the GDWQ. Since publication of the third edition, they comprise a series of free-standing monographs, including this one.

For each chemical contaminant or substance considered, a lead institution prepared a background document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Japan, the United Kingdom and the United States of America (USA) prepared the documents for the fourth edition.

Under the oversight of a group of coordinators, each of whom was responsible for a group of chemicals considered in the GDWQ, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors. The draft documents were also released to the public domain for comment and submitted for final evaluation by expert meetings.

During the preparation of background documents and at expert meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the Joint FAO/WHO Meeting on Pesticide Residues and the Joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite, in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO Internet site and in the current edition of the GDWQ.

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The work of the following working group coordinators was crucial in the development of this document and others contributing to the fourth edition:

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The draft text was discussed at the Expert Consultation for the fourth edition of the GDWQ, held on 6–8 December 2010. The final version of the document takes into consideration comments from both peer reviewers and the public. The input of those who provided comments and of participants at the meeting is gratefully acknowledged.

The WHO coordinators were Mr R. Bos and Mr B. Gordon, WHO Headquarters. Ms C. Vickers provided a liaison with the International Programme on Chemical Safety, WHO Headquarters. Mr M. Zaim, Public Health and the Environment Programme, WHO Headquarters, provided input on pesticides added to drinking-water for public health purposes.

Ms P. Ward provided invaluable administrative support at the Expert Consultation and throughout the review and publication process. Ms M. Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comments are greatly appreciated.

Acronyms and abbreviations used in the text

ATP	adenosine triphosphate
CTx	carboxy-terminal telopeptide
DNA	deoxyribonucleic acid
GAC	granular activated carbon
GDWQ	*Guidelines for Drinking-water Quality*
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
TDI	tolerable daily intake
USA	United States of America

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This review addresses only the chemical aspects of uranium toxicity. Information pertinent to the derivation of a guideline based on radiological effects is presented elsewhere in the WHO *Guidelines for Drinking-water Quality* (GDWQ) (see chapter 9, Radiological aspects).

1. GENERAL DESCRIPTION

1.1 Identity

Uranium occurs naturally in the +2, +3, +4, +5 and +6 valence states, but it is most commonly found 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 (Cothern & Lappenbusch, 1983; Lide, 1992–1993). Natural uranium consists almost entirely of the ^{238}U isotope, with the ^{235}U and ^{234}U isotopes respectively comprising about 0.72% and 0.0054% (Greenwood & Earnshaw, 1984). Uranium is widespread in nature, occurring in granites and various other mineral deposits (Roessler et al., 1979; Lide, 1992–1993).

Compound	*Molecular formula*	*Chemical Abstracts Service No.*
Uranium	U	7440-61-1
Uranyl ethanoate	$C_4H_6O_6U$	541-09-3
Uranyl chloride	Cl_2O_2U	7791-26-6
Uranyl nitrate	N_2O_8U	36478-76-9
Uranium dioxide	UO_2	1344-57-6

1.2 Physicochemical properties (Lide, 1992–1993)

Compound	*Melting point (°C)*	*Boiling point (°C)*	*Density at 20 °C (g/cm^3)*	*Water solubility (g/l)*
U	1132	3818	19.0	Insoluble
$C_4H_6O_6U$	110	275 (decomposes)	2.9	76.94
Cl_2O_2U	578	(decomposes)	—	3200
N_2O_8U	60.2	118	2.8	Soluble
UO_2	2878	—	10.96	Insoluble

1.3 Major uses

Uranium is used mainly as fuel in nuclear power stations, although some uranium compounds are also used as catalysts and staining pigments (Berlin & Rudell, 1986). Spent uranium is used in military hardware.

1.4 Environmental fate

Uranium is present in the environment as a result of leaching from natural deposits, release in mill tailings, emissions from the nuclear industry, the combustion of coal

and other fuels and the use of phosphate fertilizers that contain uranium. Its presence in drinking-water is most commonly from natural sources.

2. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

2.1 Air

Mean concentrations of uranium in ambient air have been reported to be 0.02 ng/m^3 in Tokyo, Japan (based on a 1979–1981 survey) (Hirose & Sugimura, 1981), and 0.076 ng/m^3 in New York City, United States of America (USA) (1985 and 1986) (Fisenne et al., 1987). On the assumption of a daily respiratory volume of 20 m^3 and a mean urban airborne concentration of 0.05 ng/m^3, the daily intake of uranium from air would be about 1 ng. Tobacco smoke (from two packages of cigarettes per day) contributes less than 50 ng of inhaled uranium per day (Lucas & Markun, 1970).

2.2 Water

In a survey of 130 sites (approximately 3700 samples) in Ontario, Canada, conducted between 1990 and 1995, 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 (OMEE, 1996). The mean concentration of uranium in drinking-water in New York City, USA, ranged from 0.03 to 0.08 µg/l (Fisenne & Welford, 1986). A mean uranium concentration of 2.55 µg/l was reported in groundwater-derived drinking-water from 978 sites in the USA in the 1980s (USEPA, 1990, 1991). In five Japanese cities, the mean concentration in potable water supplies was 0.9 ng/l (Nozaki et al., 1970).

However, uranium is known to occur at higher concentrations, frequently in smaller supplies. For example, uranium concentrations of up to 700 µg/l have been found in private supplies in Canada (Moss et al., 1983; Moss, 1985). A study in Finland examined a population receiving drinking-water containing uranium with a median concentration of 28 µg/l (Kurttio et al., 2002). In a study of 476 Norwegian groundwater samples, 18% had uranium concentrations in excess of 20 µg/l (Frengstad et al., 2000). Concentrations in excess of 20 µg/l have been reported in groundwater from parts of New Mexico, USA (Hakonson-Hayes, Fresquez & Whicker, 2002), and central Australia (Hostetler, Wischusen & Jacobson, 1998; Fitzgerald et al., 1999).

The mean daily uranium intake from water in Finland has been estimated to be 2.5 µg (median 0.3 µg/day) (Muikku et al., 2009). The daily intake from drinking-water in Salt Lake City, USA, is estimated to be 1.5 µg (Singh et al., 1990). On the basis of the results of the survey from Ontario (OMEE, 1996), the daily intake of uranium from drinking-water in Canada is estimated to be 0.8 µg. However, chemical speciation in water may be an important factor, due to the presence of what appear to be less toxic complexes containing calcium in a study of drilled wells in southern Finland (Prat et al., 2009). Two calcium-dependent species, $Ca_2UO_2(CO_3)_3(aq)$ and $CaUO_2(CO_3)_3^{2-}$, dominated; these species are considered to be of low toxicity for cells.

2.3 Food

Uranium has been detected in a variety of foodstuffs. The highest concentrations are found in shellfish, and lower levels have been measured in fresh vegetables, cereals and fish. The average per capita intake of uranium in food has been reported to be 1.3 µg/day (Fisenne et al., 1987) and 2–3 µg/day (Singh et al., 1990) in the USA and 1.5 µg/day in Japan (Nozaki et al., 1970).

In a review of naturally occurring sources of radioactive contamination in food, dietary intakes of ^{238}U were found to range from 12 to 45 mBq/day in several European countries, from 11 to 60 mBq/day in Japan (the higher values were found in uranium mining areas) and from 15 to 17 mBq/day in the USA. The average daily dietary intake was in the order of 20 mBq, or about 4 µg. It was often difficult to determine whether these dietary intakes included intake from drinking-water, and it was emphasized that intake from drinking-water has sometimes been found to be equal to intake from the diet (Harley, 1988).

In a study by Cheng, Lin & Hao (1993), 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 9.20 µg/l.

Landa & Councell (1992) performed leaching studies to determine the quantity of uranium leaching from 33 glass items and two ceramic items in which uranium was used as a colouring agent. Uranium-bearing glasses leached a maximum of 30 µg of uranium per litre, whereas the ceramic-glazed items released approximately 300 000 µg of uranium per litre.

2.4 Estimated total exposure and relative contribution of drinking-water

Intake of uranium through air is extremely low, and it appears that intake through food is between 1 and 4 µg/day. Intake through drinking-water is normally low; however, in circumstances in which uranium in present in a drinking-water source, the majority of intake can be through drinking-water.

3. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Although ubiquitous in the environment, uranium has no known metabolic function in animals and is currently regarded as non-essential (Berlin & Rudell, 1986). Absorption of uranium from the gastrointestinal tract depends upon the solubility of the uranium compound (Berlin & Rudell, 1986), previous food consumption (Sullivan et al., 1986; La Touche, Willis & Dawydiak, 1987) and the concomitant administration of oxidizing agents, such as the Fe^{3+} ion and quinhydrone (Sullivan et al., 1986). The average human gastrointestinal absorption of uranium is 1–2% (Wrenn et al., 1985).

The absorption of a uranium dose of approximately 800 mg/kg body weight in starved female Sprague-Dawley rats increased from 0.17% to 3.3% when iron(III) (190 mg/kg body weight) was administered simultaneously (Sullivan et al., 1986). Absorption of uranium in starved rats administered doses of uranium by gavage was reported to increase with dose; the degree of absorption ranged from 0.06% to 2.8% for uranium doses between 0.03 and 45 mg/kg body weight (La Touche, Willis & Dawydiak, 1987). Only 0.06% of ingested uranium was absorbed in Sprague-Dawley rats and New Zealand White rabbits fed ad libitum and having free access to drinking-water containing up to 600 mg of uranyl nitrate hexahydrate per litre for up to 91 days (Tracy et al., 1992).

Studies of populations in Canada suggested that absorption of uranium from the gastrointestinal tract in children and adults was approximately 3% and 2%, respectively (Chen et al., 2011).

Following ingestion, uranium rapidly appears in the bloodstream (La Touche, Willis & Dawydiak, 1987), where it is associated primarily with the red cells (Fisenne & Perry, 1985); a non-diffusible uranyl–albumin complex also forms in equilibrium with a diffusible ionic uranyl hydrogen carbonate complex (UO_2HCO^{3+}) in the plasma (Moss, 1985). Because of their high affinity for phosphate, carboxyl and hydroxyl groups, uranyl compounds readily combine with proteins and nucleotides to form stable complexes (Moss, 1985). Clearance from the bloodstream is also rapid, and the uranium subsequently accumulates in the kidneys and the skeleton, whereas little is found in the liver (La Touche, Willis & Dawydiak, 1987). The skeleton is the major site of uranium accumulation (Wrenn et al., 1985); the uranyl ion replaces calcium in the hydroxyapatite complex of bone crystals (Moss, 1985).

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. It has been estimated that the total body burden of uranium in humans is 40 µg, with approximately 40% of this being present in the muscles, 20% in the skeleton and 10%, 4%, 1% and 0.3% in the blood, lungs, liver and kidneys, respectively (Igarashi, Yamakawa & Ikeda, 1987).

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/day (Singh et al., 1990), the rate depending in part on the pH of tubular urine (Berlin & Rudell, 1986). 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, which may then impair tubular function.

For a population in southern Finland that received most of its ingested uranium from drinking-water (i.e. uranium intake above 10 µg/day), an incremental uranium intake of 1 µg/day was correlated with a 2.06 ng/l increase in urinary uranium concentration (Karpas et al., 2005).

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 (Wrenn et al., 1985). In another study using a 10-compartment model, overall half-lives for the clearance of uranium from the rat kidney and skeleton were determined to be 5–11 and 93–165 days, respectively (Sontag, 1986). The overall elimination half-life of uranium under conditions of normal daily intake has been estimated to be between 180 and 360 days in humans (Berlin & Rudell, 1986).

4. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

4.1 Acute exposure

Reported oral median lethal doses (LD_{50}s) of uranyl ethanoate dihydrate for rats and mice are 204 and 242 mg/kg body weight, respectively (Domingo et al., 1987). 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 (Berlin & Rudell, 1986; Anthony et al., 1994; Domingo, 1995); the rate of effects varies with dosage level (Leggett, 1989). It has been shown that uranyl ion inhibits both Na^+ transport-dependent and Na^+ transport-independent adenosine triphosphate (ATP) utilization as well as mitochondrial oxidative phosphorylation in the renal proximal tubule (Leggett, 1989; Domingo, 1995). 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 (Wrenn et al., 1985; Berlin & Rudell, 1986). Histopathologically, the regenerated cells are simple flattened cells with no microvilli on luminal surfaces and with reduced numbers of mitochondria (Leggett, 1989).

4.2 Short-term exposure

Forty male Sprague-Dawley rats given uranyl ethanoate dihydrate at a dose of 0, 2, 4, 8 or 16 mg/kg body weight per day (equivalent to uranium doses of 0, 1.1, 2.2, 4.5 and 9.0 mg/kg body weight per day) in drinking-water for 2 weeks exhibited a variety of biochemical effects, including increases in blood glucose levels at uranyl ethanoate dihydrate doses of 4 mg/kg body weight per day and higher, decreases in aspartate aminotransferase and alanine aminotransferase values at uranyl ethanoate dihydrate doses of 8 mg/kg body weight per day and higher, increases in several other haematological parameters at a uranyl ethanoate dihydrate dose of 16 mg/kg body weight per day and increases in total protein levels in all treated groups (Ortega et al., 1989). The authors considered the no-observed-adverse-effect level (NOAEL) to be 2 mg/kg body weight per day as uranyl ethanoate dihydrate (1.1 mg/kg body weight per day as uranium).

Groups of 15 male and 15 female weanling Sprague-Dawley rats consumed water containing uranyl nitrate hexahydrate at a concentration of <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 body weight per day in males and <0.0001, 0.09, 0.42, 2.01, 9.98 and 53.56 mg/kg body weight per day in females) for 91 days (Gilman et al., 1998a). 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 nonspecific 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 dilatation. Other statistically significant lesions in males (≥4.8 mg of uranyl nitrate hexahydrate per litre) 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 of uranyl nitrate hexahydrate per litre). 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 "non-reparable lesions". Significant treatment-related liver changes were also reported in hepatic nuclei and cytoplasm in both sexes at the lowest exposure level. The lowest-observed-adverse-effect level (LOAEL) for adverse effects on the kidney and liver 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 of uranyl nitrate hexahydrate per litre (equivalent to uranium doses of 0.09 mg/kg body weight per day in females and 0.06 mg/kg body weight per day in males). Accumulation of uranium in renal tissue did not differ significantly between the two sexes at all doses.

In a similar study, groups of 10 male New Zealand White rabbits were given uranyl nitrate hexahydrate in drinking-water at a concentration of <0.001 (controls), 0.96, 4.8, 24, 120 or 600 mg/l (determined to be equivalent to uranium doses of 0, 0.05, 0.2, 0.88, 4.82 and 28.7 mg/kg body weight per day) for 91 days (Gilman et al., 1998b). Histopathological changes were observed in the kidney tubule, liver, thyroid and aorta. Histopathological findings were observed in the kidney tubules at doses above 0.96 mg of uranyl nitrate hexahydrate per litre. 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 dilatation, hyperchromicity, tubular atrophy, changes in the interstitium collagen and reticulin sclerosis. In total, 11 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 of uranyl nitrate hexahydrate per litre (equivalent to a uranium dose of 0.05 mg/kg body weight per day). It should be noted, however, that 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 of uranyl nitrate hexahydrate per litre (equivalent to uranium doses of 0, 0.49, 1.32 and 43.02 mg/kg body weight per day) for 91 days. 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 were less marked in females than in males. The LOAEL was considered to be 4.8 mg of uranyl nitrate hexahydrate per litre (equivalent to a uranium dose of 0.49 mg/kg body weight 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 (Gilman et al., 1998a). 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 milligram per kilogram body weight per day basis, their average tissue levels were not similarly raised.

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 of uranyl nitrate hexahydrate per litre (equivalent to uranium doses of 0, 1.36 and 40.98 mg/kg body weight per day) in drinking-water for 91 days, with a recovery period of up to 91 days (Gilman et al., 1998c). Minor histopathological lesions were seen in the liver, thyroid and aorta. In the kidney, tubular injury with degenerative nuclear changes, cytoplasmic vacuolation and tubular dilatation was observed in the high-dose group, which did not exhibit consistent resolution even after a 91-day recovery period. In general, the male rabbits did not respond as dramatically as those in the earlier study (Gilman et al., 1998b), 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 (Gilman et al., 1998b), 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 was estimated by the authors to lie at or below 24 mg of uranyl nitrate hexahydrate per litre.

There is some evidence that tolerance may develop following repeated exposure to uranium (Yuile, 1973; Durbin & Wrenn, 1976; Campbell, 1985). 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 (Leggett, 1989). 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 (McDonald-Taylor et al., 1992). Persistent

ultrastructural changes in the proximal tubules of rabbits have also been reported to be associated with the kidney's ability to store uranium (McDonald-Taylor, Singh & Gilman, 1997). Cell damage in the proximal tubules was significantly more severe in animals allowed up to a 91-day recovery period than in animals in the no-recovery group.

4.3 Long-term exposure

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 (Maynard & Hodge, 1949). On the basis of very limited histopathological investigations, renal damage was reported in each species.

4.4 Reproductive and developmental toxicity

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 (Maynard & Hodge, 1949). More recent studies examined the teratogenic/embryotoxic effects and reproductive outcomes of uranyl acetate dihydrate in Swiss albino mice. Domingo et al. (1989a) evaluated the developmental toxicity of uranium by treating groups of 20 pregnant Swiss mice by gavage with uranyl acetate dihydrate doses of 0, 5, 10, 25 or 50 mg/kg body weight per day (equivalent to uranium doses of 0, 2.8, 5.6, 14 and 28 mg/kg body weight 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 fetotoxicity, including reduced fetal body weights and length, increased incidence of stunted fetuses per litter, increased incidence of both external and internal malformations and increased incidence of developmental variations, was observed in the fetuses of mice at uranium doses of 2.8 mg/kg body weight per day and higher. At uranium doses of 14 mg/kg body weight per day and higher, 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 fetotoxic effects, the authors suggested a LOAEL for uranium of 2.8 mg/kg body weight per day.

Domingo et al. (1989b) evaluated the effect of uranium on late fetal 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 with uranyl acetate dihydrate at doses of 0, 0.05, 0.5, 5 or 50 mg/kg body weight per day (equivalent to uranium doses of 0, 0.028, 0.28, 2.8 and 28 mg/kg body weight per day). Maternal deaths (2/20 at a uranium dose of 2.8 mg/kg body weight per day and 3/20 at a uranium dose of 28 mg/kg body weight per day) 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 indices, were observed in the high-dose group. Treatment with uranium at all doses had no effect on sex ratios, mean litter size, pup body weight or pup body weight throughout lactation. Based on developmental effects in pups, a no-observed-effect level (NOEL) for uranium of 2.8 mg/kg body weight per day was established.

Paternain et al. (1989) studied the effects of uranium on reproduction, gestation and postnatal survival in mice. Groups of 25 mature male Swiss mice were exposed to oral uranyl acetate dihydrate doses of 0, 5, 10 or 25 mg/kg body weight per day (equivalent to uranium doses of 0, 2.8, 5.6 and 14 mg/kg body weight per day) for 60 days prior to mating with mature females (25 per group). Females were exposed for 14 days prior to mating, 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 fetuses) was significantly increased in the high-dose group. Lethality in pups (at birth and at day 4 of lactation) was significantly increased at uranium doses of 5.6 mg/kg body weight per day and higher, 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.

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 (Maynard & Hodge, 1949; Maynard, Downs & Hodge, 1953; Malenchenko, Barkun & Guseva, 1978). In a more recent study, male Swiss mice were exposed for 64 days to uranyl acetate dihydrate in drinking-water at a dose of 0, 10, 20, 40 or 80 mg/kg body weight per day (equivalent to uranium doses of 0, 5.6, 11.2, 22.4 and 44.8 mg/kg body weight per day) prior to mating with untreated females for 4 days (Llobet et al., 1991). With the exception of interstitial alterations and vacuolation of Leydig cells at the highest dose, no effects were observed in testicular function or spermatogenesis. There was, however, a significant, non-dose-related decrease in the pregnancy rate of these animals from the lowest uranium dose of 5.6 mg/kg body weight.

4.5 Mutagenicity and related end-points

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 (Lin et al., 1993). The authors suggested that the data provide a possible mechanism for the teratogenic effects observed in the study by Domingo et al. (1989a). The genotoxic effects in this study were thought to occur through the binding of the uranyl nitrate to the phosphate groups of deoxyribonucleic acid (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 (Hu & Zhu, 1990).

4.6 Carcinogenicity

Although bone cancer has been induced in experimental animals by injection or inhalation of soluble compounds of uranium isotopes or mixtures of uranium isotopes with high specific activity, no carcinogenic effects have been reported in animals ingesting soluble or insoluble uranium compounds (Wrenn et al., 1985).

5. EFFECTS ON HUMANS

Nephritis is the primary chemically induced effect of uranium in humans (Hursh & Spoor, 1973).

In Nova Scotia, Canada, clinical studies were performed on 324 persons exposed to variable amounts of naturally occurring uranium in drinking-water (up to 0.7 mg/l) 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 and 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 a biomarker for subclinical toxicity. The group with the highest uranium concentrations 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 (Moss et al., 1983; Moss, 1985).

In a pilot study conducted in 1993 in three communities in Saskatchewan, Canada, there was a statistically significant association (P = 0.03) between increasing but normal levels of urine albumin (measured as milligrams per millimole creatinine) and the uranium cumulative index. 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 (Mao et al., 1995). The study was conducted with 100 participants in three different areas with mean uranium concentrations in drinking-water 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 levels (>3.0 mg/mmol creatinine). Three participants had serum creatinine concentrations above 120 µmol/l (range 50–170 µmol/l), which is reportedly indicative of prevalent renal damage. 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. According to the authors, microalbuminuria has been shown to be a sensitive indicator of early renal disease.

A study on two groups of subjects with chronic exposure to uranium in drinking-water, one exposed to less than 1 µg/l and one exposed to 2–781 µg/l, was carried out in Canada (Zamora et al., 1998). This study found no correlation between exposure and albumin in urine, but it did find a correlation with alkaline phosphatase and β_2-

microglobulin in urine. The authors concluded that the concentrations observed in the study affected kidney function at the proximal tubule.

A study on a Finnish population exposed to well water containing a median uranium concentration of 28 µg/l examined individuals for signs of adverse renal effects (Kurttio et al., 2002). Uranium in urine was significantly associated with increased fractional excretion of calcium, phosphate and glucose, but uranium in drinking-water was significantly associated only with fractional excretion of calcium. The data were consistent with signs of modest alterations in proximal tubular function, but there was no indication of any effect on glomerular function. There was no sign of a clear threshold to the effects observed, but the study population was relatively small, and there is significant variation within an unexposed population. The authors concluded that the clinical significance of the results could not be easily established, as tubular dysfunction occurred within the normal physiological range.

In a follow-up study on the same population, Kurttio et al. (2006a) studied groups of 95 men and 98 women aged 18–81 years who had used drinking-water from drilled wells for an average of 16 years to determine if there was any evidence of kidney cytotoxicity. There was no evidence of renal damage from 10 renal toxicity indicators of both cytotoxicity and renal function for a median uranium concentration of 25 µg/l, with an interquartile range of 5–148 µg/l and a maximum concentration of 1500 µg/l. The conclusion was that continuous uranium intake from drinking-water, even at relatively high exposures, did not have cytotoxic effects on kidneys in humans. As a consequence, there is significant doubt as to whether the small increased fractional excretion of calcium seen in the earlier study was a toxic effect, particularly in view of the lack of confirmatory data showing effects on proximal tubular function in studies carried out by the same group.

In a study in Sweden, Seldén et al. (2009) examined uranium exposure from private drilled drinking-water wells; uranium concentrations in the water ranged from less than 0.2 to 470 µg/l. The investigators concluded that although uranium concentrations in urine were strongly correlated with uranium concentrations in drinking-water, there were no clear signs of nephrotoxicity associated with uranium in drinking-water, as indicated by microglobulin levels in urine. There was some indication of an effect using uranium in urine as a measure of overall uranium exposure, but the clinical relevance of the findings remains unclear.

A study of small stable populations in Ireland compared those drinking well water with low uranium concentrations (<2 µg/l) with those drinking water with high uranium concentrations (93–142 µg/l) (O'Herlihy et al., 2005). Three groups were defined based on exposure to the supply: Group A, exposed 1989–2002; Group B, exposed 1989–1995; and Group C, never exposed. All 143 households from Group A and 75 from each of Groups B and C were offered screening, with a household response rate of 71%. Parameters examined were urinary β_2-microglobulin, retinol binding protein, microalbumin and uranium, serum urea and creatinine. There was no correlation between markers of renal dysfunction and uranium exposure, and no case of renal disease attributable to uranium exposure was identified.

A study of a family exposed to very high uranium concentrations in well water in rural north-western Connecticut, USA (866 µg/l and 1160 µg/l), showed no elevated β_2-microglobulin levels in urine when corrected for creatinine excretion except for the youngest child (3 years old). However, 3 months after ceasing exposure to the water, the child's β_2-microglobulin level had fallen significantly (Magdo et al., 2007).

A study of uranium exposure in Finland included 146 men and 142 women 26–83 years of age who, for an average of 13 years, had used drinking-water originating from wells drilled in bedrock, in areas with naturally high uranium content (Kurttio et al., 2005). Biochemical indicators of bone formation were serum osteocalcin and aminoterminal propeptide of type I procollagen, and a marker for bone resorption was serum type I collagen carboxy-terminal telopeptide (CTx). The median uranium concentration in drinking-water was 27 µg/l (interquartile range, 6–116 µg/l). There was some suggestion that elevation of CTx (P = 0.05) as well as osteocalcin (P = 0.19) could be associated with increased uranium exposure in men, but no similar relationship was found in women; therefore, the biological significance of this observation remains uncertain.

No increased risk of leukaemia (Auvinen et al., 2002), stomach cancer (Auvinen et al., 2005) or urinary organ cancers (Kurttio et al., 2006b) was observed among users of drilled wells in Finland using cancer registry data. Zamora et al. (2009) carried out a study of an Aboriginal community in Canada to assess whether fears of increased risk of cancer from uranium exposure were justified. The assessment showed that exposure to uranium at concentrations up to 845 µg/l for up to 15 years would not result in a detectable increase in cancer rate. There was a correlation between urinary uranium concentrations and effects on tubular reabsorption, which was similar to the results of the earlier studies carried out by the same group and described above. These studies provide support for the lack of threat from radioactivity of natural uranium.

6. PRACTICAL ASPECTS

6.1 Analytical methods and analytical achievability

Uranium can be determined by inductively coupled plasma mass spectrometry, which has a detection limit of 0.1 µg/l and a between-run precision of less than 6% (Boomer & Powell, 1987). Inductively coupled plasma atomic emission spectrometry can also be used, with a detection limit of 0.2 µg/l when used with a chelating resin. Alpha-spectrometry has been used for the determination of uranium in bottled waters (Gans, 1985) and environmental media (Singh & Wrenn, 1988), although the recovery is often highly variable, owing to the low specific activity of natural uranium (Singh & Wrenn, 1988).

6.2 Treatment and control methods and technical performance

A review of treatment technologies for uranium removal (Aieta et al., 1987) reported the following removals:

Coagulation/filtration at high pH (10+):	>95%
Lime softening:	85–99%
Anion exchange:	99%
Reverse osmosis:	>95%

Coagulation at pH 10 using aluminium salts would not be feasible owing to the high solubility of aluminium, but 80–89% removal of uranium can be achieved by aluminium coagulation at pH 6.

Another review (Lowry & Lowry, 1988) gave the following removals:

Coagulation/filtration:	80–89%
Lime softening:	85–99%
Anion exchange:	90–100%
Reverse osmosis:	90–99%
Activated alumina:	90%

Laboratory coagulation tests were carried out on pond water containing uranium at 83 µg/l (Sorg, 1988). With ferric sulfate, removals in the range 70–90% were obtained with iron doses of 3–7 mg/l at pH 6 and 10; at pH 4 and 8, removal was less than 30%. With aluminium (as aluminium sulfate) doses of 1.5–4 mg/l, removals were about 95% at pH 10, 50–85% at pH 6 and less than 40% at pH 4 and 8. Lime softening (50–250 mg/l) gave 85–90% removal. Anion exchange gave 99% removal and a calculated capacity of 55 mg/ml of resin. Pilot plant tests using three different resins to treat water containing uranium at 200–300 µg/l found that 8000–20 000 bed volumes of water could be treated before breakthrough (15 µg/l). In bench-scale column tests, activated alumina reduced the uranium concentration from 273–432 µg/l to approximately 1 µg/l for up to 2000 bed volumes. It was reported that granular activated carbon (GAC) treatment could reduce the uranium concentration from 26–101 µg/l to 1 µg/l, but the capacity was limited; after breakthrough, the concentrations in treated water rose to levels above the influent concentration (i.e. desorption occurred). Four different reverse osmosis membranes achieved greater than 99% removal from a groundwater containing uranium at 300 µg/l (Sorg, 1988).

The removal of uranium by a full-scale water treatment plant was monitored (Gäfvert, Ellmark & Holm, 2002). The plant treated lake water by aluminium and iron coagulation (in two streams) and rapid gravity filtration. Aluminium coagulation (aluminium at 6 mg/l, pH 6) reduced the raw water uranium concentration of 0.12 µg/l by 87%; after filtration, the total removal was 92%. With iron coagulation (iron at 15 mg/l, pH 5.2), the removal (without filtration) was 77%.

In a survey of 20 treatment plants, substantial removal of uranium was found to occur at only 2 of them. This was considered to be related to the coagulant doses and pH values used, and it was concluded that uranium removal can be achieved by adjusting the coagulant dose or pH, or both (White & Bondietti, 1983).

Tests were conducted on the ability of a strong base anion exchange resin to remove uranium (120 µg/l) from a groundwater. The test ran for 300 000 bed volumes, after which the treated water still contained uranium at concentrations below 6 µg/l (95% removal). The total uranium loading was 30 g/l of resin (Zhang & Clifford, 1994).

The operating results for small full-scale (55 m^3/day) anion exchange plants have been reported (Jelinek & Sorg, 1988). Influent uranium concentrations of 57–110 µg/l were reduced to 0.3 µg/l or less for 9750 bed volumes (1078 m^3).

Combined removal of uranium and radium can be achieved using a mixed bed containing 10% strong base anion resin (for removal of uranium) and strong acid cation resin (for removal of radium) (Clifford & Zhang, 1994).

A domestic-scale reverse osmosis unit removed greater than 99.9% of uranium from initial concentrations of 69 and 183 µg/l (Fox & Sorg, 1987).

Five nanofiltration membranes were tested for the removal of uranium (1 mg/l) from synthetic solutions. In test waters containing bicarbonate and around neutral pH, all the membranes gave removals of 95% or more (Raff & Wilken, 1999).

Other techniques that can be used for removal of uranium include adsorption onto modified GAC (Coleman et al., 2003), bone charcoal and apatite (Bostick et al., 2000) and chitosan (Gerente, Andres & Le Cloirec, 1999). Zero valent iron can also be used for uranium removal (Abdelouas et al., 1999; Farrell et al., 1999; Morrison, Metzler & Dwye, 2003).

7. PROVISIONAL GUIDELINE VALUE

Deriving a guideline value for uranium in drinking-water is complex, because the data do not provide a clear no-effect concentration.

A health-based value could be determined using the results of the most extensive subchronic study in laboratory animals that has been conducted to date, in which uranium was administered in drinking-water to rats (Gilman et al., 1998a). In this 91-day study, the LOAEL for degenerative lesions in the proximal convoluted tubule of the kidney in males was considered to be 0.96 mg of uranyl nitrate hexahydrate per litre, which is equivalent to a uranium dose of 0.06 mg/kg body weight per day. A tolerable daily intake (TDI) of 0.6 µg/kg body weight could be derived using this LOAEL and application of an uncertainty factor of 100 (for intraspecies and interspecies variation). 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 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, and there is no indication that the severity of the renal lesions would be exacerbated following continued exposure. This TDI would yield a health-based value of 15 µg/l (rounded figure) for drinking-water, assuming a 60 kg adult consuming 2 litres of drinking-water per day and an 80% allocation of the TDI to drinking-water. The allocation of 80% of the TDI to drinking-water is supported by data on the low intake of uranium from food. This value of 15 µg/l was the provisional guideline value for uranium in the third edition of the GDWQ.

However, the increasing database on humans exposed to considerably higher concentrations of uranium in drinking-water supports a health-based guideline value for uranium in drinking-water that is higher than 15 µg/l. In the studies from Finland and Sweden, there were no adverse effects reported, even at uranium concentrations in drinking-water approaching 100 µg/l, although the numbers of individuals were relatively small. In the Finnish epidemiological study (Kurttio et al., 2006a) and other studies, no evidence of renal damage was detected in the studied group of consumers. This study was chosen as the basis to support a guideline value because it is one of the most recent studies, reflects the results from other recent studies, is of high technical quality and builds on what has been learnt from previous studies. The population studied is also stable, and the authors were able to ensure that the great majority of exposure was from drinking-water.

Considering the Kurttio et al. (2006a) study group as a no-effect group, the value of the 95th percentile of the uranium exposure distribution is considered to be a NOAEL. From the analysis of the uranium exposure of approximately 200 people, the value of the 95th percentile is estimated to be 1094 µg/day, and the 95% confidence interval is calculated to be 637–1646 µg/day using a bootstrap method. The lower confidence limit of 637 µg/day is appropriate for the point of departure. After applying an uncertainty factor of 10 for intraspecies differences to this NOAEL, a TDI of 60 µg can be derived. Although the uranium intakes were calculated from actual individual water intakes in this study, a default daily intake of 2 litres would be appropriate for deriving a health-based guideline value. Therefore, a guideline value of 30 µg/l can be derived from this study.

Although some minor biochemical changes associated with kidney function have been reported to be correlated with uranium exposure at concentrations below 30 µg/l, these findings are not consistent between studies and consequently are not considered to be sufficiently robust.

No clear no-effect concentration has emerged from the human studies to date. This is not surprising, as most of the study populations are quite small, and there is substantial normal variation in the measured parameters in the human population. However, the overall indications are that there is no clear evidence of effects below an exposure concentration of 30 µg/l. In fact, the evidence for effects on the kidney, which appears to be the most sensitive organ, is equivocal until much higher exposure concentrations. Most of the affected supplies are microbiologically clean groundwaters and are also small supplies, where resources are an important

consideration. Natural uranium will not be detected by screening for radioactivity (see chapter 9 of the GDWQ) until concentrations are well above 100 µg/l. No allocation factor was used in the derivation of the guideline value because the value is based on drinking-water concentrations in an epidemiological study in humans.

The data also show that there is no significantly increased risk of radiation-induced cancers from levels of natural uranium found in drinking-water. Only at concentrations above 100 µg/l will natural uranium be detected by gross screening for beta particles.

Several methods are available for the removal of uranium from drinking-water, although some of these methods have been tested at laboratory or pilot scale only. Coagulation using ferric sulfate or aluminium sulfate at optimal pH and coagulant dosages can achieve 80–95% removal of uranium, whereas at least 99% removal can be achieved using lime softening, anion exchange resin or reverse osmosis processes. In rural areas with high natural uranium levels, uranium concentrations lower than the guideline value may be difficult to achieve with the treatment technology available (WRc, 1997).

The guideline value for uranium remains provisional because of the difficulties in identifying an exposure level at which effects might be expected from the scientific data. As most exposure is from small supplies for which resources are likely to be limited and alternative supplies that are microbiologically safe may not be readily available, care should be taken in responding to an exceedance of the provisional guideline value, which is probably conservative. Consideration should first be given to exposure from all sources and the availability of alternative safe sources.

The provisional guideline value of 30 µg/l, which is derived from recent epidemiological studies on populations exposed to high uranium concentrations, replaces the previous provisional guideline value of 15 µg/l, which was derived from experimental animal studies. It is noted that studies on human populations, when available and of good quality, are the preferred source of health-related information to be used in deriving guideline values.

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