Danish Ministry of the Environment
Environmental Protection Agency

Uranium, inorganic and soluble salts

Evaluation of health hazards and proposal of a health based quality criteria for drinking water

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Uranium, inorganic and soluble salts

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Content

Preface

The Danish Environmental Protection Agency has requested an evaluation of health hazards by exposure to inorganic and soluble salts of uranium and a proposal of health based quality criteria for drinking water. This resulted in 2008 in the present report, which was prepared by Elsa Nielsen, Krestine Greve and Ole Ladefoged, Department of Toxicology and Risk Assessment, Danish Institute for Food and Veterinary Research, i.e. the present Division of Toxicology and Risk Assessment, National Food Institute, Technical University of Denmark.

The report has been subjected to review and discussion and has been endorsed by a steering committee consisting of representatives from the following Danish authorities:

The Danish Nature Agency,
The Danish Ministry of Food, Agriculture and Fisheries (The Faculty of Agricultural Sciences),
The Danish Veterinary and Food Administration,
The National Board of Health, Denmark,
Danish Regions,
The Danish Environmental Protection Agency.

The Danish Environmental Protection Agency
Copenhagen, September 2013.

General description

Uranium is a radioactive element, member of the actinide series of the periodic table and exists naturally in the oxidation states +2, +3, +4, +5 and +6. Naturally uranium is a mixture of the three isotopes ^{234}U, ^{235}U and ^{238}U (0.005%, 0.72% and 99.3% by mass, respectively), which all behave similar chemically but have different radioactive properties. They are predominantly α-emitters and decay through two different series headed by ^{235}U and ^{238}U. The half-lives of ^{234}U, ^{235}U and ^{238}U are 2.5 x 10^5, 7.1 x 10^8 and 4.5 x 10^5 years, respectively. The shorter half-life of ^{234}U makes it the most radioactive and thus about 48.9% of the radioactivity of natural uranium is accounted for by ^{234}U, 2.2% by ^{235}U and 48.9% by ^{238}U.

In this evaluation, only the chemical aspects of toxicity of soluble inorganic uranium compounds is considered, in relation to an estimation of health based quality criteria in soil and drinking water.

Natural uranium emits very small levels of radioactivity (0.68 pCi/µg) and thus, no radiological health hazard is expected following exposure. The radioactivity of Danish drinking water has been investigated and documented in the MST Working Report No. 11 2006 (Danish EPA 2006). Data on the soluble salt uranyl acetate dihydrate are included and used in relation to an estimation of health based quality criteria for soil and drinking water as the uranium ion is considered as being the reactive species. This document is based on reviews and evaluations prepared by ATSDR (1999), WHO (2001, 2004) and IRIS (2007). The most common inorganic uranium compounds are listed below (Table 1.1 and 1.2).

In this evaluation, the term "uranium" is used in a generic sense and refers to the uranium content of the various uranium salts mentioned in this document. For the purpose of comparison, concentrations and dose levels of the various uranium salts are expressed in terms of uranium equivalents (U) whenever possible.

1.1 Identity

The identity of selected inorganic soluble uranium salts is presented in Table 1.1.

Table 1.1 Identity of selected inorganic soluble uranium salts (ChemFinder, ChemIDplus Advanced, ATSDR 1999)

	Molecular formula	**Molecular weight**	**CAS-no**	**Synonym**
Uranyl nitrate hexahydrate	$UO_2(NO_3)$, $6H_2O$	502.13	13520-83-7	Bis(nitrate-O) dioxouranium, hexahydrate
Uranyl fluoride	F_2O_2U	308.03	13536-84-0	Uranium oxyfluoride
Uranium tetrachloride	UCl_4	379.84	10026-10-5	Uranium (IV) chloride
Uranyl acetate, dihydrate	$UO_2(CH_3COO)_2$, H_2O	424.15	541-09-3	Uranyl diacetate, Uranium acetate

1.2 Physical / chemical properties

The physico-chemical properties of selected inorganic soluble uranium salts are presented in Table 1.2.

Table 1.2 Physico-chemical properties of selected inorganic soluble uranium salts (ChemFinder, ChemIDplus Advanced, ATSDR 1999)

	Description	**Melting/boiling point (°C)**	**Density (g/cm^3)**	**Solubility Water (g/l)**	**Odour/taste threshold**
Uranyl nitrate hexahydrate	Solid, yellow	60.2/ Decomposes at 100	2.81 at 13 °C	Miscible in water at 60 °C, soluble in ethanol	No data
Uranyl fluoride	Solid, pale yellow	Decomposes at 300/ Not relevant	6.37	Soluble in water and ethanol	No data
Uranium tetrachloride	Solid, dark green	590/ 792	4.87	Soluble in water and ethanol	No data
uranyl acetate, dihydrate	Solid, yellow	Loses $2H_2O$ at 110, decomposes at 275	2.89 at 15 °C	0.77 at 15 °C, soluble in ethanol	No data

1.3 Production and use

There are more than 100 uranium ores, of which carnotite ($K_2(UO_2)_2(VO_4)_2 \cdot 3H_2O$), pitchblende ($UO_2+UO_3$), coffenite ($U(SiO_4)_{1-X}(OH)_{4X}$), uraninite ($UO_2+UO_3$), tobernite ($Cu(UO_2)(PO_4)_2$,$10H_2O$), autunite ($Ca(UO_2)(PO_4)_2$, $10H_2O$) and tyuyamunite ($Ca(UO_2)_2(VO_4)_2$, $5\text{-}8H_2O$) are the main ores of commercial interest. Most uranium ores contain between 0.005 and 0.2 % uranium (Uranium institute 1996 – quoted from ATSDR 1999). After mining the uranium minerals are milled to U_3O_8 (yellowcake) and other oxides and then chemically converted to UF_6 to be used in uranium enrichment plants. (ATSDR 1999).

The leftover portion in the enrichment process with less ^{235}U than normal is called depleted uranium. Depleted uranium is used in the manufacture of armour-piercing ammunition for the military, in inertial guidance devices and gyrocompasses, as counterbalances for helicopter rotors, as counterweights for aircraft control surfaces, as radiation shielding material and as x-ray targets. (EPA 1985b, USDI 1980 – quoted from ATSDR 1999).

Uranium dioxide is used to extend the lives of filaments in large incandescent lamps used in photography and motion picture projectors. In addition, uranium compounds are used in photography for toning, in the leather and wood industries for stains and dyes, and in the silk and wood industries as mordants. Uranium carbide is a good catalyst for the production of synthetic ammonia and ammonium diuranate is used to produce coloured glazes in ceramics. (Hawley 1981 – quoted from ATSDR 1999).

No Danish data are available.

1.4 Environmental occurrence and fate

Uranium is present in the earth's crust at approximately 3 mg/kg (du Preez 1989 – quoted from ATSDR 1999). It is found in varying amounts in rocks, soil, surface and underground water, air, plants and animals. Typical concentrations in most materials are a few mg/kg (ATSDR 1999).

Both anthropogenic and natural processes cause redistribution of uranium in the environment. These activities include re-suspension of soils containing uranium through wind and water erosion, volcanic eruptions, operation of coal-burning power plants, mining, milling, production of phosphate fertilizers that contains uranium and processing of uranium end products. Natural processes account for most of the redistribution of uranium in the total environment; however, industries may release large quantities of uranium in specific locations. The exchanges between air, water and soil are dependent upon factors such as chemical and physical form of the uranium compounds, environmental media, organic material present, oxidation-reduction potential, nature of sorbing materials, and size and composition of sorbing particles. (ATSDR 1999).

The uranium oxidation-reduction reactions that occur in the environment and in microbial reactions may result in the formation of complexes with organic matter (Premuzie et al. 1995 – quoted from ATSDR 1999).

1.4.1 Air

Limited information is available regarding the transformation and degradation of uranium compounds in the atmosphere. On contact with moisture in the air uranium hexafluoride (UF_6) immediately hydrolyses to form uranyl fluoride (UO_2F_2). Uranyl fluoride is a stable compound, which is soluble in water and thus will increase uranium's mobility in the environment once deposition from the air has occurred (Bostick et al. 1985 – quoted from ATSDR 1999).

Airborne uranium may deposit by wet (rain, sleet, or snow) or dry (gravitation or wind turbulence) deposition. Degree of air turbulence, particle size distribution, particle density, and chemical form determine the rate of dry deposition; particle size and solubility the rate of wet deposition. According to UNSCEAR (1988) particulate uranium in the atmosphere is assumed to behave like atmospheric dust, for which meteorological models exist. (ATDRS 1999).

In Tokyo, Japan the mean levels of uranium in ambient air have been reported to be 0.02 ng U/m^3 (Hirose and Sugimura 1981 – quoted from WHO 2004), in New York City, USA 0.076 ng U/m^3 (Fisenne et al. 1987 – quoted from WHO 2004) and in 51 urban and rural areas across the USA 0.15 to 0.40 ng U/m^3 (US EPA – quoted from WHO 2001).

No Danish data are available.

1.4.2 Water

Uranium is a naturally occurring element in groundwater. It gets into drinking water when groundwater dissolves minerals that contain uranium. The amount of uranium in well water is variable and will vary depending upon its concentration in surrounding bedrocks. (ATSDR 1999).

Uranium enters surface water by deposition of particles from air or by erosion of rock and soil. Uranium in surface water can disperse over large distances to ponds, rivers, and oceans. (Brunskill & Wilkinson 1987; Swanson 1985 – quoted from ATSDR 1999).

Uranium in water is transformed by formation of complexes and oxidation-reduction reactions. Oxidised forms of uranium are relatively soluble and can be leached from rocks to migrate in the environment. In strong reducing environments precipitation of soluble uranium will occur. (Boniforti 1987 – quoted from ATSDR).

A screening investigation of radioactivity in Danish drinking water has been carried out during 2001-2003. The samples of drinking water were collected from 296 water supplies representing more than 40% of the water delivered from water works in Denmark. Total alpha and total beta radioactivity was determined in the samples and compared with screening levels of 0.1 Bq/l total alpha and 1 Bq/l total beta radioactivity. The levels for total beta radioactivity were met in all the water works while total alpha radioactivity exceeded the screening levels for 13 water supplies near the following locations: Skjern, Ebeltoft, Grenå, Solrød, Stege, Vordingborg, Ishøj, Gedser, Jægerspris, Frederikssund, Hvidovre and Fanø. The highest levels of total alpha radioactivity in drinking water were found at Grenå and Ebeltoft with levels up to 0.13 Bq/l and in Frederikssund with levels up to 0.2 Bq/l. The waterworks in these areas were subject to a closer investigation with repeated sampling from individual boreholes and determination of total alpha and beta radioactivity including uranium and radium in these samples. The results demonstrated that the increased alpha radioactivity was due mainly to uranium in the drinking water. The variation of uranium concentrations was large between different boreholes from the same area. At Grenå (11 boreholes) the concentrations of ^{234}U and ^{238}U were found in the range 0.021-0.14 Bq/l (2-10 µg/l), in Ebeltoft (6 boreholes) in the range 0.008-0.27 Bq/l (0.8-2 µg/l), and in Frederikssund (13 boreholes) in the range 0.00002-0.22 Bq/l (2 ng/l - 15 µg/l). (Danish EPA 2006).

Of 476 Norwegian groundwater samples, 18% were found to have uranium concentration in excess of 20 µg U/l (Frengstad et al. 2000 – quoted from WHO 2004). Concentrations in excess of 20 µg U/l have also been reported in groundwater from parts of New Mexico, USA (Hakonson-Hayes et al. 2002 – quoted from WHO 2004) and central Australia (Hostetler et al. 1998, Fitzgerald et al. 1999 – quoted from WHO 2004).

United Kingdom surveys of 35 groundwater and spring waters samples showed uranium concentrations in the range <0.1 to 10 µg/l (Edmunds et al. 1989 – quoted from WHO 2001).

From 130 sites in Ontario, Canada, the average uranium concentrations in treated drinking water were reported to be in the range of 0.05 to 4.21 µg U/l (OMEE 1996 – quoted from WHO 2004). In private supplies in Canada uranium concentrations of up to 700 µg U/l have been found (Moss et al. 1983, Moss 1985 – quoted from WHO 2004).

In New York City, USA, the mean concentration of uranium in drinking water ranged from 0.03 to 0.08 µg U/l (Fisenne & Welford 1986 – quoted from WHO 2004). From 978 sites in the USA a mean uranium concentration of 2.5 µg U/l was reported (US EPA 1990, 1991 – quoted from WHO 2004).

In five Japanese cities, the mean level in portable water supplies was 0.9 ng U/l (Nozaki et al. 1970 – quoted from WHO 2004).

1.4.3 Soil

The concentration in soil varies and reflects the abundance of uranium in the parent geological materials from which the soils were formed and soil development processes (WHO 2001).

Uranium deposited on land can be reincorporated into soil, re-suspended in the atmosphere, washed from the land into surface water, incorporated into groundwater, or deposited on or adsorbed onto plant roots. Little or none uranium enters the plant through leaves or roots. (Van Netten & Morley 1983 – quoted from ATSDR 1999).

Uranium may not leach readily from soil surface to groundwater in soils containing clay and iron oxide. Significant reactions of uranium in soil are formation of complexes with anions and ligands or humic acid, and reduction of U^{+6} to U^{+4} (Allard et al. 1982, Brunskill & Wilkinson 1987, Herczeg et al. 1988, Premuzie et al. 1995, Sheppard et al. 1987 – quoted from ATSDR 1999).

In the United Kingdom concentrations of uranium ranged from 0.05 to 76 mg/kg in profile soils over central and eastern England. Urban soils sampled in 5 major cities ranged from 0.25 to 5.5 mg U/kg in topsoil and 0.25 to 9.2 mg U/kg in profile soil. There is no information whether the concentrations are average, median or percentiles (British Geological Survey 1997 – quoted from WHO 2001).

The concentration of uranium in phosphate rock from Florida, Texas and south-eastern Idaho for production of phosphorous used in phosphate fertilizers is 120 mg U/kg (NCRP 1975 – quoted from ATSDR 1999).

The average concentration of natural uranium in the U.S. soil is approximately 0.003 mg U/g (du Preez 189, NCRP 1984a – quoted from ATSDR 1999). In some parts of the U.S. the uranium levels is higher due to natural geological formations. Concentrations of uranium in Louisiana soils ranged from 0.0024 to 0.0040 mg U/g (Meriwether et al. 1988 – quoted from ATSDR 1999). The concentrations of uranium in soil samples taken adjacent to Los Alamos, New Mexico during 1974–1977 ranged from 0.0001 to 0.0051 mg U/g with a mean concentration of 0.0024 mg U/g (Purtymun et al. 1987 – quoted from ATSDR 1999).

No Danish data are available.

1.4.4 Bioaccumulation

Bioconcentration factors (BCFs) for uranium not exceeding a value of 38 were observed in fish. The highest BCF values were observed in fillet of rainbow trout (*Salmo gairdneri*), white and finescale suckers (*Castastomus catactomus*), and lake whitefish (*C. clupeaformis*) (Mahon 1982, Poston 1982, Swanson 1983, 1985 – quoted from ATSDR 1999).

BCF values for uranium of 1,576 and 459 have been measured in algae and plankton, respectively (Mahon 1982 – quoted from ATSDR 1999).

Concentration ratio (CR) values for plant/soil interaction were reported in the range 0.0025–0.81 (Garten 1978, Ibrahim & Wicker 1988, Mortvedt 1994 – quoted from ATSDR 1999). Some studies indicate that CR values in plants do not vary linearly with the concentration of uranium in the soil (Mortvedt 1994 – quoted from

ATSDR 1999); other reported studies show a linear relationship between plant content and soil content of uranium (NCRP 1984a – quoted from ATSDR 1999).

1.4.5 Foodstuffs

The highest concentrations of uranium in foodstuffs are observed in shellfish, molluscs and winkles (9.5 to 31 µg U/kg). Lower levels have been observed in fresh vegetables and bread (approximately 2 µg U/kg). Uranium concentrations in foods such as rice and meat are in the range 0.1 to 0.2 µg U/kg (WHO 2001).

Concentrations of uranium in nine different prepared beverages, including tea and coffee, was found to be in the range of 0.26 to 1.7 µg U/l (Cheng et al. 1993 – quoted from WHO 2001).

1.5 Human exposure

Human exposure to uranium can result from consumption of food and drinking water, inhalation of air or incidental ingestion of soil or dust contaminated with uranium.

Using the highest reported concentration of ^{234}U and ^{238}U in Danish drinking water of about 15 µg/l (Danish EPA 2006), and the consumption rate of 0.08 l/kg bw/day (for children 1-10 years old), the intake from drinking water would be 1.2 µg uranium/kg bw/day. For an adult (body weight of 70 kg),the daily exposure of uranium from drinking water would be 84 µg.

According to the WHO, the average per capita intake of uranium in food has been reported to be 1.3 µg/day (Fisenne et al. 1978 – quoted from WHO 2004) and 2-3 µg/day (Singh et al. 1990 – quoted from WHO 2004) in USA and 1.5 µg/day in Japan (Nozaki et al 1970 – quoted from WHO 2004).

Estimates of dietary intakes of uranium in several European countries ranged between 0.5 and 2 µg/day, for instance 0.5 to 0.9 µg/day in the UK (Harley 1998 – quoted from WHO 2001).

As uranium is adsorbed onto the roots of plants, unwashed potatoes, radishes, and other root vegetables, are a primary source of uranium in the diet. Based on consumption rates, root crops such as potatoes, parsnips, turnips, and sweet potatoes contribute approximately 38% of total dietary intake of uranium. Cutting away or thorough cleansing the outer membrane on root vegetables may remove all or most of the uranium. (EPA 1985j, Welford & Baird 1967 – quoted from ATSDR 1999).

The uptake of uranium by the inhalation route has been estimated to be 10 ng/day (Cothern 1987 – quoted from ATSDR 1999) and 1.0 ng/day (UNSCEAR 1988 – quoted from ATSDR 1999).

Using the mean level of uranium in air reported to be 0.076 ng U/m^3 in New York City (Fisenne et al 1987 – quoted from WHO 2004), and assuming the inhalation rate as 0.5 m^3/kg bw/day (for children 1-5 years old), the inhalation exposure of uranium will be 0.038 ng uranium/ kg bw/day. For an adult (body weight of 70 kg), the daily exposure of uranium from air would be 2.66 µg.

2 Toxicokinetics

2.1 Absorption, distribution and excretion

Absorption of uranium is low by all exposure routes depending on the solubility of the uranium compound. Generally absorption increases with increasing solubility (ATSDR 1999).
In humans, absorbed uranium is found in all tissues regardless of the route of exposure. The body burden is considered to be approximately 90 µg. About 66% of this is in bone, 16% in the liver, 8% in the kidneys, and 10% in other tissues (ICRP 1979, 1995, 1996 – quoted from ATSDR 1999).

Mean concentrations of uranium were measured in the organs of persons representing all age groups from different parts of the United States. The uranium values for lungs, liver, kidney, and bone (vertebrae, rib, and skeleton) were 0.5–1.17 µg/kg, 0.12–0.33 µg/kg, 0.39–1.00 µg/kg and 0.25–1.9 µg/kg, respectively (Fisenne et al.1988, Fisenne & Welford 1986, Singh et al. 1986b – quoted from ATSDR 1999).

The concentrations of uranium in human blood from New York City donors averaged 0.14 mg U/kg in both whole blood and red cells. Globally values ranged from <0.04 to 86 mg U/kg (Fisenne & Perry 1985 – quoted from ATSDR 1999).

In rats, the half-life of uranium was estimated to be approximately 15 days in the kidneys. The clearance from the skeleton was estimated based on a two-compartment model and was 300 and 5000 days. (Wrenn er al. 1985 – quoted from WHO 2004).

In a study in rats, using a 10-compartment model, the overall half-lives for the clearance of uranium from the rat kidney and skeleton were estimated to be 5-11 days and 93-165 days, respectively (Sontag 1986 – quoted from WHO 2004).

In humans, the overall elimination half-life of uranium under conditions of normal daily intake was estimated to be in the range 180-360 days (Berlin & Rudell 1986 – quoted from WHO 2004).

2.1.1 Inhalation

In uranium mill workers, the absorption of uranium into the blood was derived from excretion data. The daily mean absorption of inhaled uranium was estimated to be 0.76% (range 0.4-1.6%) (Wrenn et al. 1985 – quoted from ATSDR 1999).

In active uranium mill crushermen exposed to ore dust, analysis of excreta indicated that 1-5% of uranium was excreted in the urine, and 95-99% was eliminated in the faeces. Absorption could have taken place in the lungs or in the gastrointestinal tract from swallowed particles cleared from the lungs (Fisher et al. 1983 – quoted from ATSDR 1999).

In animal studies, the solubility of the uranium compound and the size of the inhaled particles determined absorption. Reported absorption of inhaled aerosols of purified uranium compounds was 18-40% in rats and 20-31% in guinea pigs for

uranium hexafluoride. The amount of the intake distributed to the skeleton was reported to be 28-78% in rats and 34-43% in guinea pigs. (Leach et al. 1984 – quoted from ATSDR 1999).

2.1.2 Oral intake

In humans, the average gastrointestinal absorption of uranium is 1-2%, depending on the solubility of the uranium compound, previous food consumption and concomitant exposure to oxidising agents (Wrenn et al. 1985 - quoted from WHO 2004).

In four males, ingesting 10.8 mg uranium in a soft drink, absorptions were reported to be in the range 0.5-5% (Hursh et al. 1969 – quoted from ATSDR 1999).

In 12 volunteers, given drinking water high in uranium, absorptions were reported to be less than 0.25-4% (Wrenn et al. 1989 – quoted from ATSDR 1999).

In animals, absorption of uranium generally increases with increasing solubility of the uranium compound. ICRP determined that an absorption of 2% for soluble compounds and 0.2% for insoluble compounds should be used in modelling the kinetics of dietary uranium in humans (ICRP 1995 – quoted from ATSDR 1999).

In rats and rabbits fed ad libitum and having free access to drinking-water containing uranyl nitrate hexahydrate (up to 600 mg/l, up to 91 days), 0.06% of ingested uranium was absorbed (Tracy et al., 1992 - quoted from WHO 2004).

In rats, 99% of ingested uranium was not absorbed but was eliminated in the faeces. Most of the absorbed uranium leaved the body within a few days in urine with a half-life of 2–6 days (Durbin & Wrenn 1975 – quoted from ATSDR 1999).

In neonatal rats and pigs, the absorption of uranium was increased when compared to adults. Absorption in 2-day-old rats given uranyl nitrate was estimated to be 1-7%, two orders of magnitude greater than for adults (ICRP 1995 – quoted from ATSDR 1999). According to another study in rats, exposed by gavage to uranyl nitrate hexahydrate, absorption of uranium increased 3.6 times in neonates as compared to adults (Sullivan 1980b – quoted from ATSDR 1999).

In animals, absorbed uranium accumulates largely on the surface of all types of bone. Uranium on the bone surface may diffuse into the mineral portion of the bone. Autoradiography provides confirming evidence that, in the long term, uranium accumulates in the bones (Wrenn et al. 1987 – quoted from ATSDR 1999).

2.1.3 Dermal contact

No human data on absorption of uranium through the skin have been found.

In rats, electron microscopy and X-ray microanalytical methods showed that uranium as uranyl nitrate hexahydrate penetrated the stratum corneum within 15 minutes and accumulated in the intracellular space between the viable epidermis and the stratum corneum. After 48 hours, uranium was no longer found in the skin and toxicity developed, indicating that the uranium had been absorbed into the blood. No penetration was observed with the insoluble compounds uranium dioxide, uranyl acetate, or ammonium diuranate. (De Rey et al. 1983 – quoted from ATSDR 1999).

2.2 Mode of action

In the blood, uranium usually complexes with citrate, bicarbonate or protein, and is transported to the kidneys where it is released and accumulates in the renal tubular epithelium by forming complexes with phosphate ligands and proteins. This induces cellular necrosis, and atrophy in the tubular wall, resulting in decreased re-absorption efficiency in the renal tubule. Uranium is not tightly bound and is released again within a few days. Within a week following exposure, most uranium is cleared from the kidneys, and the tubules begin to regenerate. Although the regenerated epithelium show histological differences from its normal state, it is often difficult to detect histological signs of kidney damage a month after exposure because all remaining functional damage is subtle. Uranyl ions are also effective in delaying or blocking the cell division process, thereby magnifying the effects of cell necrosis (Brady et al. 1989 – quoted from ATSDR 1999).

In another proposed mechanism for renal toxicity, uranyl ion inhibits both sodium ion transport-dependent and sodium ion transport-independent ATP utilization as well as mitochondrial oxidative phosphorylation in the renal proximal tubule leading to kidney damage (Leggett, 1989, Domingo, 1995 - quoted from WHO 2004).

Uranyl nitrate has been shown to be cytotoxic and genotoxic in Chinese hamster ovary cells. It has been suggested that the genotoxic effects occur through the binding of the uranyl nitrate to the phosphate groups of DNA, and that this may be a possible mechanism for the teratogenic effects observed following uranium exposure (Lin et al. 1993 - quoted from WHO 2004).

Tolerance may develop following repeated exposure to uranium; however, this tolerance does not prevent chronic damage to the kidney (Leggett 1989 - quoted from WHO 2004). 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. Persistent ultrastructural changes in the proximal tubules of rabbits have also been reported to be associated with the ability of the kidney to store uranium (McDonald-Taylor et al. 1992, 1997 - quoted from WHO 2004).

Uranium also accumulates in the skeleton, where the uranyl ion exchanges with Ca^{2+} on the surfaces of bone mineral crystals, although it does not participate in crystal formation or enter existing crystals. Uranium initially deposits on all bone surfaces but is most highly concentrated in areas of growth. Depending on the microscopic structure of the bone of each species, uranium on bone surfaces may gradually diffuse into bone volume (ICRP 1995 – quoted from ATSDR 1999).

Uranium has a low specific activity but emits high LET (linear energy transfer) alpha particles that are densely ionizing along their track length. The alpha particles from uranium travel through 40–70 μm in soft tissue, incrementally transferring their kinetic energy to the series of atoms and molecules with which they interact along their short, straight paths. Consequently, structures within this range from the site of the deposition of uranium may be affected. If a DNA molecule is intersected and damaged without resulting in cell death, a range of theoretical effects can result. DNA has been found to be the most radiosensitive biological molecule, and ionizing radiation has been observed to damage individual chromosomes. The main result from low level ionizing radiation exposure is DNA damage or fragmentation. Viable cells repair the damage, but repair errors can result which produce gene mutations or chromosomal aberrations. Such events may

result in such highly rare events as carcinogenesis or teratogenesis, but there is currently no evidence for radiation mutagenesis in humans. Chromosomal aberrations following large radiation doses have been demonstrated in humans and in research animals, showing that ionizing radiation can both initiate and promote carcinogenesis, and interfere with reproduction and development. Cancer is a well-known effect of ionizing radiation exposure, but it has never been associated with exposure to uranium. Likewise, no genetic changes due to radiation have ever been observed in any human population exposed at any dose (BEIR 1980, 1988, 1990, Leach et al. 1970, Morris et al. 1990, Muller et al. 1967, Otake and Schull 1984, Sanders 1986, Stokinger et al. 1953, UNSCEAR 1982, 1986, 1988 – quoted from ATSDR 1999).

The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) has stated that limits for natural (and depleted) uranium in drinking water (the most important source of human exposure) should be based on the chemical toxicity rather than on a hypothetical radiological toxicity in skeletal tissues, which has not been observed in either humans or animals (Wrenn et al. 1985). The US-EPA also used chemical toxicity as the basis for their 20 µg/L interim drinking water limit for uranium published in 1991 (currently withdrawn) (ATSDR 1999).

3 Human toxicity

3.1 Single dose toxicity

In a male worker at a uranium enrichment plant, accidentally exposed by inhalation to a high concentration of uranium tetrafluoride, delayed renal effects were observed beginning at post-accident day 68 as indicated by significantly elevated levels of urinary proteins, nonprotein nitrogen, amino acid nitrogen/creatinine, and decreased phenolsulfonpthalein excretion rate. These abnormalities persisted through day 1065 but gradually returned to normal values. From the 6th to the 8th day nausea, loss of appetite, abdominal pain, diarrhea, tenesmus, and pus and blood in the stool were reported. (Lu & Zhao 1990 – quoted from ATSDR 1999, WHO 2001).

In a male that deliberately ingested 15 g (approximately 131 mg/kg bw) uranyl acetate along with benzodiazepine (unknown quantity), a diagnosis of acute nephrotxicity from heavy metal exposure was made 16 hours after admission. After 6 month the patient still suffered from renal tubular acidosis. Myocarditis and increasing rhabdomyolysis and liver dysfunction were reported up to 6 month post-exposure. (Pavlakis et al. 1996 – quoted from ATSDR 1999).

A volunteer given a single oral dose of 1 g uranyl nitrate (14.3 mg/kg) and observed for clinical signs and symptoms within 24 hours after intake suffered acute nausea, vomiting, and diarrhoea within a few hours of administration. All clinical signs returned to normal within 24 hours after administration. (Butterworth 1955 – quoted from ATSDR 1999).

Elevations in urinary excretion of catalase, albumin and non-protein nitrogen, and casts in the urine were noted in terminal brain tumour patients injected a single dose of 120 µg U/kg. Trace changes in urinary catalase were noted in patients injected with uranyl nitrate 55 or 71 µg U/kg. (Lussenhop et al. 1958, Hursh & Spoor 1973 – quoted from IRIS 2007).

3.2 Irritation

No dermal effects were found in a man accidentally exposed to powdered uranium tetrafluoride for 5 minutes (Lu & Zhao 1990 – quoted from ATSDR 1999, WHO 2001).

3.3 Sensitisation

No data have been located.

3.4 Repeated dose toxicity

3.4.1 Inhalation

In uranium miners who worked for <5–20 years (ambient uranium concentration not known), small but significant decreases in the haemoglobin concentration and

the mean corpuscular haemoglobin concentration and significant increases in red blood cells counts and mean corpuscular volume were found; however, all values were within the normal range (Vich & Kriklava 1970 – quoted from ATSDR 1999).

Uranium mill workers exposed for more than a year to insoluble uranium dioxide dust (concentrations exceeding the occupational standard) had renal tubular dysfunction, manifested by mild proteinuria, aminoaciduria and a concentration-related clearance of ß-2-microglobulin relative to that of creatinine when compared to a referent group of cement workers. The incidence and severity of these nephrotoxic signs correlated with the length of time that the uranium workers had spent in the area where insoluble uranium oxide yellowcake was dried and packaged. According to WHO the data from this study are indicative of reduced re-absorption in the proximal renal tubules (Saccomanno et al. 1982, Thun et al. 1985 – quoted from ATSDR 1999, WHO 2001).

3.4.2 Oral intake

Clinical studies were performed on 324 persons in Canada, 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 ß-2-microglobulin and increasing concentration of uranium in well water was observed. 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, according to WHO, that the suspected tubular defect might well be rapidly reversible. (Moss et al. 1983, Moss 1985 – quoted from WHO 2004).

A pilot study was conducted in Canada, with 100 participants in three different areas with mean uranium levels in drinking water of 0.71 (control, range 0.48-0.74 µg/l), 15 µg/l (range <0.1-50 µg/l) and 20 µg/l (range <0.1-48 µg/l). 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. Urine albumin levels ranged from 0.165 to 16.1 mg/mmol creatinine, with eight participants having elevated urine albumin concentrations (>3.0 mg/mmol creatinine). Three participants had serum creatinine concentrations of >120 µmol/litre, which is reportedly indicative of prevalent renal damage. According to the authors, microalbuminuria has been shown to be a sensitive indicator of early renal disease. (Mao et al. 1995 – quoted from WHO 2001, 2004, Livsmedelsverket 2005).

A study was conducted in Canada, on two groups of subjects with chronic exposure to uranium in drinking water. All individuals who had a uranium concentration in their drinking water of <1 µg U/l (0.02+/-0.004 µg U/l) were pooled in a low-exposure group (20 persons) and all with a uranium concentration of > 1 µg (U/l to 2–781 µg/l) in a high-exposure group (30 persons). Duplicate portions of food and water were collected for 3 days and urine was analysed. In the high exposure group, uranium intake ranged from 3 to 570 µg/day of which 31-98% was from water. In the low exposure group, uranium intake ranged from 0.32 to 20 µg/day of which 1-9% was from water. There were significant correlations between uranium

intake and urinary glucose, alkaline phosphatase (ALP) and ß-microglobulin (BMG). The authors concluded that the concentrations observed in the study affected kidney function at the proximal tubule. According to Livsmedelsverket, the findings of the exposure-related effects on the excretion of glucose, BMG and ALP are in principle compatible with a discrete effect on renal tubule at uranium concentrations in water of less than 780 µg/l; however, they are not conclusive. (Zamora et al. 1998 – quoted from WHO 2004, Livsmedelsverket 2005).

In a study on a Finnish population (798 households in 28 towns) exposed to well water containing a median uranium concentration of 28 µg/litre, individuals were examined for signs of adverse renal effects. Uranium in urine was significantly associated with increased excretion of calcium, phosphate and glucose, but uranium in drinking water was significantly associated only with excretion of calcium. According to WHO, the data were consistent with signs of modest alterations in proximal tubular function, but there was no indication of any effect on glomerular function. The authors concluded that the clinical significance of the results could not be easily established, since tubular dysfunction occurred within the normal physiological range. (Kurttio et al. 2002 - quoted from WHO 2004, Livsmedelsverket 2005).

3.4.3 Dermal contact

No data have been located.

3.5 Toxicity to reproduction

Studies of a mining population were located that associated reproductive effects in humans following inhalation exposure to uranium. The studies reported that male uranium miners were found to have more first-born female children than expected, suggesting that uranium's alpha radiation damaged the y-chromosomes of the miners. It is not certain if the effect described is from exposure to uranium because the workers were also exposed to ^{222}Rn, chlorine, hydrofluoric acid, lead sulphate, nickel, nitric acid and nitrogen oxides, silicon dioxide, and sulphuric acid. ((Muller et al. 1967, Waxweiler et al. 1981b, Wiese 1981, Dupree et al. 1987 – quoted from ATSDR 1999).

3.6 Mutagenic and genotoxic effects

In a study with uranium miners in Czechoslovakia, no increased incidence of aberrant DNA or chromosomes attributable to exposure to uranium was found (Sram et al. 1993 – quoted from ATSDR 1999).

A cytogenic study of male workers occupationally exposed to uranium found higher levels of chromosome aberrations in the miners than in controls. The investigators of this study concluded that this increase may be attributable to smoking. In addition, because the miners were also concurrently exposed to chlorine, hydrofluoric acid, lead sulphate, nickel, nitric acid and nitrogen oxides, silicon dioxide, diesel smoke, and sulphuric acid in addition to ^{222}Rn, it is unlikely that the effects described in these studies were related in any way to exposure to uranium (Martin et al. 1991, Dupree et al. 1987 – quoted from ATSDR 1999).

Uranium is a predominantly alpha-emitting radionuclide and current theories on gene mutation and chromosomal aberrations by high-LET alpha radiation suggest a potential for genotoxicity from uranium's radioactivity (BEIR 1980, 1988, 1990,

Leach et al. 1970, Morris et al. 1990, Muller et al. 1967, Otake & Schull 1984, Sanders 1986, Stokinger et al. 1953, UNSCEAR 1982, 1986, 1988 – quoted from ATSDR 1999).

3.7 Carcinogenic effects

Several studies on uranium miners found increased incidences of deaths from lung cancer. The miners were concurrently exposed to known cancer-inducing agents like tobacco smoke, radon, silica and other dusts and diesel engine exhaust fumes (Archer et al. 1973a, Auerbach et al. 1978, Band et al. 1980, Gottlieb and Husen 1982, Kusiak et al. 1993, Lundin et al. 1969, Saccomanno et al. 1971, 1976, 1986, Samet et al. 1984, Whittemore and McMillan 1983 – quoted from ATSDR 1999).

No carcinogenic effects have been reported in humans following ingestion of uranium compounds (ATSDR 1999).

4 Animal toxicity

4.1 Single dose toxicity

4.1.1 Inhalation

Long-Evans rats and Hartley guinea pigs were exposed to uranium hexafluoride, nose-only, for up to 10 minutes and observed for 14 days. An LC_{50}-value in guinea pigs of 35011 mg U/m^3 was estimated for a 2-minute inhalation exposure. In rats an LC_{50}-value of 26098 mg U/m^3 was estimated for a 5-minute inhalation exposure and a LC_{50}-value of 8114 mg U/m^3 for a 10-minute inhalation exposure. Urinalysis and histopathological examination indicated that renal injury was the primary cause of death. Nasal haemorrhage was reported in rats after a 5-minute inhalation exposure to 54,503 mg U/m^3. (Leach et al. 1984 – quoted from ATSDR 1999).

For uranium hexafluoride, the mortality in rats, mice, and guinea pigs was 10, 20, and 13%, respectively, following a 10-minute inhalation exposure of 637 mg U/m^3. Gasping and severe irritation to the nasal passages were reported after 10 minutes. Severe degeneration of the cortical tubules was reported after 5–8 days in rats. (Spiegl 1949 – quoted from ATSDR 1999).

4.1.2 Oral intake

For uranyl acetate dihydrate, oral LD_{50}-values in male rats and male mice were reported to be 114 and 136 mg U/kg bw, respectively, following single gavage administrations. No adverse effects on the respiratory system were reported in rats given a single dose of118 mg U/kg bw. Slight renal dysfunction and minimal microscopic lesions in the tubular epithelium were observed in rats given a single dose of 5.6 mg U/kg. Microhaemorrhagic foci in the liver were observed in rats given a single dose of 5.6 or 118 U/kg bw. Rats given single gavage doses (11-717 mg U/kg bw) of uranyl acetate dihydrate showed piloerection, tremors, hypothermia, pupillary size decreases and exophthalmos at all dose levels. The signs became more severe as the number of days post-treatment increased. (Domingo et al. 1987 – quoted from ATSDR 1999, WHO 2001).

4.1.3 Dermal contact

For uranyl nitrate hexahydrate, dermal LD_{50}-values in New Zealand rabbits, guinea pigs and mice was reported to be 28, 1190 and 4286 mg U/kg bw, respectively, in an ethereal solution after 4-hour exposures followed by washing with detergent and a 30-day observation period. According to the citation in ATSDR, insufficient fatalities occurred to calculate an LD_{50} value for rats, but the mortality curve fell between that of the rabbits and the guinea pigs. Deaths mainly occurred 5 to 7 days after exposure and were due to renal failure. (Orcutt 1949 – quoted from ATSDR 1999).

In rabbits, 4-hour exposures to uranium compounds using a lanolin vehicle showed that water-soluble compounds (uranyl fluoride, uranium tetrachloride, uranium pentachloride) were the most toxic; the slightly soluble compounds (uranium trioxide, sodium diuranate, ammonium diuranate) were less toxic, and the water

insoluble compounds (uranium tetrafluoride, uranium dioxide, uranium peroxide, triuranium octoxide) caused no deaths. Rabbits exposed to a single dermal dose of 1.4, 3, 6, 30, or 85 mg U/kg as uranyl nitrate hexahydrate, showed neurological signs including irritability, hyperactivity, upset equilibrium, limb rigidity, and respiratory arrest at all doses tested. (Orcutt 1949 – quoted from ATSDR 1999).

4.2 Irritation

4.2.1 Skin irritation

Uranium pentachloride produced mild skin irritation when 41 mg U/kg bw was applied to the shaved backs of New Zealand white rabbits. Uranyl nitrate hexahydrate produced superficial coagulation necrosis and inflammation of the epidermis when 56.4 mg U/kg bw was dermally applied to New Zealand white rabbits. A dose of 4.2 mg U/kg bw as uranyl nitrate hexahydrate dermally applied for 5 weeks resulted in severe dermal ulcers (no untreated controls were used). A single application of 1.4 mg U/kg bw as uranyl nitrate hexahydrate resulted in moderate erythema in male and female rabbits. (Orcutt 1949 – quoted from ATSDR 1999).

Ammonium diuranate resulted in mild lesions when a dose of 2670 mg U/kg bw was applied to the shaved backs of rats for 10 days, while a dose of 237 mg U/kg as uranyl nitrate hexahydrate resulted in disrupted membranes in the cell, mitochondria, and cell nucleus, as revealed by transmission electron microscopy (TEM). Light microscopy revealed swollen and vacuolated epidermal cells and damage to hair follicles and sebaceous glands in the uranyl nitrate hexahydrate-treated animals. A dose of 3929 mg U/kg bw as uranyl acetate dihydrate or 2103 mg U/kg bw as ammonium uranyl tricarbonate in water-Vaseline® emulsion to backs of 20 male Wistar rats in 10 daily applications had no effect on the skin of the rats. (De Rey et al. 1983 – quoted from ATSDR 1999).

4.2.2 Eye irritation

Conjunctivitis and eye irritation have been reported in animals after exposure to uranium hexafluoride and to uranium tetrachloride (Spiegl 1949, Dygert 1949a – quoted from ATSDR 1999).

4.3 Sensitisation

No data have been found.

4.4 Repeated dose toxicity

The toxicity of uranium compounds following repeated exposure have been extensively studied in a number of animal species using inhalation (rat, mouse, rabbit, guinea pig, dog, cat, monkey), oral (rat, mouse, rabbit, dog) and dermal (guinea pig, rabbit) routes, in studies with durations ranging from 5 days to 5 years. Inhalation and dermal repeated dose studies are only briefly described in each of its sections with a focus on renal effects. Further details of uranium toxicity following inhalation or dermal application can be found in ATSDR (1999). Oral repeated dose studies are briefly described with a focus on renal effects. In addition the most relevant and valid oral repeated dose studies are selected for a more detailed description. Details of all oral studies can be found in ATSDR (1999) and WHO (2004).

4.4.1 Inhalation

Following inhalation, renal toxicity has been observed in rats at exposure concentrations from 0.13 mg U/m^3 (slight tubular degeneration – uranyl nitrate hexahydrate for 30 days, lowest concentration in the study, Roberts 1949), in mice from 2.9 mg U/m^3 (slight tubular degeneration – carnotite uranium ore for 30 days, only concentration in the study, Pozzani 1949), in rabbits from 0.13 mg U/m^3 (increased urinary catalase – uranyl nitrate hexahydrate for 30 days, lowest concentration in the study, Roberts 1949), in guinea pigs from 0.2 mg U/m^3 (minimal microscopic lesions in tubular epithelium – uranium tetrachloride for 34 weeks, only concentration in the study, Stokinger 1953), in dogs from 0.05 mg U/m^3 (minimal microscopic lesions in renal tubule – uranium hexafluoride for 1 year, lowest concentration in the study, Stokinger 1953), and in cats from 9.2 mg U/m^3 (severe degeneration of renal tubular epithelium – uranyl fluoride for 5 weeks, Rothstein 1949a). No renal effects were observed in monkeys exposed to 5.1 mg U/m^3 uranium dioxide for 5 years. (All references quoted in ATSDR 1999).

4.4.2 Oral

Following oral administration (dietary, drinking water, gavage), renal toxicity has been observed in rats at dose levels from 0.06 mg U/ kg bw/day (lesions of the tubules, glomeruli and interstitium – uranyl nitrate hexahydrate in drinking water for 91 days, Gilman et al. 1998a), in mice from 452 mg U/ kg bw/day (nodular development on surface – uranyl fluoride in diet for 48 days, lowest dose in the study, Tannenbaum and Silverstone 1951), in rabbits from 0.05 mg U/ kg bw/day (Anisokaryosis, nuclear vesiculation – uranyl nitrate hexahydrate in drinking water for 91 days, lowest dose in the study, Gilman et al. 1998b) and in dogs from 15.4 mg U/ kg bw/day (moderate degeneration in tubular epithelium – uranyl fluoride in diet for 30 days; Maynard & Hodge 1949). (All references quoted in ATSDR 1999 or WHO 2004).

Selected oral repeated dose studies on uranium compounds are summarised in Table 4.4.3 and supplementary information on the studies is given in the text. The NOAELs and LOAELs presented in this section are those stated in the reviews and criteria documents.

<u>Rats, 91 days, uranyl nitrate hexahydrate (Gilman et al. 1998a – quoted from WHO 2004, ATSDR 1999)</u>
Test dose levels were females: <0.0001 (control), 0.09, 0.42, 2.01, 9.98, 53.6 mg U/kg bw/day, males: <0.0001 8control), 0.06, 0.31, 1.52, 7.54, 36.7 mg U/kg bw/day. Histopathological changes were observed mainly in the liver, thyroid and kidney. Statistically significant treatment-related kidney lesions, reported at all doses in males, included nuclear vesiculation, cytoplasmic vacuolation and tubular dilatation. Other statistically significant lesions in males (0.31 mg U/kg bw/day) included glomerular adhesions, apical displacement of the proximal tubular epithelial nuclei and cytoplasmic degranulation. Statistically significant changes in the kidney of females included nuclear vesiculation of the tubular epithelial nuclei (all doses) and anisokaryosis (all doses except 0.42 mg/kg bw/day). Capsular sclerosis of glomeruli and reticulin sclerosis of the interstitial membranes occurred in all dose groups.

Table 4.4.3 Animal repeated dose toxicity studies on uranium, oral administration

Species/strain	Duration/ Dose levels/ Chemical form	Effects (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Reference
Rat (10 ♂, 10 ♀) Sprague-Dawley	4 weeks ♀: 0, 0.07, 0.33, 1.65, 7.82, 40 mg U/kg bw/day ♂: 0, 0.05, 0.27, 1.34, 6.65, 35.3 mg U/kg bw/day uranyl nitrate hexahydrate in drinking water	No clinical signs. No dose-related effects on haematological parameters. No significant histopathological or weights change in lung, heart, stomach, intestinal, liver, kidney, adrenal, pancreas, parathyroid, pituitary, thymus or thyroid. No effects on brain, haematological parameters or the musculoskeletal system. No significant dose-related effects on body weight gain or food and water intake. 40: ↑ Serum uric acid (39%) (♀) ↑ Uranium level in kidney and bone tissue, significant (♀) (not measured in ♂)	35.3 (♂), 40 (♀) (resp, cardio, gastro, haemato, musc, hepatic, endocr, bd wt, immun, neuro, repro) (ATSDR)	40 (renal (♀))	Gilman et al.1998a – in ATSDR 1999 and WHO 2001, 2004
Rat (15 ♂, 15 ♀) Sprague-Dawley	91 days ♀: 0, 0.09, 0.42, 2.01, 9.98, 53.6 mg U/kg bw/day ♂: 0, 0.06, 0.31, 1.52, 7.54, 36.7 mg U/kg bw/day uranyl nitrate hexahydrate in drinking water	No treatment-related clinical signs. No significant effects on body weight gain, food and water intake. No significant dose-related relative weight change in kidneys. No dose-related effect on haematological parameters. 0.06 (♂), 0.09 (♀): Liver lesions, including accentuation of zonation and anisokaryosis, significant. Renal lesions of the tubules, glomeruli and enterstitium. 0.31 (♂), 2.01 (♀): Multifocal reduction of follicular size, increased epithelial height in thyroid. ↓ Amount and density of colloid in thyroids (♂). 7.54 (♂), 9.98 (♀): ↑ Terminal body weights, significant (♀).	0.06 (♂), 0.42 (♀) (endocr) (ATSDR) 7.54 (♂), 9.98 (♀) (immun) (ATSDR) 36.7 (♂), 53.6 (♀) (resp, cardio, gastro, haemato, musc, bd wt, neuro, repro) (ATSDR)	0.06 (♂), 0.09 (♀) (hepatic, renal) (ATSDR, WHO) 0.31 (♂) 2.01 (♀) (endocr) (ATSDR) 36.7(♂), 53.6 (♀) (immun) (ATSDR)	Gilman et al. 1998a – in ATSDR 1999 and WHO 2001, 2004

Species/strain	Duration/ Dose levels/ Chemical form	Effects (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Reference
		↑ Uranium levels in bone and kidney. 36.7 (♂), 53.6 (♀): Sinus hyperplasia in spleen. ↑ Body weight gain, significant (♀).			
Rabbit (10 ♂, 10 ♀) New Zealand	91 days ♀: 0, 0.49, 1.32, 43.0 mg U/kg bw/day ♂: 0, 0.05, 0.2, 0.88, 4.82, 28.7 mg U/kg bw/day uranyl nitrate hexahydrate in water	No significant effects on body weight gain, food and water intake. No statistically significant effects on relative organ weights. No statistically significant effect on haematological and biochemical parameters. Changes in thyroid gland. 0.05, (♂), 0.49 (♀): Kidney changes, statistically significant (♀, ♂). Liver lesions, accentuationof zonation and anisokaryosis. 0.88 ♂), 43.0 (♀): Interstitial collagen and/or reticulin sclerosis in kidney.	28.7 (♂), 43.0 (♀) (resp, cardio, gastro, haemato, musc, hepatic, endocr, bs wt, immun, neuro, repro) (ATSDR)	0.05 (♂), 0.49 (♀) (renal) ATSDR, WHO)	Gilman et al. 1998b – in ATSDR 1999 and WHO 2001, 2004
Rabbit (♂) New Zealand	91 days 0, 1.36, 40.98 mg U/kg bw/day uranyl nitrate hexahydrate in drinking water Recovery periode up to 91 days.	No significant effects on body weight gain, food and water intake. No significant effect on haematological parameters. 1.36: Histopathological changes in kidney and liver. 40.38: Changes in urinary parameters (not after 91-days recovery). ↑ Relative kidney weight (not after 91-days recovery). ↑ Percentage and total lymphocyte counts (only after 91-days recovery).	40.98 (♂) (resp, cardio, gastro, haemato, musc, endocr, bd wt) (ATSDR)	1.36 (♂) (hepatic, renal) (ATSDR) Between 1.36 and 40.98 (WHO)	Gilman et al. 1998c – in ATSDR1999 and WHO 2001, 2004
Rabbit (♂) New Zealand	91 days 0, 0.93, 23 mg U/kg bw/day uranyl nitrate hexahydrate in drinking water	0.93: Tubular debris, interstitial fibrosis, splitting and thickening of basal lamina, increased size of lysosomes and mitochondria		0.93 (♂) (renal)	McDonald-Taylor et al 1997 – in ATSDR 1999
Rabbit	1 year	No effect on serum urea, creatinine or chlorides			Novikov and Yudina 1970 – in

Species/strain	Duration/ Dose levels/ Chemical form	Effects (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Reference
(♀ 6-8/group)	0, 0.02, 0.2, 1 mg U/kg bw/day uranyl nitrate hexahydrate				IRIS 2007

Bd wt = body weight
Bw = body weight
Cardio = cardiovascular
Gastro = gastrointestinal
Haemato = haematological
Metab = metabolic
Skel = musculoskeletal
Repro = reproduction
Develop = development
Immun = immunological/lympho-reticular
Ns = not specified
♂ = male, ♀ = female

Rabbit, 91 days, uranyl nitrate hexahydrate (Gilman et al. 1998b – quoted from WHO 2004, ATSDR 1999)

Test dose levels were: females: 0.49, 1.32, 43.0 mg U/kg bw/day, males: 0.05, 0.2, 0.88, 4.82, 28.7 U/kg bw/day.

Histopathological changes were observed in the kidney tubule, liver, thyroid and aorta.

Changes in the aorta were not dose-dependent. Changes in the thyroid gland consisted of an irregular increase in epithelial height and vesiculation of nuclei. Hepatic changes were minimal, consisting of accentuation of zonation and anisokaryosis. Histopathological changes in the kidney in females were generally less marked than in males. In males histopathological findings were observed in the kidney tubules from 0.05 mg U/kg bw/day. 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 in males 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 of males. In females a significant dose-related and treatment-related nuclear changes in the kidney tubule included anisokaryosis and vesiculation. Other treatment-related changes in the kidney included cytoplasmic vacuolation, tubular atrophy and nuclear pyknosis.

Rabbit (specific pathogen-free (SPF)), 91 days, uranyl nitrate hexahydrate (Gilman et al. 1998c – quoted from ATSDR 1999, WHO 2004)

The study was conducted in order to examine the reversibility of renal injury in male rabbits. Test dose levels 1.36 and 40.98 mg U/kg bw/day. Histopathological changes were observed in the kidney, thyroid gland, liver and aorta. According to the authors, changes in thyroid and aorta were not treatment-related. In the liver an irregular accentuation of zonation was observed accompanied by increased variation in hepatocellular nuclear size, nuclear pyknosis and extensive cytoplasmic vacuolation. Hepatic changes were found to be treatment-related but not dose-related. Renal tubular injury with degenerative nuclear changes, cytoplasmic vacuolation and tubular dilation was seen at 40.98 mg U/kg bw/day, without consistent resolution even after 91 days recovery. The relative kidney weight t was not significantly increased after 45 days of exposure. Focal dilation of renal proximal tubules and cytoplasmic vacuolation were observed in both treated groups. Tubular basement membranes were normal early in injury but thickened focally during recovery. Changes induced by exposure at 40.98 mg U/kg/day persisted for up to 45 days and in some cases for 91 days. The authors suggest that the SPF rabbits are less sensitive to uranium injury than non-SPF rabbits, explaining the histopathological changes that were only observed in this study at much higher doses than in the studies using non-SPF rabbits.

Rabbits, 91 days, uranyl nitrate hexahydrate (MacDonald-Taylor et al 1997 – quoted from ATSDR 1999)

Test dose levels were 0.93 and 23 mg U/kg bw/day. Each treatment group was divided into 3 subgroups (immediate sacrifice and either 45-day or 91-day recovery period). Thickness of the glomerular basement membrane (GBM) was measured from electron micrographs. Uranium exposure resulted in thickening of the membrane in the rabbits. Control thickness was approximately 80 µm. Initial thickness after 91 days exposure in the low dose group was 96.3 µm and had increased to 103 µm after a 91-day recovery. Initial thickness after 91 days exposure in the high-dose group was 109 µm and had increased to 117 µm after a 91-day recovery period.

4.4.3 Dermal

Following dermal administration, renal toxicity has been observed in rats at 237 mg U/kg bw/day (renal failure – uranyl nitrate hexahydrate or ammonium uranyl tricarbonate for 5 days, lowest dose in the study, De Rey et al. 1983), in guinea pigs at 47 mg U/kg bw/day (proteinuria – uranyl nitrate haxahydrate epicuticle for 4 weeks, lowest dose in the study, Orcutt 1949), and in rabbits at 2.3 mg U/kg bw/day (proteinuria – uranyl nitrate haxahydrate epicuticle for 5 weeks, only dose in the study, Orcutt 1949). (All references quoted in ATSDR 1999).

4.5 Toxicity to reproduction

The oral studies on toxicity to reproduction are summarised in Table 4.5 and supplementary information on the studies is given in the text. The NOAELs and LOAELs presented in this section are those stated in the reviews and criteria documents.

Mouse, exposed from gestation day 13 to postnatal day 21 by gavage, uranyl acetate dihydrate
(Domingo et al. 1989b – quoted from ATDSR 1999, WHO 2004)
Test dose levels were 0.028, 0.28, 2.8 and 28 mg U/kg bw/day. The viability index (number of pups viable at day 21/number of pups born) and the lactation index (number of pups viable at day 21/number of pups retained at day 4) were significantly decreased in the 28 mg U/kg bw/day group. Treatment with uranium had no significant effect on length of gestation and sex ratios and on mean litter size at birth or postnatal day 4 as well as on body weight or pup body length throughout lactation. There was no significant effect on food consumption during the periods of late gestation and lactation. Maternal deaths (2/20 at 2.8 mg of mg U/kg bw/day, and 3/20 at 28 mg U/kg bw/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. Structural variations were not assessed in this study report.

Mouse, exposed from gestation day 6 to15 by gavage, uranyl acetate dihydrate (Domingo et al. 1989a – quoted from ATDSR 1999, WHO 2001, 2004)
Test dose levels were 3, 6, 14, or 28 mg U/kg bw/day. Dose-related foetotoxicity was reported in the offspring (reduced foetal body weight and length, an increase in the incidence of stunted foetuses and external and skeletal malformations, and developmental variations). External malformations included a significant increase in the incidence of cleft palate (6 mg U/kg/day) and haematomas (at 3 and 28 mg U/kg/day). The underdeveloped renal papillae were seen in the 3 and 14 mg U/kg/day groups. An increase in the incidence of skeletal abnormalities (bipartite sternebrae and reduced or delayed ossification of the hind limb, fore limb, skull, and tail) was seen in the 14 and 28 mg U/kg/day groups. Embryolethality was not found at any of the dose levels tested.

Mouse, males exposed intra-gastrically 38-60 days prior to mating, females exposed 14 days prior to mating through nursing of litters, uranyl acetate dihydrate (Paternain et al. 1989 – quoted from ATDSR 1999, WHO 2004).
Test dose levels were 2.8, 5.6, or 14 mg U/kg bw/day. The average number of total implantations observed was only different in the 2.8 mg U/kg/day group. A dose-response relationship was observed for reduced offspring growth as determined by body weight and body length.

Table 4.5 Toxicity to reproduction, oral administration

Species/strain	**Duration/ Dose levels (mg U/kg bw/day)/ Chemical form**	**Effects (mg U/kg bw/day)**	**NOAEL (mg/kg bw/day)**	**LOAEL (mg/kg bw/day)**	**Reference**
Rat (10 ♂, 10 ♀) Sprague-Dawley	28 days ♀: 0.07, 0.33, 1.65, 7.82, 40. ♂: 0.05, 0.27, 1.34, 6.65, 35.3. uranyl nitrate hexahydrate in water	No reproductive effects or changes in reproductive organ weights were found in the epididymis, testes, ovary, or uterus.	35. (♂) 40 ((♀)		Gilman et al. 1998a – in ATSDR 1999 and WHO 2001, 2004
Rat (15 ♂, 15 ♀) Sprague-Dawley	91 days ♀: 0.0001, 0.09, 0.42, 2.01, 9.98, 53.6. ♂: 0.0001, 0.06, 0.31, 1.52, 7.54, 36.7. uranyl nitrate hexahydrate in water	No reproductive effects or changes in reproductive organ weights were found in the epididymis, testes, ovary, or uterus.	36.7 (♂) 53.6 (♀)		Gilman et al. 1998a – in ATSDR 1999
Mouse Swiss-Webster	From GD 13 to PND 21 1 time/day 0.028, 0.28, 2.8, 28. uranul acetate by gavage	No developmental effects. 2.8: 10% maternal mortality. 28: ↓ Litter size, significant at PND 21. ↑ Offspring mortality.		2.8 (mortality) 28 (develop)	Domingo et al. 1989b – in ATSDR 1999
Mouse (20 ♀) Swiss albino mice	GD 6-15. Termination on GD 18 3, 6, 14, or 28. uranyl acetate dihydrate by gavage	No embryolethality. 3: ↑ Incidence of hematomas, significant. Undeveloped renal papillae ↓ Maternal weight gain and food consumption. ↑ Maternal relative liver weight 6: ↑ Incidence of cleft palate. 14: ↑ Incidence of skeletal abnormalities			Domingo et al. 1989a - in ATSDR and WHO 2001, 2004
Mouse (♂) Swiss-Webster Females mated with the treated males	64 days 5.6, 11.2, 22.4 and 45. uranul acetate dihydrate in drinking water	No significant differences in the total implantations, early and late resorptions or the number of live and dead foetuses. (♀) 11.2:		11.2 (repro) ATSDR	Llobet et al. 1991 – in ATSDR 1999

Species/strain	Duration/ Dose levels (mg U/kg bw/day)/ Chemical form	Effects (mg U/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Reference
		↓ Sperm counts (significantly) 45: Interstitial alterations and vacuolization of Leydig cells.			
Mouse (25 ♀, 25 ♂) Swiss-Webster	38-60 days prior to mating (♂). 14 days prior to mating (♀). 2.8, 5.6, 14. uranyl acetate dihydrate by gavage	No effects on mating or fertility. 5.6: ↑ Offspring mortality, significant. 14: ↑ Embryo lethality, significant.	5.6 (develop) 14 (repro) (ATSDR)	14 (develop) (ATSDR) 5.6 (mortallity) (ATSDR)	Paternain et al. 1989 – in ATSDR 1999 and WHO 2004
Rabbit (10 ♂, 10 ♀) New Zealand	91 days ♀: 0.49, 1.32, 43.0. ♂: 0.05, 0.2, 0.88, 4.82, 28.7. uranyl nitrate hexahydrate in water	No histopathological or organ weight changes were found in the epididymis, ovary, testes, or uterus.	28. (♂) 43.0 (♀) (ATSDR)		Gilman et al. 1998b – in ATSDR 1999 and WHO 2001, 2004

GD = gestation day
PND = postnatal day
♂ =male
♀ = female

4.6 Mutagenic and genotoxic effects

4.6.1 *In vitro* studies

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. The authors suggest that the genotoxic effects in this study were thought to occur through the binding of the uranyl nitrate to the phosphate groups of DNA, and that this may be a possible mechanism for the teratogenic effects observed in the studies by Domingo et al. (1989a). (Lin et al., 1993 – quoted from WHO 2004).

No other *in vitro* tests on genotoxic effects of uranium are available.

4.6.2 *In vivo* studies

No data have been found.

4.7 Carcinogenic effects

4.7.1 Inhalation

Beagle dogs were exposed to 5 mg U/m^3 uranium dioxide for 5 years. Pulmonary neoplasms and atypical epithelial proliferation in 30–46% of the animals were found. The incidence of spontaneous tumours found in this study was 50–100 times higher than the expected rate. (Leach et al. 1973 – quoted from ATSDR 1999).

4.7.2 Oral intake

No evidence of cancer induction was found in the available oral long-term studies in rats, mice, dogs, and rabbits (ATSDR 1999).

No carcinogenic effects have been reported in animals following ingestion of uranium compounds (Wrenn et al. 1985 – quoted from WHO 2004).

4.7.3 Dermal contact

No data have been located.

5 Regulations

5.1 Ambient air

Denmark (C-value):	-
ATSDR (1999):	0.008 mg/m^3 (MRL, insoluble) and 0.0004 mg/m^3 (MRL, soluble)

5.2 Drinking water

Denmark:	-
WHO (2004):	Guideline value: 15 μg/l (provisional). Provisional because of outstanding uncertainties regarding the toxicology and epidemiology as well as difficulties concerning its technical achievability in smaller supplies.
California EPA (1997)	A Public Health Goal (PHG) of 1 μg/l is set for natural uranium based on genotoxicity.
Health Canada (2006)	The interim maximum acceptable concentration (IMAC) is 20 μg/l (this guideline value is the result of a risk management decision and exceeds the health-based guideline value of 10 μg/l (based on renal effects)).

5.3 Soil

Denmark:	-
The Netherlands:	-

5.4 Occupational Exposure Limits

Denmark:	0.2 mg U/m^3 (At 2007)
ACGIH:	Maximum permissible concentration: 0.2 mg/m^3 (medium term exposure) and 0.6 mg/m^3 (short-term exposure limit) for soluble and insoluble natural uranium in air (ACGIH 2001).

5.5 Classification

Uranium: Tx;R26/28 R33 R53
Uranium compounds: Tx;R26/28 R33 N;R51/53
(MM 2002).

5.6 IARC

There is inadequate evidence in humans for the carcinogenicity of natural uranium. There is limited evidence in experimental animals for the carcinogenicity of natural uranium. There is inadequate evidence in experimental animals for the carcinogenicity of uranium-233. (IARC 2001).

5.7 US-EPA

Oral reference dose (RfD) of 3 μg/kg bw/day, based on a LOAEL of 0.02 mg/l (2.8 mg/kg bw/day) uranyl nitrate hexahydrate for initial body weight loss and moderate nephrotoxicity, observed in a 30-day oral study in rabbits (Maynard and Hodge, 1949) and an uncertainty factor (UF) of 1000 consisting of 10 for both interspecies and interspecies variability and 10 for use of a LOAEL from an animal study. An extra UF of 10 for less-than-lifetime exposure is not included since experiments of acute/subacute duration have been shown to be adequately sensitive for determining doses which cause chronic nephrotoxicity. (IRIS 2007).

5.8 WHO

TDI of 0.6 μg/kg bw/day.
Based on the application of an uncertainty factor of 100 (for inter- and inraspecies variation) to a LOAEL (60 μg/kg bw/day) for degenerative lesions in the proximal convoluted tubule of the kidney in male rats in a 91-day study (uranyl nitrate hexahydrate in drinking water – Gilman et al. 1998a). An additional uncertainty factor for the use of a LOAEL instead of a NOAEL was considered unnecessary, because of the minimal degree of severity and the short half-life of uranium in the kidneys, with no indication that the severity of the renal lesion will be exacerbated following continued exposure. This is supported by data from epidemiological studies. (WHO 2004).

6 Summary and evaluation

6.1 Description

Uranium is a radioactive element and belongs to the actinide series of the periodic table. Naturally uranium is a mixture of the three isotopes ^{234}U, ^{235}U and ^{238}U (0.005%, 0.72% and 99.3% by mass, respectively), which all behave similar chemically but have different radioactive properties. They are predominantly α-emitters and decay through two different series headed by ^{235}U and ^{238}U. About 48.9% of the radioactivity of natural uranium is accounted for by ^{234}U, 2.2% by ^{235}U and 48.9% by ^{238}U. The half-life of ^{234}U, ^{235}U and ^{238}U are 2.5×10^5, $7{,}1 \times 10^8$ and 4.5×10^5 years, respectively.

In this evaluation, the term “uranium” is used in a generic sense and refers to the uranium content of the various uranium salts mentioned in this document. For the purpose of comparison, concentrations and dose levels of the various uranium salts are expressed in terms of uranium equivalents (U) whenever possible.

6.2 Environment

Uranium makes up approximately 3 mg/kg of the earth’s crust. It is found in varying amounts in rocks, soil, surface and underground water, air, plants and animals. Typical concentrations in most materials are a few mg/kg. There are more than 100 uranium ores of which most contain between 0.005 and 0.2 % uranium. Both anthropogenic and natural processes cause redistribution of uranium in the environment. Natural processes account for most of the redistribution of uranium in the total environment; however, industries may release large quantities of uranium in specific locations.

Uranium is naturally occurring in groundwater and gets into drinking water when groundwater dissolves minerals that contain uranium. The amount of uranium in well water is variable and will vary depending upon its concentration in surrounding bedrocks. Uranium in water is transformed by formation of complexes and oxidation-reduction reactions. Oxidised forms of uranium are relatively soluble but in strong reducing environments uranium will precipitate. In a screening investigation of radioactivity in Danish drinking water the highest concentrations of ^{234}U and ^{238}U in drinking water were estimated to be about 15 µg U/l. Uranium concentration in excess of 20 µg U/l were found in 18% of 476 Norwegian groundwater samples, in groundwater from parts of New Mexico, USA and from central Australia. From 978 sites in the USA a mean uranium concentration of 2.5 µg U/l was reported.

The concentration in soil varies and reflects the abundance of uranium in the parent geological materials from which the soils were formed and soil development processes. Uranium in soil can be re-suspended in the atmosphere, washed from the land into surface water, incorporated into groundwater, or deposited on or adsorbed onto plant roots. In the United Kingdom concentrations of uranium in soil ranging from 0.05 to 76 mg U/kg have been reported. In New Mexico a mean concentration of 0.0024 mg/g were reported.

Uranium on land can be re-suspended in the atmosphere. In Japan and New York City, USA, the mean level of uranium in ambient air has been reported to be 0.02 and 0.075 ng U/m^3, respectively. In urban and rural air areas across the USA, mean levels ranged from 0.15 to 0.40 ng U/m^3.

Bioconcentration factor (BCF) values for uranium of 1,576, 459 and up to 38 have been measured in algae, plankton and fish, respectively. Concentration ratio (CR) values for plant/soil interaction were reported to be in the range 0.0025–0.81

The highest concentrations of uranium in foodstuffs are observed in shellfish, molluscs and winkles and range from 9.5 to 31 µg U/kg. Approximately 2 µg U/kg have been observed in fresh vegetables and bread, 0.1 to 0.2 µg U/kg have been observed in foods such as rice and meat and 0.26 to 1.7 µg U/l in different prepared beverages.

6.3 Human exposure

Human exposure to uranium can result from consumption of food and drinking water, inhalation of air or incidental ingestion of soil or dust contaminated with uranium.

Using the highest reported concentrations of ^{234}U and ^{238}U in Danish drinking water of 15 µg/l, and the consumption rate of 0.08 l/kg bw/day (for children 1-10 years old), the intake from drinking water would be 1.2 µg uranium/kg bw/day. For an adult (body weight of 70 kg), the daily exposure of uranium from drinking water would be 84 µg.

Values reported, for the average dietary intake of uranium in food, were in the range 0.5 to 3 µg/day.

Using the mean level of uranium in air reported to be 0.076 ng U/m^3 in New York City, and assuming the inhalation rate as 0.5 m^3/kg bw/day (for children 1-5 years old), the inhalation exposure of uranium will be 0.038 ng uranium/ kg bw/day. For an adult (body weight of 70 kg), the daily exposure of uranium from air would be 2.66 µg.

6.4 Toxicokinetics

In humans, the average gastrointestinal absorption of uranium is 1-2%, depending on the solubility of the uranium compound, previous food consumption and concomitant exposure to oxidising agents. In animal studies absorption of ingested uranium was reported to be 0.06-1%. Increased absorption was reported in neonatal rats and pigs (compared to adults) and in rats that were fasted (compared to not fasted rats). In uranium mill workers, the absorption of inhaled uranium was estimated to be 0.76%. Soluble uranium compounds can be absorbed through the skin, as demonstrated in rabbits, guinea pigs and mice, where toxicity occurred following acute dermal exposure to uranyl nitrate hexahydrate.

In humans, absorbed uranium is found in all tissues regardless of the route of exposure. The body burden is considered to be approximately 90 µg. About 66% of this is in bone, 16% in the liver, 8% in the kidneys, and 10% in other tissues.

A study in rats showed that 99% of the ingested uranium is eliminated in the faeces without being cycled through the bile and that half of the absorbed uranium is excreted in urine in 2-6 days.

The overall elimination half-life of uranium in humans under conditions of normal daily intake has been estimated to be in the range 180-360 days. In rats, the half-life of uranium has been estimated to be 5-15 days in the kidneys and 93-165 days in the skeleton.

6.5 Mode of action

Exposure to uranium can lead to kidney damage. From the blood uranium is transported to the kidneys where it is released and accumulates in the renal tubular epithelium by forming complexes with phosphate ligands and proteins. This induces cellular necrosis and atrophy in the tubular wall, resulting in decreased re-absorption efficiency in the renal tubule. Uranium is not tightly bound and is released again within a few days. Within a week following exposure, uranium is largely cleared from the kidneys, and the tubules begin to regenerate. Although the regenerated epithelium has histological differences from its normal state, it is often difficult to detect histological signs of kidney damage a month after exposure because all remaining functional damage is subtle. Heavy metal ions, such as uranyl ions, are also effective in delaying or blocking the cell division process, thereby magnifying the effects of cell necrosis. It has been suggested that the genotoxic effect of uranyl nitrate, observed in Chinese hamster ovary cells, may occur through the biding of uranyl nitrate to the phosphate groups of DNA, which may also be a mechanism for the teratogenic effects observed following uranium exposure. Uranium also accumulates in the skeleton, where the uranyl ion exchanges with Ca^{2+} on the surfaces of bone mineral crystals, although it does not participate in crystal formation or enter existing crystals. Uranium initially deposits on all bone surfaces but is most highly concentrated in areas of growth. Depending on the microscopic structure of the bone of each species, uranium on bone surfaces may gradually diffuse into bone volume.

6.6 Human toxicity

6.6.1 Single dose toxicity

In a male worker at a uranium enrichment plant, accidentally exposed by inhalation to a high concentration of uranium tetrafluoride, delayed renal effects were observed as indicated by significantly elevated levels of urinary proteins, nonprotein nitrogen, amino acid nitrogen/creatinine, and decreased phenolsulfonpthalein excretion rate.

In a male, that deliberately ingested 15 g (approximately 131 mg/kg bw) uranyl acetate along with benzodiazepine (unknown quantity), a diagnosis of acute nephrotxicity from heavy metal exposure was made 16 hours after admission.
A volunteer given a single oral dose of 1 g uranyl nitrate (14.3 mg/kg) suffered from acute nausea, vomiting, and diarrhea within a few hours of administration. In terminal brain tumour patients, injected a single dose of 120 μg U/kg, elevations in urinary excretion of catalase, albumin and non-protein nitrogen, and casts in the urine were noted. Trace changes in urinary catalase were noted in patients injected with uranyl nitrate 55 or 71 μg U/kg.

6.6.2 Irritation and sensitisation

No dermal effects were found in a man accidentally exposed to powdered uranium tetrafluoride for 5 minutes.

No data have been located regarding sensitisation in humans.

6.6.3 Repeated dose toxicity

Uranium mill workers exposed to insoluble uranium dioxide had renal tubular dysfunction, manifested by mild proteinuria, aminoaciduria and a concentration-related clearance of ß2-microglobulin relative to that of creatinine when compared to a referent group of cement workers. The incidence and severity of these nephrotoxic signs correlated with the time of exposure.

Several epidemiological studies have been conducted in which renal effects of uranium in drinking water (concentrations from <1 to 781 µg U/l) were investigated. A trend towards increasing excretion of BMG and increasing uranium concentration in well water was observed in a clinical study on 324 persons in Canada. Significant correlations between uranium intake and urinary glucose, alkaline phosphatase (ALP) and ß-microglobulin (BMG) were observed in another study conducted in Canada which included two groups of subjects who had a uranium concentration in their drinking water of <1 µg U/l or 2-781 µg U/l. A significant association was also observed between uranium in urine and increased fractional excretion of calcium, phosphate and glucose (within the normal physiological range) in a study on a Finnish population exposed to well water containing a median uranium concentration of 28 µg U/l. No studies in humans have reported a dose-response relationship. Conclusions by the authors suggest, that uranium in drinking water affect kidney function, probably at the proximal tubule.

6.6.4 Toxicity to reproduction

Male uranium miners were found to have more first-born female children than expected, suggesting that uranium's alpha radiation damaged the y-chromosomes of the miners but it is not certain if this effect is from exposure to uranium because the workers were also exposed to ^{222}Rn, chlorine, hydrofluoric acid, lead sulphate, nickel, nitric acid and nitrogen oxides, silicon dioxide, and sulphuric acid.

6.6.5 Mutagenic and genotoxic effects

In uranium miners in Czechoslovakia, no increased incidence of aberrant DNA or chromosomes attributable to exposure to uranium was found.

A cytogenetic study of males occupationally exposed to uranium found higher levels of chromosome aberrations in the miners than in controls. The investigators of this study concluded that this increase in chromosome aberrations may be attributable to smoking and exposure to chlorine, hydrofluoric acid, lead sulphate, nickel, nitric acid and nitrogen oxides, silicon dioxide, diesel smoke, and sulphuric acid in addition to ^{222}Rn. It is unlikely that the effects described in these studies were related in any way to exposure to uranium.

6.6.6 Carcinogenic effects

No carcinogenic effects have been reported in humans following ingestion of uranium compounds.

6.7.1 Single dose toxicity

In guinea pigs the LC_{50}-value for uranium hexafluoride was 35011 mg U/m^3 for a 2-minute inhalation exposure. In rats, the LC_{50}-value for uranium hexafluoride was 26098 and 8114mg U/m^3 for a 5 and 10-minute inhalation exposure, respectively. Renal injury was reported to be the primary cause of death.

In rats and mice, oral LD_{50}-values for uranyl acetate dihydrate were 114 and 136 mg U/kg bw, respectively. Slight renal dysfunction, minimal microscopic lesions in the tubular epithelium and microhaemorrhagic foci in the liver were observed in rats given a single oral dose of 5.6 mg U/kg as uranyl acetate dihydrate. Piloerection, tremors, hypothermia, pupillary size decreases and exophthalmos were observed in rats given single oral dose of 11 mg U/kg bw as uranyl acetate dihydrate.

In rabbits, guinea pigs and mice, dermal LD_{50}-values for uranyl nitrate hexahydrate were 28, 1190 and 4286 mg U/kg bw, respectively. Insufficient fatalities occurred to calculate an LD_{50} for rats, but the mortality curve fell between that of the rabbits and the guinea pigs.

6.7.2 Irritation

Dermal application to rabbits of uranyl nitrate hexahydrate produced superficial coagulation necrosis and inflammation of the epidermis (56.4 mg U/kg bw), severe dermal ulcers (4.2 mg U/kg bw, for 5 weeks) and moderate erythema (1.4 mg U/kg bw, single application).

Conjunctivitis and eye irritation have been reported in animals after exposure to uranium hexafluoride and to uranium tetrachloride.

6.7.3 Sensitisation

No data have been located.

6.7.4 Repeated dose toxicity

The toxicity of uranium compounds following repeated exposure have been extensively studied in a number of animals species using inhalation, oral and dermal routes. The studies have identified uranium as a nephrotoxin.

Following oral administration, renal toxicity has been observed in rats at dose levels from 0.06 mg U/kg bw/day (lesions of the tubules, glomeruli and interstitium – uranyl nitrate hexahydrate in drinking water for 91 days) and in rabbits from 0.05 mg U/kg bw/day (anisokaryosis, nuclear vesiculation – uranyl nitrate hexahydrate in drinking water for 91 days, lowest dose in the study).

A number of other effects in rats and rabbits have been reported following oral exposure to uranium. Effects on the liver were observed in rats from 0.06 mg U/kg bw/day (non-specific nuclear and cytoplasmic changes) and in rabbits from 0.06 mg U/kg bw/day. Sinus hyperplasia in the spleen was reported in rats from 36.7 mg U/kg bw/day.

6.7.5 Toxicity to reproduction

Decreased fertility (11.2 mg U/kg bw/day as uranyl acetate dihydrate in drinking water for 64 days), embryolethality (14 mg U/kg bw/day as uranyl acetate dihydrate by gavage 38-60 days (♂) or 14 days (♀) prior to mating) and foetotoxicity including teratogenicity (3 mg U/kg bw/day as uranyl acetate dihydrate by gavage gestation day 6-15) have been observed in mice following oral exposure to uranium. Maternal toxicity has been observed in mice exposed to 3 mg U/kg bw/day as uranyl acetate dihydrate by gavage from gestation day 6 to 15. No toxicity to reproduction was observed in rats and rabbits exposed to doses up to 53.6 and 43 mg U/kg bw/day, respectively.

6.7.6 Mutagenic and genotoxic effects

Uranyl nitrate was cytotoxic and genotoxic in Chinese hamster ovary cells at concentrations ranging from 0.01 to 0.3 mmol/litre. No other data are available.

6.7.7 Carcinogenic effects

Beagle dogs were exposed to 5 mg U/m3 (3.4 nCi/m) uranium dioxide for 5 years. Pulmonary neoplasms and atypical epithelial proliferation in 30–46% of the animals were found. The incidence of spontaneous tumours found in this study was 50–100 times higher than the expected rate.

6.8 Evaluation

The exposure of the general population to uranium is primarily from food and drinking water.

Human data indicate that the average gastrointestinal absorption of uranium is 1-2%, depending on the solubility of the uranium compound, previous food consumption and concomitant exposure to oxidising agents. In animal studies absorption of uranium following ingestion was reported to be 0.06-1%. In humans, absorbed uranium is found in all tissues regardless of the route of exposure. The body burden is considered to be approximately 90 µg. About 66% of this total is in the skeleton, 16% in the liver, 8% in the kidneys, and 10% in other tissues. The overall elimination half-life of uranium in humans under conditions of normal daily intake has been estimated to be in the range of 180-360 days. In rats, the half-life of uranium in the kidneys was estimated to be approximately15 days.

The acute toxicity of uranium acetate dihydrate in experimental animals is high with a reported LD_{50}-value for rats of 114 mg U/kg bw and for mice of 136 mg U/kg bw. Effects observed following a single oral dose of 5.6 mg U/kg bw as uranyl acetate dihydrate included slight renal dysfunction, minimal microscopic lesions in the tubular epithelium and microhaemorrhagic foci in the liver.

Uranium pentachloride, uranyl nitrate hexahydrate and ammonium diuranate resulted in irritation after dermal application to rabbits.

In humans, chronically exposed to uranium in drinking water, impairment of the kidney function has been reported. Correlations were found between uranium exposure and the urinary excretion of beta-microglobulin, albumin, alkaline phosphatase, calcium, phosphate and glucose, which is consistent with signs of

alterations in proximal tubular function. However, none of the studies in humans have reported a dose-response relationship.

Repeated dose toxicity of uranium has been extensively studied in a number of animal species using inhalation (rat, mouse, rabbit, guinea pig, dog, cat monkey), oral (rat, mouse, rabbit, dog) and dermal (rat, rabbit, guinea pig) routes. The studies have shown that long-term exposure to uranium causes renal effects that ranged from minimal microscopic lesion in the tubular epithelium to tubular necrosis. Uranium compounds may cause pulmonary effects at high inhalation exposures; however, long-term exposure to lower concentrations has usually no effect on the lungs. No consistent or confirmed chemically induced adverse effects have been reported for other organs.
The association between the levels of uranium exposure following ingestion and effects on the kidneys has been investigated in studies with durations ranging from 4 weeks to 2 years. In the most valid studies, renal effects were observed at dose levels from 0.05 mg U/kg bw/day in the rabbit and from 0.06 mg U/kg bw/day in the rat, see Table 6.7. Based on these oral studies, a LOAEL of 0.06 mg U/kg bw/day is considered for the rat and a LOAEL of 0.05 mg U/kg bw/day is considered for the rabbit.
Overall a LOAEL for repeated dose toxicity of 0.05 mg U/kg bw/day is considered based on the 91-days oral study (Gilman et al. 1998b) in rabbits in which changes in the tubular cell nuclei were observed in males at the lowest dose level in the study.

Table 6.8 NOAEL/C and LOAEL/C for renal effects in oral repeated dose toxicity

Species	**NOAEL/ mg U/kg bw**	**LOAEL/ mg U/kg bw**
Rat	3.3 - 12342	0.06 – 10611
Mouse	-	452
Rabbit	-	0.05
Dog	6.3 - 47	15.4 – 5653

Data on genotoxicity and mutagenicity of soluble uranium compounds are very limited and no definitive studies have been located. In an *in vitro* test with Chinese hamster ovary cells, uranyl nitrate 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 leading to the conclusion that uranyl nitrate was genotoxic under the conditions of the assay. According to WHO (2004), the genotoxic effects in this study were thought to occur through the binding of the uranyl nitrate to the phosphate groups of DNA. Based on these very limited data, no firm conclusion can be drawn.

No carcinogenic effects have been reported in humans following ingestion of uranium compounds and no evidence of cancer induction was found in the available oral long-term studies in rats, mice, dogs, and rabbits.
Uranium is a predominantly an alpha-emitting radionuclide and current theories on gene mutation and chromosomal aberrations by high-LET alpha radiation suggest a potential for genotoxicity from uranium's radioactivity. However, cancer has never been associated with exposure to uranium. Likewise, no genetic changes due to radiation have ever been observed in any human population exposed at any dose (ATSDR 1999). For further details, see section 2.2.
Based on the available data, soluble uranium compounds are not considered to have a carcinogenic potential following oral intake.

Effect on reproductive parameters and developmental effects have been reported in mice following oral administration of uranyl acetate dihydrate. Reduced sperm counts were observed at levels from 11.2 mg U/kg bw (reproductive parameters); however, no effects on mating and fertility were observed at 14 mg U/kg bw. Increased mortality was observed from 5.6 mg U/kg bw (developmental). No reproductive effects were observed in rats (up to 53.6 mg U/kg bw) or rabbits (up to 43 mg U/kg bw). Based on the oral studies in mice a LOAEL of 11.2 mg U/kg bw is considered for reproductive toxicity (reduced sperm counts) and a NOAEL of 2.8 mg U/kg bw for developmental toxicity (offspring mortality) in the mouse.

6.8.1 Critical effect and NOAEL

Uranium is both a chemical and a radioactive compound; however, only the chemical aspects of toxicity of soluble inorganic uranium compounds are considered in this evaluation in relation to an estimation of health based quality criteria in drinking water.

Animal and human data indicate that renal effects are the critical effects following oral exposure to soluble inorganic uranium compounds. Minimal renal changes in the proximal tubule were observed in experimental animals following exposure to low doses, in uranium mill workers and in humans exposed to uranium in drinking water.

A LOAEL for renal effects of 0.05 mg U/kg bw/day is considered based on the 91-days oral study in rabbits (Gilman et al. 1998b) in which changes in the tubular cell nuclei were observed in males, the most sensitive sex and species, exposed to uranyl nitrate in drinking water at the lowest dose level in the study. This LOAEL will form the basis for the estimation of quality criteria in drinking water.

7 TDI and quality criteria

7.1 TDI

The TDI is calculated based on a LOAEL of 0.05 mg U/kg bw/day observed for renal changes in male rabbits (Gilman et al. 1998b):

$$TDI = \frac{LOAEL}{UF_I * UF_{II} * UF_{III}} = \frac{0.05 \text{ mg U/kg bw/day}}{10 * 10 * 3} = 0.17 \text{ µg U/kg bw/day}$$

The uncertainty factor UF_I accounting for interspecies variability is set to 10 assuming that humans are more sensitive than the rabbit. The UF_{II} accounting for intraspecies variability is set to 10 reflecting the range in biological sensitivity within the human population. The UF_{III} is set to 3 because of using a LOAEL instead of a NOAEL and because the data on genotoxicity and carcinogenicity are inadequate. An extra factor taking into account that the study is not a chronic one is not considered relevant as the half-time for uranium in kidneys is only approximately 15 days and thus the renal effects of uranium exposure are more dependent on the dose than on the duration of the exposure.

7.2 Allocation

The general population is predominantly exposed to uranium from food and drinking water.

Values reported, for the average dietary intake of uranium in food, were in the range 0.5-3 µg/day (Fisenne et al. 1978, Singh et al. 1990, Nozaki et al 1970 – quoted from WHO 2004; Harley 1998 – quoted from WHO 2001).

The highest concentrations of uranium in foodstuffs are observed in shellfish, molluscs and winkles (9.5 to 31 µg U/kg). Lower levels have been observed in fresh vegetables and bread (approximately 2 µg U/kg). Uranium concentrations in foods such as rice and meat are in the range 0.1 to 0.2 µg U/kg. (WHO 2001). Concentrations of uranium in nine different prepared beverages, including tea and coffee, was found to be in the range 0.26 to 1.7 µg U/l (Cheng et al. 1993 – quoted from WHO 2001).

Using the highest reported concentrations of ^{234}U and ^{238}U in Danish drinking water of about 15 µg/l (Danish EPA 2006), and the consumption rate of 0.08 l/kg bw/day (for children 1-10 years old), the intake from drinking water would be 1.2 µg uranium/kg bw/day. For an adult (body weight of 70 kg), the daily exposure of uranium from drinking water would be 84 µg.

Based on the average dietary intake reported for uranium in food (0.5 to 3 µg/day), the contribution of uranium from food in general is considered as being low compared to the contribution of uranium from the drinking water. Some food items (shellfish, molluscs and winkles) have higher concentrations of uranium than food in general; however, such food items are not consumed on a daily basis.

Furthermore, the bioavailability of uranium from food is very low (1-2%) and probably lower than the bioavailability from drinking water at least if drinking water is consumed on an empty stomach.
Therefore, 100% of the TDI is allocated to ingestion of drinking water.

7.3 Quality criterion in drinking water

The quality criterion in drinking water QC_{dw} is calculated based on the TDI of 0.17 µg/kg bw per day and assuming a daily ingestion of 0.08 l/kg bw of drinking water for children 1-10 years old:

$$QC_{dw} = \frac{TDI * Y}{ingestion_{dw}} = \frac{0.17\ \mu g/kg\ bw/day * 1}{0.08\ l/kg\ bw/day}$$

$$= 2.1\ \mu g\ U/l$$

7.3.1 Quality criterion in drinking water

2 µg U/l.

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Uranium, inorganic and soluble salts

The Danish Environmental Protection Agency has requested an evaluation of health hazards by exposure to the inorganic and soluble salts of uranium. This resulted in 2008 in the present report which includes estimation of a quality criterion in drinking water for the mentioned substances.

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