

Uranium in Drinking-water

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

© World Health Organization 2004

Requests for permission to reproduce or translate WHO publications - whether for sale or for non-commercial distribution - should be addressed to Publications (Fax: +41 22 791 4806; e-mail: permissions@who.int).

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

The World Health Organization does not warrant that the information contained in this publication is complete and correct and shall not be liable for any damage incurred as a result of its use.

Preface

One of the primary goals of 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 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/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 examined in drinking-water.

For each chemical contaminant or substance considered, a lead institution prepared a health criteria document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America prepared the requested health criteria documents.

Under the responsibility of the coordinators for a group of chemicals considered in the guidelines, 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 before the documents were submitted for final evaluation by the experts meetings. A “final task force” meeting reviewed the health risk assessments and public and peer review comments and, where appropriate, decided upon guideline values. During preparation of the third edition of the GDWQ, it was decided to include a public review via the world wide web in the process of development of the health criteria documents.

During the preparation of health criteria documents and at experts 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 Meetings 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.

Acknowledgements

The first draft of Uranium in Drinking-water, Background document for development of WHO *Guidelines for Drinking-water Quality*, was prepared by Ms M. Giddings, Health Canada, and revised by Mr J. Fawell, United Kingdom, to whom special thanks are due.

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

Mr J.K. Fawell, United Kingdom (*Organic and inorganic constituents*)
Dr E. Ohanian, Environmental Protection Agency, USA (*Disinfectants and disinfection by-products*)
Ms M. Giddings, Health Canada (*Disinfectants and disinfection by-products*)
Dr P. Toft, Canada (*Pesticides*)
Prof. Y. Magara, Hokkaido University, Japan (*Analytical achievability*)
Mr P. Jackson, WRc-NSF, United Kingdom (*Treatment achievability*)

The contribution of peer reviewers is greatly appreciated. The draft text was posted on the world wide web for comments from the public. The revised text and the comments were discussed at the Final Task Force Meeting for the third edition of the GDWQ, held on 31 March to 4 April 2003, at which time the present version was finalized. The input of those who provided comments and of participants in the meeting is gratefully reflected in the final text.

The WHO coordinators were as follows:

Dr J. Bartram, Coordinator, Water Sanitation and Health Programme, WHO Headquarters, and formerly WHO European Centre for Environmental Health
Mr P. Callan, Water Sanitation and Health Programme, WHO Headquarters
Mr H. Hashizume, Water Sanitation and Health Programme, WHO Headquarters

Ms C. Vickers provided a liaison with the International Chemical Safety Programme, WHO Headquarters.

Ms Marla 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 comment are greatly appreciated.

Acronyms and abbreviations used in the text

ATP	adenosine triphosphate
CAS	Chemical Abstracts Service
DNA	deoxyribonucleic acid
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

Table of contents

1. GENERAL DESCRIPTION	1
1.1 Identity	1
1.2 Physicochemical properties	1
1.3 Major uses.....	1
1.4 Environmental fate.....	1
2. ANALYTICAL METHODS	2
3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE.....	2
3.1 Air	2
3.2 Water.....	2
3.3 Food	3
3.4 Estimated total exposure and relative contribution of drinking-water.....	3
4. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS	3
5. EFFECTS ON LABORATORY ANIMALS AND <i>IN VITRO</i> TEST SYSTEMS	5
5.1 Acute exposure.....	5
5.2 Short-term exposure.....	5
5.3 Long-term exposure.....	8
5.4 Reproductive and developmental toxicity	8
5.5 Mutagenicity and related end-points.....	9
5.6 Carcinogenicity	9
6. EFFECTS ON HUMANS.....	10
7. PROVISIONAL GUIDELINE VALUE.....	11
8. REFERENCES	12

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* (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 ($^{\text{nat}}\text{U}$) is a mixture of three radionuclides (^{234}U , ^{235}U and ^{238}U), all of which decay by both alpha and gamma emissions (Cothorn & 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).

<i>Compound</i>	<i>CAS No.</i>	<i>Molecular formula</i>
Uranium	7440-61-1	U
Uranyl ethanoate	541-09-3	$\text{C}_4\text{H}_6\text{O}_6\text{U}$
Uranyl chloride	7791-26-6	$\text{Cl}_2\text{O}_2\text{U}$
Uranyl nitrate	36478-76-9	$\text{N}_2\text{O}_8\text{U}$
Uranium dioxide	1344-57-6	UO_2

1.2 Physicochemical properties (Lide, 1992–1993)

<i>Compound</i>	<i>Melting point (°C)</i>	<i>Boiling point (°C)</i>	<i>Density at 20 °C (g/cm³)</i>	<i>Water solubility (g/litre)</i>
U	1132	3818	19.0	insoluble
$\text{C}_4\text{H}_6\text{O}_6\text{U}$	110	275 (decomposes)	2.9	76.94
$\text{Cl}_2\text{O}_2\text{U}$	578	(decomposes)	–	3200
$\text{N}_2\text{O}_8\text{U}$	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).

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.

URANIUM IN DRINKING-WATER

2. ANALYTICAL METHODS

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/litre) (Kreiger & Whittaker, 1980). 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/litre) and a between-run precision of less than 6% (Boomer & Powell, 1987). 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).

3. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Air

Mean levels of uranium in ambient air have been reported to be 0.02 ng/m³ in Tokyo, Japan (based on a 1979–1981 survey) (Hirose & Sugimura, 1981), and 0.076 ng/m³ in New York City, USA (1985 and 1986) (Fisenne et al., 1987). On the assumption of a daily respiratory volume of 20 m³ and a mean urban airborne concentration of 0.05 ng/m³, 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).

3.2 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/litre; detection limit 0.05 µg/litre) in treated drinking-water was 0.40 µg/litre (OMEE, 1996). The mean concentration of uranium in drinking-water in New York City, USA, ranged from 0.03 to 0.08 µg/litre (Fisenne & Welford, 1986). A mean uranium concentration of 2.55 µg/litre was reported in drinking-water from 978 sites in the USA in the 1980s (US EPA, 1990, 1991). In five Japanese cities, the mean level in potable water supplies was 0.9 ng/litre (Nozaki et al., 1970).

However, uranium is known to occur at higher levels, frequently in smaller supplies. For example, uranium concentrations of up to 700 µg/litre 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/litre (Kurttio et al., 2002). In a study of 476 Norwegian groundwater samples, 18% had uranium concentrations in excess of 20 µg/litre (Frengstad et al., 2000). Concentrations in excess of 20 µg/litre have been reported in groundwater from parts of New Mexico, USA (Hakonson-Hayes et al., 2002), and central Australia (Hostetler et al., 1998; Fitzgerald et al., 1999).

The daily uranium intake from water in Finland has been estimated to be 2.1 µg (Kahlos & Asikainen, 1980). 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.

3.3 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 ²³⁸U 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 et al. (1993), the mean uranium concentration in nine different beverages was 0.98 µg/litre (range 0.26–1.65 µg/litre), and the mean concentration of uranium in mineral water was 9.20 µg/litre.

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.

3.4 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 is present in a drinking-water source, the majority of intake can be through drinking-water.

4. 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

URANIUM IN DRINKING-WATER

et al., 1986; La Touche et al., 1987) and the concomitant administration of oxidizing agents, such as the iron(III) 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 of body weight in starved female Sprague-Dawley rats increased from 0.17 to 3.3% when iron(III) (190 mg/kg of 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 doses between 0.03 and 45 mg of uranium per kg of body weight (La Touche et al., 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).

Following ingestion, uranium rapidly appears in the bloodstream (La Touche et al., 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 ($\text{UO}_2\text{HCO}_3^{3+}$) 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 et al., 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 et al., 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 $\mu\text{g}/\text{day}$ (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.

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).

5. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

5.1 Acute exposure

Reported oral LD₅₀s of uranyl ethanoate dihydrate for rats and mice are 204 and 242 mg/kg of 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 recently been shown that uranyl ion inhibits both Na⁺ transport-dependent and Na⁺ transport-independent 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).

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 et al., 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.

5.2 Short-term exposure

Forty male Sprague-Dawley rats given 0, 2, 4, 8 or 16 mg of uranyl ethanoate dihydrate per kg of body weight per day (equivalent to doses of 0, 1.1, 2.2, 4.5 or 9.0 mg of uranium per kg of body weight per day) in drinking-water for 2 weeks exhibited a variety of biochemical effects, including increases in blood glucose levels at ≥ 4 mg of uranyl ethanoate dihydrate per kg of body weight per day, decreases in aspartate aminotransferase and alanine aminotransferase values at ≥ 8 mg of uranyl

URANIUM IN DRINKING-WATER

ethanoate dihydrate per kg of body weight per day, increases in several other haematological parameters at 16 mg of uranyl ethanoate dihydrate per kg of body weight per day and increases in total protein levels in all treated groups (Ortega et al., 1989). The authors considered the NOAEL to be 2 mg of uranyl ethanoate dihydrate per kg of body weight per day (1.1 mg of uranium per kg of body weight per day).

Groups of 15 male and 15 female weanling Sprague-Dawley rats consumed water containing <0.001 (control), 0.96, 4.8, 24, 120 or 600 mg of uranyl nitrate hexahydrate per litre (equivalent to doses of <0.0001, 0.06, 0.31, 1.52, 7.54 and 36.73 mg of uranium per kg of body weight per day in males and <0.0001, 0.09, 0.42, 2.01, 9.98 and 53.56 mg of uranium per kg of 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 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 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 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 0.09 mg of uranium per kg of body weight per day in females and 0.06 mg of uranium per kg of body weight 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.

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/litre (determined to be equivalent to doses of 0, 0.05, 0.2, 0.88, 4.82 and 28.7 mg of uranium per kg of 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 0.05 mg of uranium per kg of 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 doses of 0, 0.49, 1.32 and 43.02 mg of uranium per kg of 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 in females were generally less marked than in males. The LOAEL was considered to be 4.8 mg of uranyl nitrate hexahydrate per litre (equivalent to 0.49 mg of uranium per kg of 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 mg/kg of body weight per day basis, their average tissue levels were not similarly raised. 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 (Gilman et al., 1998a).

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 0, 1.36 and 40.98 mg of uranium per kg of 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

URANIUM IN DRINKING-WATER

data in the kidney, a LOAEL for the male New Zealand rabbits in this study is estimated to lie between 24 and 600 mg of uranyl nitrate hexahydrate per litre.

5.3 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.

5.4 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 have 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 doses of 0, 5, 10, 25 or 50 mg of uranyl acetate dihydrate per kg of body weight per day (equivalent to 0, 2.8, 5.6, 14 and 28 mg of uranium per kg of 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 ≥ 2.8 mg of uranium per kg of body weight per day. At doses of ≥ 14 mg of uranium per kg of body weight per day, specific malformations included cleft palate and bipartite sternbrae, and developmental variations included reduced ossification and unossified skeletal variations. There was no evidence of embryoletality at any dose. Based on both the maternal and fetotoxic effects, a LOAEL of 2.8 mg of uranium per kg of body weight per day could be considered.

A second study by 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 to doses of 0, 0.05, 0.5, 5 or 50 mg of uranyl acetate dihydrate per kg of body weight per day (equivalent to 0, 0.028, 0.28, 2.8 and 28 mg of uranium per kg of body weight per day). Maternal deaths (2/20 at 2.8 mg of uranium per kg of body weight per day, and 3/20 at 28 mg of uranium per kg of 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. Based on developmental effects in pups, a NOEL of 2.8 mg of uranium per kg of 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 doses of 0, 5, 10 or 25 mg of uranyl acetate dihydrate per kg of body weight per day (equivalent to 0, 2.8, 5.6 and 14 mg of uranium per kg of 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. Embryoletality (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 ≥ 5.6 mg of uranium per kg of body weight 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.

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 et al., 1953; Malenchenko et al., 1978). 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 of body weight per day (equivalent to 0, 5.6, 11.2, 22.4 and 44.8 mg of uranium per kg of body weight per day) prior to mating with untreated females for 4 days (Llobet et al., 1991). 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.

5.5 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/litre. 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 suggest that the data provide a possible mechanism for the teratogenic effects observed in the studies 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 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).

5.6 Carcinogenicity

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 (Wrenn et al., 1985).

6. EFFECTS ON HUMANS

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

Little information is available on the chronic health effects of exposure to environmental uranium in humans. 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/litre) 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 an index of 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 mg/mmol 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 levels ranging from 0.71 (control) to 19.6 μ g/litre. 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 μ mol/litre (range 50–170 μ mol/litre), 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 <1 μ g/litre and one exposed to 2–781 μ g/litre, was carried out in Canada (Zamora et al., 1998). This study found no correlation between exposure and albumin in urine but 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 μ g/litre examined individuals for signs of adverse renal effects (Kurtio 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, since tubular dysfunction occurred within the normal physiological range.

7. PROVISIONAL GUIDELINE VALUE

There are insufficient data regarding the carcinogenicity of uranium in humans and experimental animals. The guideline value for the chemical toxicity of uranium was therefore derived using a TDI approach. As no adequate chronic study was identified, the TDI was derived using the results of the most extensive subchronic study conducted to date in which uranium was administered in drinking-water to the most sensitive sex and species (Gilman et al., 1998a). 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 of uranyl nitrate hexahydrate per litre, which is equivalent to 0.06 mg of uranium per kg of body weight per day.

A TDI of 0.6 µg/kg of body weight per day was derived using the LOAEL of 60 µg/kg of body weight per day and an uncertainty factor of 100 (for intra- 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 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, and there is no indication that the severity of the renal lesions will be exacerbated following continued exposure.

This TDI yields a guideline value of 15 µg/litre (rounded figure), 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. The guideline value is supported by data from epidemiological studies.

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 is therefore provisional because it may be difficult to achieve with the treatment technology available and because of limitations in the

URANIUM IN DRINKING-WATER

database on health effects and the need for more analytical epidemiological studies. It must be noted that the concentration of uranium in drinking-water associated with the onset of measurable tubular dysfunction remains uncertain, as does the clinical significance of the observed changes at low exposure levels. Indeed, a guideline value of up to 30 µg/litre may be protective of kidney toxicity because of uncertainty regarding the clinical significance of changes observed in epidemiological studies.

8. REFERENCES

- Anthony ML et al. (1994) Studies of the biochemical toxicology of uranyl nitrate in the rat. *Archives of Toxicology*, 68:43–53.
- Berlin M, Rudell B (1986) Uranium. In: Friberg L, Nordberg GF, Vouk VB, eds. *Handbook on the toxicology of metals*, 2nd ed. Amsterdam, Elsevier Science Publishers, pp. 623–637.
- Blanchard RL et al. (1985) Radiological sampling and analytical methods for national primary drinking water regulations. *Health Physics*, 48(5):587–600.
- Boomer DW, Powell MJ (1987) Determination of uranium in environmental samples using inductively coupled plasma mass spectrometry. *Analytical Chemistry*, 59:2810–2813.
- Campbell DCC (1985) *The development of an animal model with which to study the nephrotoxic effects of uranium-contaminated drinking water*. Halifax, Nova Scotia, Dalhousie University (M.Sc. thesis).
- Cheng YL, Lin JY, Hao XH (1993) Trace uranium determination in beverages and mineral water using fission track techniques. *Nuclear Tracks and Radiation Measurements*, 22(1–4):853–855.
- Cothorn CR, Lappenbusch WL (1983) Occurrence of uranium in drinking water in the US. *Health Physics*, 45:89–99.
- Domingo JL (1995) Chemical toxicity of uranium. *Toxicology and Ecotoxicology News*, 2(3):74–78.
- Domingo JL et al. (1987) Acute toxicity of uranium in rats and mice. *Bulletin of Environmental Contamination and Toxicology*, 39:168–174.
- Domingo JL et al. (1989a) The developmental toxicity of uranium in mice. *Toxicology*, 55(1–2):143–152.
- Domingo JL et al. (1989b) Evaluation of the perinatal and postnatal effects of uranium in mice upon oral administration. *Archives of Environmental Health*, 44(6):395–398.
- Durbin PW, Wrenn ME (1976) Metabolism and effects of uranium in animals. In: *Conference on occupational health experience with uranium*. Washington, DC, US Energy Research and Development Administration, pp. 68–129 (available from US National Technical Information Service).
- Fisenne IM, Perry PM (1985) Isotopic U concentration in human blood from New York City donors. *Health Physics*, 49:1272–1275.
- Fisenne IM, Welford GA (1986) Natural U concentration in soft tissues and bone of New York City residents. *Health Physics*, 50(6):739–746.
- Fisenne IM et al. (1987) The daily intake of $^{235,235,238}\text{U}$, $^{228,230,232}\text{Th}$ and $^{226,228}\text{Ra}$ by New York City residents. *Health Physics*, 53:357–363.

- Fitzgerald J et al. (1999) *Groundwater quality in the Anangu Pitjantjatjara Lands, South Australia*. Canberra, Bureau of Rural Sciences.
- Frengstad B et al. (2000) The chemistry of Norwegian groundwaters: III. The distribution of trace elements in 476 crystalline bedrock groundwaters, as analysed by ICP-MS techniques. *The Science of the Total Environment*, 31:21-40.
- Gans I (1985) Natural radionuclides in mineral waters. *The Science of the Total Environment*, 45:93-99.
- Gilman AP et al. (1998a) Uranyl nitrate: 28-day and 91-day toxicity studies in the Sprague-Dawley rat. *Toxicological Sciences*, 41:117-128.
- Gilman AP et al. (1998b) Uranyl nitrate: 91-day toxicity studies in the New Zealand white rabbit. *Toxicological Sciences*, 41:129-137.
- Gilman AP et al. (1998c) Uranyl nitrate: 91-day exposure and recovery studies in the New Zealand white rabbit. *Toxicological Sciences*, 41:138-151.
- Greenwood NN, Earnshaw A (1984) *Chemistry of the elements*. Oxford, Pergamon Press.
- Hakanson-Hayes AC, Fresquez PR, Whicker FW (2002) Assessing potential risks from exposure to natural uranium in well water. *Journal of Environmental Radioactivity*, 59:29-40.
- Harley JH (1988) Naturally occurring sources of radioactive contamination. In: Harley JH, Schmidt GD, Silini G, eds. *Radionuclides in the food chain*. Berlin, Springer-Verlag.
- Hirose K, Sugimura Y (1981) Concentration of uranium and the activity ratio of $^{234}\text{U}/^{238}\text{U}$ in surface air: effect of atmospheric burn-up of Cosmos-954. *Meteorology and Geophysics*, 32:317 [cited in Fisenne & Welford, 1986].
- Hostetler S, Wischusen J, Jacobson G (1998) *Groundwater quality in the Papunya-Kintore region, Northern Territory*. Canberra, Australian Geological Survey Organisation.
- Hu Q, Zhu S (1990) Induction of chromosomal aberrations in male mouse germ cells by uranyl fluoride containing enriched uranium. *Mutation Research*, 244:209-214.
- Hursh JB, Spoor NL (1973) Data on man. In: Hodge HC et al., eds. *Handbook of experimental pharmacology*. Vol. 36. *Uranium, plutonium, transplutonic elements*. Berlin, Springer-Verlag, pp. 197-240.
- Igarashi Y, Yamakawa A, Ikeda N (1987) Plutonium and uranium in Japanese human tissues. *Radioisotopes*, 36:433-439.
- Kahlos H, Asikainen M (1980) Internal radiation doses from radioactivity of drinking water in Finland. *Health Physics*, 39:108-111.
- Kreiger HL, Whittaker EL (1980) *Prescribed procedures for measurement of radioactivity in drinking water*. Washington, DC, US Environmental Protection Agency (EPA-600/4-80-032) [cited in Blanchard et al., 1985].
- Kurtio P et al. (2002) Renal effects of uranium in drinking water. *Environmental Health Perspectives*, 110:337-342.
- Landa ER, Cuncell TB (1992) Leaching of uranium from glass and ceramic foodware and decorative items. *Health Physics*, 63:343-348.

URANIUM IN DRINKING-WATER

La Touche YD, Willis DL, Dawydiak OI (1987) Absorption and biokinetics of U in rats following an oral administration of uranyl nitrate solution. *Health Physics*, 53(2):147–162.

Leggett RW (1989) The behaviour and chemical toxicity of U in the kidney: a reassessment. *Health Physics*, 57(3):365–383.

Lide DR, ed. (1992–1993) *Handbook of chemistry and physics*. Boca Raton, FL, CRC Press.

Lin RH et al. (1993) Cytogenetic toxicity of uranyl nitrate in Chinese hamster ovary cells. *Mutation Research*, 319:197–203.

Llobet JM et al. (1991) Influence of chronic exposure to uranium on male reproduction in mice. *Fundamental and Applied Toxicology*, 16:821–829.

Lucas HF, Markun F (1970) Thorium and uranium in blood, urine and cigarettes. In: *Argonne National Laboratory Radiation Physics Division annual report, Part 2*. Argonne, IL, Argonne National Laboratory, pp. 47–52 (ANL-7760).

Malenchenko AF, Barkun NA, Guseva GF (1978) Effect of uranium on the induction and course of experimental autoimmune ophthalmitis and thyroiditis. *Journal of Hygiene, Epidemiology, Microbiology and Immunology*, 22(3):268–277.

Mao Y et al. (1995) Inorganic components of drinking water and microalbuminuria. *Environmental Research*, 71:135–140.

Maynard EA, Hodge HC (1949) Studies of the toxicity of various uranium compounds when fed to experimental animals. In: Voegtlin C, ed. *Pharmacology and toxicology of uranium compounds*. New York, NY, McGraw-Hill, pp. 309–376.

Maynard EA, Downs WL, Hodge HC (1953) Oral toxicity of uranium compounds. In: Voegtlin C, Hodge HC, eds. *Pharmacology and toxicology of uranium compounds. Chronic inhalation and other studies*. New York, NY, McGraw-Hill, pp. 1121–1369.

McDonald-Taylor CK, Singh A, Gilman A (1997) Uranyl nitrate-induced proximal tubule alterations in rabbits: a quantitative analysis. *Journal of Toxicologic Pathology*, 25(4):381–389.

McDonald-Taylor CK et al. (1992) Uranyl nitrate-induced glomerular basement membrane alterations in rabbits: a quantitative analysis. *Bulletin of Environmental Contamination and Toxicology*, 48:367–373.

Moss MA (1985) *Chronic low level uranium exposure via drinking water — clinical investigations in Nova Scotia*. Halifax, Nova Scotia, Dalhousie University (M.Sc. thesis).

Moss MA et al. (1983) Uranium in drinking water — report on clinical studies in Nova Scotia. In: Brown SS, Savory J, eds. *Chemical toxicology and clinical chemistry of metals*. London, Academic Press, pp. 149–152.

Nozaki T et al. (1970) Neutron activation analysis of uranium in human bone, drinking water and daily diet. *Journal of Radioanalytical Chemistry*, 6:33–40.

OMEE (1996) *Monitoring data for uranium — 1990–1995*. Toronto, Ontario, Ontario Ministry of Environment and Energy, Ontario Drinking Water Surveillance Program.

Ortega A et al. (1989) Evaluation of the oral toxicity of uranium in a 4-week drinking-water study in rats. *Bulletin of Environmental Contamination and Toxicology*, 42:935–941.

Paternain JL et al. (1989) The effects of uranium on reproduction, gestation, and postnatal survival in mice. *Ecotoxicology and Environmental Safety*, 17:291–296.

Roessler CE et al. (1979) Uranium and radium-226 in Florida phosphate materials. *Health Physics*, 37:267–269.

Singh NP, Wrenn ME (1988) Determinations of actinides in biological and environmental samples. *The Science of the Total Environment*, 70:187–203.

Singh NP et al. (1990) Daily U intake in Utah residents from food and drinking water. *Health Physics*, 59(3):333–337.

Sontag W (1986) Multicompartment kinetic models for the metabolism of americium, plutonium and uranium in rats. *Human Toxicology*, 5:163–173.

Sullivan MF et al. (1986) Influence of oxidizing or reducing agents on gastrointestinal absorption of U, Pu, Am, Cm and Pm by rats. *Health Physics*, 50(2):223–232.

Tracy BL et al. (1992) Absorption and retention of uranium from drinking water by rats and rabbits. *Health Physics*, 62(1):65–73.

US EPA (1990) *Occurrence and exposure assessment for uranium in public drinking water supplies*. Report prepared by Wade Miller Associates, Inc. for the Office of Drinking Water, US Environmental Protection Agency, 26 April 1990 (EPA Contract No. 68-03-3514).

US EPA (1991) *Review of RSC analysis*. Report prepared by Wade Miller Associates, Inc. for the US Environmental Protection Agency, 9 May 1991 [follow-up to US EPA, 1990].

WRc (1997) *Treatment technology for aluminium, boron and uranium*. Document prepared for the World Health Organization by the Water Research Centre, Medmenham, and reviewed by S. Clark, US Environmental Protection Agency; A. van Dijk-Looijaard, Kiwa, Netherlands; and D. Green, Health Canada.

Wrenn ME et al. (1985) Metabolism of ingested U and Ra. *Health Physics*, 48:601–633.

Yuile CL (1973) Animal experiments. In: Hodge HC et al., eds. *Handbook of experimental pharmacology*. Vol. 36. *Uranium, plutonium, transplutonic elements*. Berlin, Springer-Verlag, pp. 165–195.

Zamora ML et al. (1998) Chronic ingestion of uranium in drinking water: a study of kidney bioeffects in humans. *Toxicological Sciences*, 43:68–77.