European Food Safety Authority

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SCIENTIFIC OPINION

Uranium in foodstuffs, in particular mineral water[1]

Scientific Opinion of the Panel on Contaminants in the Food Chain

(Question No EFSA-Q-2007-135)

Adopted on 25 March 2009

This opinion, published on 29th May 2009, replaces the earlier version published on 28th April 2009[2].

PANEL MEMBERS

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SUMMARY

The European Food Safety Authority (EFSA) was asked to conduct a risk assessment on uranium at the European level because of the existence of differing regulations and also due to existing gaps in the knowledge base concerning the chronic toxicity of uranium. This opinion focuses on uranium's chemical toxicity, while the radiological risk will be addressed by the Group of Experts established under Article 31 of the European Atomic Energy Community (EURATOM) Treaty under the Directorate-General for Energy and Transport[3].

[1] For citation purposes: Scientific Opinion of the Panel on Contaminants in the Food Chain on a request from German Federal Institute for Risk Assessment (BfR) on uranium in foodstuff, in particular mineral water. *The EFSA Journal* (2009) 1018, 1-59.

[2] After adoption of the opinion, EFSA was notified on the following two items: i) the Human Biomonitoring Commission is a commission of the German Federal Environment Agency (UBA) and not of the German Federal Institute for Risk Assessment (BfR). This has been corrected in chapter 8 on page 31, ii) the water data provided by France were erroneously classified as bottled water (sample size: 736), however, the data supplied were both bottled and tap water (sample size: 94 and 642, respectively). As a result, in the revision of the opinion figures have been changed in the following tables: Table 5, 7, 8a, 8b, 9a, 12 and 13, in the respective text related to these tables and in the summary and conclusions. These changes do not change the overall conclusions of the opinion. To avoid confusion, the original version of the opinion has been removed from the website, but is available on request as is a version showing all the changes made.

[3] http://ec.europa.eu/dgs/energy_transport/index_en.htm

Uranium (U) is a silvery-white metal occurring in a number of minerals such as uraninite, carnotite and pitchblende. Uranium is also a naturally occurring radioactive element. Several different radioisotopes of uranium occur, showing almost identical physico-chemical characteristics, yet with different radioactive properties. Uranium can be present in water, air, food and feed in varying concentrations through leaching from natural deposits such as soil or rocks, emission from nuclear industry, nuclear weapons, dissolution in fertilizers and combustion of coal and other fuels.

Analytical methods for the determination of uranium in the different matrices are available. Depending on the method, uranium can be measured either as the activity of the radionuclide or as the mass fraction of the isotopes.

In June 2008, the EFSA issued a specific call to selected countries for data on uranium concentrations in individual water and food samples. A total of eight countries (France, Germany, Hungary, Italy, Portugal, Sweden, Switzerland and the UK) sent 9,045 analytical results to EFSA. The number of samples below the limit of detection (LOD) varied considerably across country and food group with 5 % and 27 % in tap and bottled water, 41.3 % for vegetables and 94.7 % and 100 % for cereals and eggs, respectively. Tap and bottled water had mean concentrations of uranium of slightly above 2 μg/L while soft drinks had concentrations less than half of this. Concentrations in food are less representative since they are reported only from one country and there are few samples in selected categories only. Moreover, occasional high LOD for the analytical method were reported.

Several exposure scenarios were explored for adults in Europe. The first scenario included mean consumption with mean occurrence values as a general situation, a second scenario the 95th percentile consumption with mean occurrence values as a high consumption situation, and a third scenario the mean consumption with 95th percentile occurrence values as a local high contamination situation. Based on these scenarios, the overall lower- and upper-bound uranium exposure estimates varied between 0.05 and 0.28 μg/kg body weight (b.w.) per day. For an average consumer and average occurrence values (first scenario), food contributed about 50 %, while less in the other two scenarios. However, there are uncertainties in the concentrations in food. In an additional fourth scenario including high local contamination situations together with a high consumption, the lower- and upper-bound uranium exposure estimates varied between 0.39 to 0.45 μg/kg b.w. per day. This scenario is, however, unlikely. For infants, the exposure scenario included mean and high consumption of infant formula reconstituted with water containing both average and high levels of uranium. The lower- and upper-bound uranium exposure estimates varied between 0.18 and 1.42 μg/kg b.w. per day, for both bottled and tap water.

Oral bioavailability is limited, and only up to 1-2 % of soluble uranium and 0.2 % of insoluble uranium is absorbed. Almost all uranium that is ingested is cleared by the systemic circulation according to a two-phase process. About one third of the absorbed uranium is retained in the body, initially in the kidney and liver, then redistributed to the skeleton. Terminal half-life of uranium in humans has been estimated to range from 180 to 360 days.

Toxicity of ingested uranium is related to the solubility of the uranium compound; the higher the oral uranium compound solubility is, the greater its toxicity is expected to be. The kidney is recognized as the primary target organ for uranium both in experimental animals and humans. Kidney damage results from the accumulation of uranium in the renal tubular epithelium, where it can cause cell necrosis and atrophy of the tubules, leading to a compromised tubular secretion of organic anions and reabsorption of filtered glucose and

amino acids. Besides nephrotoxicity, reproductive and developmental alterations (e.g. decreased pup growth and internal/external malformations), diminished bone growth and neurotoxicity have been documented in animal models but only at higher doses.

The World Health Organization (WHO) has established a tolerable daily intake (TDI) for soluble uranium of 0.6 μg/kg b.w. per day, based on the lowest-observed-adverse-effect-level (LOAEL) for uranium nephrotoxicity of 0.06 mg/kg b.w. per day from a 91-day study in male rats. The Panel on Contaminants in the Food Chain (CONTAM Panel) noted that no new data were identified that would require a revision of this TDI and endorsed it.

Using individual values of participant's weight in the EFSA Concise European Food Consumption Database, the average overall dietary exposure to uranium across European countries was estimated to range from 0.05 to 0.09 μg/kg b.w. per day, assuming lower- and upper-bound scenarios for values below the LOD and between the LOD and the limit of quantification (LOQ), respectively. For high consumers the dietary exposure to uranium was estimated to be between 0.09 and 0.14 μg/kg b.w. per day. These dietary exposure estimates are all well below the TDI of 0.6 μg/kg b.w. per day.

Two specific sub-groups of the population were looked at in more detail. It is considered plausible that some local communities with high uranium concentrations in their water supply can be exposed at the 95th percentile concentration level for a longer period or a lifetime. Normally for chronic exposure it is considered unlikely for such a situation to occur. At the same time there might be high consumers of water among these sub-populations at the 95th percentile consumption level. In such a situation, water could contribute 0.36 μg/kg b.w. per day as a median across the countries studied or a country maximum of 0.51 μg/kg b.w. per day. Contribution from food is not considered likely at the 95th percentile concentration level of uranium at the same time, but more likely at the mean concentration level leading to an exposure of 0.04 μg/kg b.w. per day and possibly 0.07 μg/kg b.w. per day in a high consumption scenario. Thus, also in such a situation the TDI would not be exceeded.

The CONTAM Panel noted that for all exposure scenarios evaluated for infants fed with infant formula reconstituted with water containing uranium, the exposure may be up to 3 times higher than the uranium exposure of adults on the body weight basis. The CONTAM Panel concluded that such exposure in infants should be avoided.

Key words: uranium, tap water, bottled water, public health, infants, dietary exposure, TDI.

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BACKGROUND AS PROVIDED BY THE GERMAN FEDERAL INSTITUTE FOR RISK ASSESSMENT

Background

In its latest opinion on uranium[4], the German Federal Institute for Risk Assessment (BfR) comes to the conclusion that the European Food Safety Authority (EFSA) should be commissioned to conduct a risk assessment on uranium at the European level and to derive from this a maximum tolerable intake level for this heavy metal in particular for drinking and mineral water.

With its letter from May 18th 2007 the Federal Ministry for nutrition, agriculture and consumer protection (BMELV) requests the BfR to proceed for this request/petition according to the national proceedings of the Federal republic of Germany authorised governmental authorities for the coordination of requests for scientific opinions to the EFSA.

Rationale for this request

Uranium is a radioactive heavy metal which is ubiquitous in the environment. As a result of its natural occurrence it can be found at different concentrations and in the form of different compounds in rocks, water, soil and air. Additionally, uranium can also enter the environment from anthropogenous sources – for example via the application of phosphate containing fertilizers. Due to the wide distribution, traces of uranium can also be detected in foodstuff, drinking water and mineral waters.

Uranium exhibits a chemical toxicity which can, in the case of continuous intake, lead to e.g. nephrotoxicity. Furthermore, due to the radioactive decay of uranium and its radioactive decay products it can also cause cancers.

The joint opinion of the BfR and the Federal Office for Radiation Protection (Bundesamt für Strahlenschutz, BfS) on uranium[4] comes to the conclusion that the radiological risk from uranium, which is taken up via foodstuff as well as drinking water and mineral water, is very low for the German consumer. The exposure to radiation lies well below the guideline values, since the dose coefficients used for the calculation of the radiation exposure and the concentrations of uranium are mostly very low. Comparably more significant in this range of concentrations, is the chemical toxicity of uranium.

The reasons why the BfR and BfS in their joint opinion came to the conclusion that a risk assessment by the EFSA would be required for uranium in foodstuff, can be summarized as follows:

A) An assessment of legal requirements for uranium in various matrices in other EU-countries, Japan and the US has shown that these, if existent, were mainly for mineral and drinking water.

   i) Among the examined countries, the uranium content in mineral waters is regulated in Slovakia, the Czech Republic, Lithuania and the USA. The corresponding regulations are not identical. In part they refer to the radiological properties of uranium, and in part they apply to the chemical properties of uranium. For the other examined countries either no legal regulations exist or no information was provided.

4 http://www.bfr.bund.de/cm/208/bfr_empfiehlt_die_ableitung_eines_europaeischen_hoechstwertes_fuer_uran_in_trink_und_mineralwasser.pdf (available only in German).

ii) For drinking water in Slovakia, the Czech Republic and the USA the legal regulations were provided. The corresponding regulations also differ in the same way as the regulations on mineral water. The other countries have either not provided any information or do not have national regulations on uranium in drinking water. Three countries regulate the uranium content indirectly via the total yearly effective dose.

B) A seminar in the BfR on 21st July 2005 on this subject showed that drinking water and mineral waters can, depending on the local geology, have in some cases uranium contents which could be sufficient to endanger consumer health.

C) In Germany, a national maximum level for uranium in natural mineral waters, spring waters and table waters as well as packed drinking waters which are "suitable for the preparation of infant food" has been set in the regulation on natural mineral water, spring water and table water (Bundesrat Drucksache 711/06; MinTafWV 1984, last modification on 1st December 2006) which was finally based on the joint opinion of the BfS and the BfR from the 16th January 2006[5].

D) Up to the year 1998 uranium had been toxicologically assessed on the basis of its radiological properties and corresponding threshold and guideline values established. Due to the comparably low radiological potential of uranium, the up until that point derived values were higher than those which had been derived since 1998 from a chemical point of view as toxicological threshold values and guideline values for drinking water. Since then the different bodies have derived guideline values for uranium levels according to the growing body of knowledge[4].

The EFSA is kindly requested to conduct a risk assessment on uranium at the European level because of the existence of differing regulations and also due to still existing gaps in the knowledge base concerning the chronic toxicity of uranium at the low dose level (e.g. IRSN 2005[6]).

TERMS OF REFERENCE AS PROVIDED BY THE GERMAN FEDERAL INSTITUTE FOR RISK ASSESSMENT

The European Food Safety Authority (EFSA) was asked to advice on a maximum tolerable intake of uranium in foodstuffs particularly mineral water that will not pose a health risk to consumers in Europe.

ACKNOWLEDGEMENTS

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5 http://www.bfr.bund.de/cm/208/bfr_korrigiert_hoechstmengenempfehlung_fuer_uran_in_waessern_zur_zubereitung_von_saeuglingsnahrung.pdf (available only in German).

6 http://net-science.irsn.org/scripts/net-science/publigen/content/templates/show.asp?L=FR&P=2997

ASSESSMENT

1. Introduction

The discovery of uranium (U) is credited to the German chemist Martin Heinrich Klaproth in 1789 who named the metal after the planet Uranus. The metal's radioactive properties were uncovered in 1896 by Antoine Becquerel.

Uranium compounds have traditionally been used for more than a thousand years to colour ceramic glazes and glass, producing orange-red to lemon yellow hues. Research by Enrico Fermi and others starting in 1934 led to uranium's use as a fuel in the nuclear power industry and in nuclear weapons directly or after enrichment in the isotope ^{235}U, which is capable of fission. The by-product of the enrichment process is called depleted uranium (DU), which by definition is uranium that contains the isotope ^{235}U with an abundance lower than 0.711 % (NRC, 2000). Depleted uranium presents lower radioactivity than natural uranium (40 % less) and it is used for its very high density in counterweights in aircraft, radiation shielding and in defensive armour plating and armour-piercing projectiles (Priest, 2001; Miller and McClain, 2007; Harper and Kantar, 2008).

Uranium is ubiquitous throughout the natural environment, being found in varying but small amounts in rocks, soils, and plants. Uranium is present in water, air, food and feed in varying concentrations through leaching from natural deposits, emission from nuclear industry, dissolution in fertilizers and combustion of coal and other fuels. Compared to other radionuclides, uranium has a low specific activity because of its extremely long half-life. Although there is a risk of radiological toxicity from orally ingested natural uranium, the principal health effects are chemical toxicity (Milvy and Cothem, 1991; Zamora *et al.*, 2002).

Reported background levels of uranium in air vary widely. For example, the World Health Organization (WHO) quoted values in ambient air from 0.02 ng/m^3 to 0.076 ng/m^3 (WHO, 2001), while the United States Environmental Protection Agency (US-EPA) quoted a range of 0.15 to 0.40 ng/m^3 in 51 urban and rural areas across the United States of America (USA) (US-EPA, 1986). Elevated levels of uranium of 3 ng/m^3 have been found downwind of coal fired power stations associated with their discharges (NCRP, 1975) and of up to 200 ng/m^3 around uranium milling and processing facilities at distances of up to 2 km from site boundaries (ATSDR, 1990; 1999).

The concentrations in water can vary considerably depending on the mineralogical and geochemical composition of the soil and rock, chemical composition of the water, and the residence time of groundwater in the soil and bedrock. Concentrations of uranium from below 0.01 μg/L to in excess of 1,500 μg/L water have been reported. The probability of a drinking water source containing uranium at a concentration of about 2 μg/L is relatively high, getting progressively smaller over the range 5 to 10 μg/L and becoming very small above 10 μg/L (WHO, 1998). Under local circumstances water can be the major contributor to uranium exposure.

Although the concentration of uranium can reach up to 15 mg/kg in farmland soil due to use of phosphate fertilizers, it is not readily transferred from soil to crops, and also has a low transfer factor from grass to animals (ATSDR, 1999). Nevertheless, as a component of the natural environment, uranium is likely to be present as a trace constituent in all foodstuffs. The determination of uranium in a variety of foodstuffs from the USA and UK indicates that the highest recorded concentrations have been found in shellfish of 9.5 to 31 μg/kg. Typical

concentrations in staple foods such as bread and fresh vegetables were around 2 μg/kg whereas uranium concentrations in other foods such as rice and meat were in the range of 0.1 to 0.2 μg/kg (WHO, 2001).

The military use of depleted uranium is likely to have an impact on the environmental levels of uranium in specific places where depleted uranium munitions have been used. The exposure to depleted uranium is mainly through the inhalation of relatively insoluble depleted uranium oxide particles from munitions in conflict zones (Parrish *et al*., 2008) and the ingestion of food or drinking water contaminated with depleted uranium. The dermal contact is relatively unimportant except when open wounds or embedded depleted uranium fragments are present (WHO, 2001).

A person can be exposed to natural uranium by inhaling dust in air or by ingesting contaminated water and food. The amount of uranium in air is usually very small; however, people who work in factories that process phosphate fertilizers, live near facilities that made or tested nuclear weapons, live or work near a modern battlefield where depleted uranium weapons have been used, or live or work near a coal-fired power plant, facilities that mine or process uranium ore, or enrich uranium for reactor fuel, may have increased exposure to uranium. The daily intake of uranium from each source for adults is estimated to be: air 0.001 μg; drinking water 0.8 μg; food 1.4 μg. Thus, the total daily intake is approximately 2.2 μg, or 0.037 μg/kg body weight (b.w.) for a 60-kg adult, the majority of which originates from food (WHO, 1998).

This opinion will only focus on the exposure to natural uranium through ingestion of water and food. The gastrointestinal absorption of uranium is low. The absorbed uranium fraction rapidly enters the bloodstream and is distributed to the kidney and bones, where it tends to accumulate. The kidney is recognized as the primary target organ for uranium both in experimental animals and humans.

The German Federal Institute for Risk Assessment (BfR) has asked the European Food Safety Authority (EFSA) to conduct a risk assessment on uranium intake at European level, thus providing information on the maximum tolerable intake levels of uranium from foodstuffs, in particular tap and bottled waters. The work will focus on the chemical toxicity related to the exposure to natural uranium through food and water ingestion, without taking into account the radioactivity content in water and foodstuff. This latter part will be addressed by the Group of Experts established under Article 31 of the European Atomic Energy Commission (EURATOM) Treaty under the Directorate-General for Energy and Transport. Since significant exposure to depleted uranium is strictly related to its military use and is therefore confined to limited conflict areas, the present opinion will not address this peculiar type of exposure.

2. Chemical characteristics

Uranium is a silvery-white metal occurring in a number of minerals such as uraninite, carnotite and pitchblende. It can be found in low concentrations in soil and rocks, as well as in surface and ground water. It is a member of the actinide series and has an atomic number of 92 and atomic mass of 238.03 g/mol. It is malleable, ductile and slightly paramagnetic. The density of uranium is very high (18.95 g/cm^3 at 20 °C), around 1.5 fold more dense than lead. In air, it is oxidized and the metal becomes coated with a layer of oxide. At ambient temperature uranium metal is pyrophoric, and ignites spontaneously when finely divided.

Radiological properties

Uranium is a naturally occurring radioactive element. Several different radioisotopes of uranium exist, although all undergo the same chemical reactions in nature and possess almost identical physical characteristics, such as melting point, boiling point and volatility. The radioactive properties (half-life, specific activity, decay mode etc.) of the isotopes are, however, different. Natural uranium consists of three main isotopes, i.e. ^{234}U, ^{235}U and ^{238}U. The natural abundance, the specific activities and the half-life are shown in Table 1. All three isotopes decay while emitting α-particles and weak γ rays, with the ^{235}U isotope being capable of fission. The decay process of the isotopes leads to stable non-radioactive isotopes such as ^{206}Pb in the case of ^{234}U and ^{238}U, and ^{207}Pb in the case of ^{235}U. The isotope ratio $^{235}U/^{238}U$ has a constant value (0.7253) in natural samples. However, this ratio can change due to the presence of contaminants such as depleted uranium (Tagami and Uchida, 2007).

Table 1. Natural abundance, specific activity and half-life of the three main uranium isotopes (Pfenning *et al*., 1998; WHO, 2001).

	Natural abundance (%)	Specific Activity (pCi/μg)	Half-life (years)
^{234}U	0.0054	6208.2	2.446×10^5
^{235}U	0.7200	2.17	7.038×10^8
^{238}U	99.2745	0.336	4.47×10^9

Chemical properties

Chemical properties are identical for all uranium isotopes. The main oxidation forms are +III, +IV, +V and +VI, resulting in the ions U^{3+} (red), U^{4+} (green), UO_2^+ (unstable) and UO_2^{2+} (yellow), respectively. The mobility of uranium is highly dependent on the oxidation state, the pH and the presence of inorganic/organic ligands, resulting in different solubility, complexation and distribution. The major oxidation states in the environment are +IV and +VI (Harper and Kantar, 2008). Under reductive conditions, the uranous species (oxidation state +IV) tend to bind to organic material and precipitate, thus having a reduced mobility (Sheppard *et al*., 2005). However, under oxidising conditions this form is readily oxidised to the +VI state forming the uranyl ion (UO_2^{2+}) which is the most prevalent and stable species in nature (Sheppard, 1980). The uranyl ion can form soluble complexes with carbonate, phosphate and sulphate ions, enhancing its mobility. Uranyl tricarbonate species are very stable and soluble in aqueous solutions, while uranyl phosphates show low solubility under neutral pH conditions (Gorman-Lewis *et al*., 2008).

Solid oxides such as uranium dioxide (UO_2), mainly used for nuclear reaction fuel, and triuranium octaoxide (U_3O_8), produced during the uranium mining and milling process, have a low solubility in water and are stable over a wide range of environmental conditions. At ambient temperatures, UO_2 will gradually convert to U_3O_8. Other compounds formed during the manufacturing of uranium for industrial purposes are uranium fluorine compounds. Uranium hexafluoride (UF_6) is used in the uranium enrichment process while uranium tetrafluoride (UF_4) is frequently produced as an intermediate in the processing of uranium. Both forms are soluble uranium compounds (Sheppard *et al*., 2005).

3. Legislation

There are currently no maximum levels for uranium in foodstuffs, mineral water or drinking water in the European Union (EU). However, some Member States and Third Countries have set maximum levels for uranium in various commodities (Table 2).

Table 2. Maximum levels for uranium in water (BfR, 2005; WHO, 2005; US-EPA, 2003).

Country/Bodies	Drinking water	Mineral water [(a)]	Water for infant formula
Czech Republic	12 Bq/L (964 µg/L) [(b)]	24 Bq/L (1929 µg/L) [(b)]	5 Bq/L (402 µg/L) [(b)]
Germany	10 µg/L [(c)]	2 µg/L	2 µg/L
Bulgaria	60 µg/L		
Finland	100 µg/L [(c)]		
Slovenia	6.8 µg/L	6.8 µg/L	
Slovakia	^{234}U: 3.9 Bq/L ^{235}U: 4.1 Bq/L ^{238}U: 4.3 Bq/L (346 µg/L) [(b)]	^{234}U: 12.1 Bq/L ^{235}U: 12.6 Bq/L ^{238}U: 13.2 Bq/L (1061 µg/L) [(b)]	^{234}U: 1.8 Bq/L ^{235}U: 1.9 Bq/L ^{238}U: 2.0 Bq/L (161 µg/L) [(b)]
US-EPA	30 µg/L	30 µg/L	
WHO	15 µg/L		

(a): Defined as spring water and table water
(b): For ^{238}U a specific activity of 1 Becquerel/L (Bq/L) represents 0.0803 µg/g or 80.37 µg/L
(c): Recommended value

4. Sampling and methods of analysis

In the EU no official method is prescribed for the determination of uranium in drinking and mineral water or in foodstuffs. The US-EPA adopted Method 908.0 for the measurement of total uranium in drinking water by using radiochemical methods (US-EPA, 1999) and Method 200.8 for the determination of trace elements in ground waters, surface waters and drinking water, including uranium, by inductively coupled plasma-mass spectrometry (ICP-MS) (US-EPA, 1994).

A number of analytical methods for the determination of uranium in different matrices can be found in the literature. The choice of one or another depends on the nature of the samples to be analysed and consist usually of a pre-concentration step followed by the instrumental determination, mainly carried out by means of radiometric or spectrometric methods. Depending on the method, uranium can be measured either as the activity of the radionuclide or as the mass fraction of the isotopes. Since the regulatory limits of uranium in drinking water are in some cases expressed in mass units (see chapter 3), when results are provided in radioactivity units they must be converted to the suitable mass units. This conversion requires knowledge of the concentration of the three natural uranium isotopes (^{234}U, ^{235}U and ^{238}U), since isotopic disequilibrium can exist within uranium nuclides (Vesterbacka, 2005). The conversion from activity units to mass concentration units is done by relating the specific activity expressed as decays per unit time, curies (Ci) or Becquerels (Bq), to the number of

atoms by using the decay constant (related to the half-life of the specific radionuclide). For ^{238}U, a specific activity of 1 Bq/L represents 0.0803 μg/g or 80.37 μg/L.

Pre-concentration

The low concentration of uranium in water and food together with the presence of a complex matrix makes it difficult to measure directly the uranium content. In order to improve the sensitivity and avoid interference from other radionuclides and matrix components, a pre-concentration step is usually applied. Food samples typically undergo acid digestion prior to quantification (FSA, 2004). For water samples, techniques such as co-precipitation, liquid-liquid extraction (solvent extraction), ion exchange and solid-phase-extraction (SPE) have been used (Unsworth *et al*., 2001; Sadeghi *et al*., 2003; Sadeghi and Sheikhzadeh, 2009; Prasada Rao *et al*., 2008). The use of SPE offers a number of advantages over liquid-liquid extraction such as a higher enrichment factor and lower consumption of reagents and, therefore, cost (Prasada Rao *et al*., 2008).

Analytical determination

The instrumental techniques applied for the determination of trace concentrations of natural uranium in water include mainly radiometric and mass spectrometric (MS) methods, the latter group being more sensitive for long-lived radionuclides such as uranium (May *et al*., 2008). For the radiometric methods the atom number of the radionuclide of interest is calculated based on the decay using its half-life, while for the MS methods, the atom numbers are directly measured (Hou and Roos, 2008).

Different radiometric methods such as γ-spectrometry, α-spectrometry and β-counting have been traditionally employed. Although α-spectrometry is a cheap and easy to maintain technique, a chemical separation of the uranium isotopes from other interfering isotopes present in the matrix is needed prior to analysis since the α-particles energies of many isotopes differ by as little as 10-20 KeV. Therefore, the use of this technique suffers from long analysis time in addition to the usually required long counting times (Wallner *et al*., 2008).

MS methods have been also used for the determination of long-lived radionuclides in water and other matrices such as secondary ion MS (SIMS), glow discharge MS (GDMS), thermal ionization MS (TIMS) and especially ICP-MS. The latter offers high sensitivity, precision and good accuracy, and is currently the technique of choice replacing the use of TIMS (Hou and Roos, 2008; D'Ilio *et al*., 2007). In this case for fresh water samples no radiochemical separation is needed (Tagami and Uchida, 2007). The major drawbacks are the isobaric interferences of other elements at the same mass and interferences from polyatomic atoms commonly formed in the plasma or interface system from the plasma gas, reagents or samples matrix, that have the same mass-to-charge ratio. The introduction of collision/reaction cells significantly suppresses these interferences by choosing a suitable reaction gas as well as the use of high-resolution (magnetic sector) instruments (Hou and Roos, 2008). Several studies in drinking water have compared the results obtained by radiochemical methods and ICP-MS. Wallner *et al*. (2008) compared the results obtained for uranium in drinking water by α-spectrometry and ICP-MS. For α-spectrometry, the natural uranium concentration (μg/L) was calculated based on the ^{238}U activity concentration. The two methods provided similar results for the ten samples analysed, although α-spectrometry might overestimate the radionuclide concentration when close to the limit of detection (LOD) (40 ng/L). LODs for ICP-MS were reported to be 40 times lower (1 ng/L). In addition, the use of ICP-MS allowed reducing the total analysis time by half. Pawlak and Rabiega (2002) compared the performance of US-EPA Method 200.8 using ICP-MS and US-EPA Method 908.0 using radiochemical methods. Using

radiochemical methods, sample pre-concentration was needed and the whole procedure took five days for four samples and three standards. On the other hand, the use of ICP-MS allowed direct measurement. Discrepancies in the concentrations obtained by the two methods were found and were mainly attributed to the long sample preparation procedure using the radiochemical method.

Other techniques used for natural uranium determination in waters include X-Ray Fluorescence Spectrometry (XRF) and laser fluorimetry or laser induced spectroscopy. Total reflection XRF (TXRF) is increasingly being used for trace elemental determinations, although when dealing with seawater, the increased amount of salt and the low concentrations of uranium demand complex pre-concentration steps (Misra *et al*., 2006). Regarding laser induced spectroscopy, uranium is a strong fluorophore which absorbs well in the region of 260-350 nm and emits strongly in the region 450-600 nm. However, when dealing with complex samples, the fluorescence may be quenched by a number of other species present in the analyte solution, which is a common problem to other fluorophores (Kumar *et al*., 2008).

5. Occurrence in water and food

5.1. Literature data

Studies on the occurrence of natural uranium in food and particularly in water have been carried out worldwide in the last decades. Most of them reported average levels of uranium in different types of drinking waters below 3 μg/L (Table 3), but very often the maximum values exceeded the WHO guidance limit of 15 μg/L (WHO, 2005).

In a study of 1,456 samples of mineral water in Germany, only 2.1 % of them were found to have uranium at a level above 15 μg/L. The German Federal Office of Consumer Protection and Food Safety (BVL) presented in the report from 2006 that from 772 water samples tested (bottled water, mineral water, groundwater, table water, and well water), most of them originating in Germany, 319 contained measurable levels of uranium. The average concentration of uranium was higher in mineral water and groundwater (1.1 μg/L) than in well water and table water (average 0.4 μg/L). Only two samples contained uranium above the level of 15 μg/L (35 and 39 μg/L) (BVL, 2006).

Anke *et al*. (2009) found that tap water in Thuringia contained uranium nine times higher than in Mecklenburg-Western Pomerania and eight times higher than in Brandenburg. The range of uranium concentrations in bottled mineral water was much wider (0.015 to 24.5 μg/L) than that of tap water (0.05 to 8.6 μg/L). Uranium content in German beverages followed the pattern: white wine > coke > lemonade > red wine > vermouth > fruit juice > beer, with average concentrations ranging between 0.30 μg/L and 1.3 μg/L.

In Finland, the uranium concentration in drilled wells may reach a few mg/L. Most of the highest concentrations were found in the southern part of the country (maximum 12.4 mg/L) (Huikuri *et al*., 2001). These data are supported by the study of Kurttio *et al*. (2002) (average uranium concentration, 131 μg/L) and the study of Vesterbacka *et al*. (2005), who reported that approximately 18 % of the 472 privately drilled wells in Finland exceeded the WHO guidance value of 15 μg/L. Similar results have been reported in groundwater samples from boreholes in Norwegian crystalline bedrock; 18 % of the samples contained uranium at a level higher than 20 μg/L (Frengstad *et al*., 2000).

A relatively high concentration of uranium (average, 30 μg/L) has been found in source water from Bathinda district, India (Kumar *et al*., 2006), whereas in other regions of the country most of the water samples contained uranium at levels below 15 μg/L (Singh *et al*., 2008). The authors explained that the high uranium concentration in water was caused by the rich granite hills of the neighbouring region. As suggested by Katsoyiannis *et al*. (2007), the presence of uranium in groundwater is highly associated with the oxidative conditions of the soil. Under reductive conditions uranium occurs in insoluble form and is therefore immobile.

In an assessment of ground water quality and its environmental implications in a region of an abandoned uranium mine in central Portugal, Neves and Matias (2008) reported concentrations of uranium in mine water of up to 6,000 μg/L, in contaminated wells of up to 2,000 μg/L, whereas in uncontaminated wells they reported concentrations below 39 μg/L.

The reported occurrence data demonstrate that uranium levels in water may vary considerably with the type of water, geological origin, and anthropogenic uranium emissions. An overview is given in Table 3.

The uranium content in foodstuffs may also be very different and depends on the uranium content in water and soil. Anke *et al*. (2009) found that wild and cultivated plants from the immediate vicinity of uranium waste dumps stored eight-fold more uranium than the control plants. Leafy plant species accumulated much uranium, whereas tubers, thick parts of stalks, fruits and grains stored less uranium. Foodstuffs like margarine, bee honey and pearl barley are generally low in uranium with concentrations between 0.8-1.9 μg uranium/kg dry matter (DM). In asparagus 50 μg uranium/kg DM was found while mixed mushrooms contained more than 100 μg uranium/kg DM. Foodstuffs rich in sugar, starch, and fat (fruits, seeds, flour) proved to contain less uranium compared to leafy vegetables, tea and herbs (Anke *et al*., 2009).

The highest concentration of ^{238}U among 125 individual types of food from Yokohama City was found in boiled and dried hijiki (a seaweed, *Sargassum fusiforme*, syn. *Hizikia fusiformis*). However, almost all fish and shellfish samples contained lower uranium concentrations (Kuwahara *et al*., 1997).

In a total diet study by the UK Food Standards Agency (FSA), fish and bread were found to have the highest concentrations of uranium (average, 3.5 μg/kg, each) among the 20 food groups analysed (FSA, 2004).

Generally, animal foodstuffs accumulate less uranium, but higher concentrations can be found in shellfish and fish, that accumulate more uranium than the terrestrial animals (Ribera *et al*., 1996; WHO, 2001; Anke *et al*., 2009).

Uranium content in infant and follow-on formulae was low, but it can dramatically increase if it is prepared with uranium rich mineral water (Anke *et al*., 2009).

Drinking water and beverages are important contributors to the natural uranium exposure in humans, especially among population groups where the local drinking water source has elevated uranium concentrations (Schnug *et al*., 2005; WHO, 2005; BfR, 2007). Anke *et al*. (2009) calculated that 41 % of the ingested uranium is delivered by water and beverages, and 59 % by food (33 % through vegetables and 26 % through animal foodstuffs).

Table 3. Occurrence of uranium in water.

Country/Area	Type of sample	n	Uranium concentration, µg/L		Reference
			Average	Range (min – max)	
Canada/Ontario	Treated drinking water	3,700	0.40	0.05-4.21	OMEE, 1996
USA, New York City	Drinking water	978	2.55		US-EPA, 1990, 1991
Germany	Mineral water	1,456	2.64	< 0.2-44.2	BfR, 2005
Northern Germany	Wells water	48	0.87	0.015-8.95	Schnug *et al.*, 2005
	Tap water	39	0.18	0.015-1.44	
	Favourite bottled water	17	1.84	0.015-10.6	
Northern Greece	Wells water	42		0.061-10.02	Katsoyiannis *et al.*, 2007
Austria	Mineral water	9		0.012-5.4	Wallner *et al.*, 2008
Germany	Tap water	152	1.3	0.05-8.6	Anke *et al.*, 2009
	Mineral and medicinal	252		< 0.015-24.5	
Iran	Drinking water	200		1-10.9	Alirezazadeh and Garshasbi, 2003
India, Upper Silwaliks	Drinking water	34		1.08-19.68	Singh *et al.*, 2008
Western Uzbekistan	Drinking water	11		0.01-27.63	Kawabata *et al.*, 2006
	River and canal water	22		1.54-11.31	
Poland	Bottled mineral water	28		< 0.04-0.62 [(a)] (< 0.5-7.7 mBq/L)	Kozlowska *et al.*, 2007
Italy	Bottled water	8 brands		0.15-8	Bagatti *et al.*, 2003
Italy	Mineral water	17		0.017 - 8.3[(a)] (0.21-103 mBq/L)	Jia *et al.*, 2006
Northern Spain	Treated water	4 water treatment plants	0.064[(a)]	0.003 - 0.23[(a)] (0.039-2.90 mBq/L)	Herranz *et al.*, 1997
India, Punjab [(b)]	Drinking water	24	30	2.23-87.05	Kumar *et al.*, 2006
Southern Finland [(b)]	Wells water	325	131	0.001-1920	Kurttio *et al.*, 2002

(a): Conversion of the ^{238}U activity concentration using the conversion factor of 1 Becquerel/L (Bq/L) equivalent to 80.37 µg/L
(b): Regions with high natural uranium concentration in soil and water (hot spots)

5.2. Current uranium occurrence in water and food

In June 2008, the EFSA issued a specific call to selected countries for data on uranium concentrations in individual water and food samples. Between June and November 2008, a total of eight countries (France, Germany, Hungary, Italy, Portugal, Sweden, Switzerland and the UK) sent data to EFSA, as detailed in Table 4. The submitted samples covered the period between 2000 and 2008.

Data on uranium concentrations in water in Italy were sent directly by researchers involved in uranium data collection (Desideri *et al.*, 2007). In UK, data from a monitoring report were extracted (Radioactivity in Food and the Environment, RIFE, 2007). For Finland, a total of 288 and 184 samples of uranium activity concentrations in water from drilled and dug wells, respectively, were reported in a PhD thesis (Vesterbacka, 2005). The document was sent to EFSA, but data were not used as the information was reported at the aggregate level only.

For the analyses, 13 observations from Germany were excluded because of sparse data in two food categories. Some 76 observations from Hungary were removed because of missing information on food category (n=19) or because of limited sample size in individual food categories (n=57). A total of 7,097 uranium concentration values for tap water, bottled water and soft drinks and 1,387 values for foodstuffs were retained for statistical analyses.

Table 4. Water- and food-specific sample sizes of uranium concentration values collected in a selection of European countries in the period 2000-2008, and received by EFSA.

Country	n (water)	n (food)
Finland	472 [(a)]	
France	736	
Germany	1,391	1,387
Hungary	101	
Italy	51	
Portugal	77	
Sweden	255	
Switzerland	4,491	
UK	84	
Total	7,658	1,387

(a): Aggregated data only. Not used for exposure assessment calculations

5.3. Distribution of samples across food categories

Occurrence data were grouped in two broad categories (water and food), and a number of sub-categories, as detailed in Table 5. Information on uranium concentration in foodstuffs was received from Germany only (n=1,387). German data on food were organised according to the categories used in the Concise European Food Consumption Database (EFSA, 2008). No information on Coffee, Tea, Cocoa (7A), Beer (9A), Fats (Group 3), Wine (9B) and other alcoholic beverages (9C) were available in the data received by EFSA. Water-based products included Tap Water (15), Bottled Water (7C), Soft drinks, Coffee, Tea (8), and Beer (9A). All other food categories were grouped in the respective food group. Uranium concentration

values are reported in the RIFE report (RIFE, 2007). These data were not included in the present work because the amount of available information was very sparse.

Table 5. Sample size distribution according to the aggregated categories of the EFSA Concise European Food Consumption Database.

Water	EFSA Category	Sample size
Tap water	15	5,475
Bottled water	7C	1,545
Soft drinks	7B	57
Coffee, Tea, Cocoa	8	-
Beer	9A	-
Foodstuffs		
Cereal and cereal products	1	171
Sugar and sugar products including chocolate	2	38
Fats (vegetable and animal)	3	-
Vegetables	4	676
Starchy roots or potatoes	5	79
Fruits	6	167
Fruit and vegetable juices	7A	11
Wine	9B	-
Other alcoholic beverages	9C	-
Meat and meat products	10	67
Fish and seafood	11	22
Eggs	12	17
Milk and dairy based products	13	15
Miscellaneous	14	110

5.4. Analytical methods used and limits of detection

Although this report focuses on the chemical content of uranium in water and foodstuffs, in some countries only information on the radiological content of ^{238}U in water was available, as detailed in Table 6. Radiological data were expressed in Bq/L, and were converted in μg/L using a standard formula, e.g. 1 Bq/L ^{238}U= 80.37 μg/L ^{238}U. Similar conversion formulas were not applied for ^{234}U and ^{235}U because their mass contribution can be considered negligible.

Chemical concentration values were uniformly expressed in μg/L for water and μg/kg for foodstuffs. As already mentioned in section 5.1., in this report occurrence data on only natural uranium were collected.

Table 6. Type of measurement and unit of measure for concentration data from the respective country.

Country	Type of measurements	Method	Unit
France	Radiological activity	α-spectrometry	Bq/L
Germany	Chemical concentration	ICP-MS	mg/kg
Hungary	Radiological activity	α-spectrometry	Bq/L
Italy	Radiological activity	α-spectrometry	mBq/L
Portugal	Radiological activity	α-spectrometry	mBq/L
Sweden	Chemical concentration	ICP-MS	μg/L
Switzerland	Chemical concentration	ICP-MS	μg/L
UK	Radiological activity	α-spectrometry	Bq/L

Although the two methods for uranium quantification were used evenly across countries that contributed to data collection, ICP-MS (n=7,333) was used for a larger number than α-spectrometry (n=331).

The frequency of samples below the LOD varied sizably in water-based groups and food (Table 7). The percentage was equal to 5.3 % and 17.5 % in tap and bottled water, respectively, while an additional 2.5 % and 12.7 % of samples were between LOD and the limit of quantification (LOQ). On the contrary, in foodstuffs values below LOD ranged between 13.7 % for miscellaneous to 94.7 % and 100 % for cereals and eggs, respectively. In practice, the vast majority of samples from foods were either below LOD or between LOD and the LOQ. This is mainly attributed to a notable degree of heterogeneity of LOD values in the different water and food groups. A comparison of LOD values in water and food groups performed in samples from Germany revealed that higher LOD values were observed for foods, particularly in cereal (mean=2.77 μg/kg) and sugar products (2.60 μg/kg), than in tap (0.65 μg/L) and bottled waters (0.44 μg/L).

In addition, the number of samples below LOD varied considerably across countries (results not shown), although LOD values below 1.2 μg/L were consistently observed. France, Hungary and Portugal provided occurrence values above the LOD. In Switzerland and Germany, information on the LOQ was also provided.

Consistently in this opinion, two scenarios were assumed. First, according to a lower-bound scenario, values below the LOD and values between the LOD and LOQ were set to zero and to LOD, respectively. Second, according to an upper-bound scenario values below LOD and values between the LOD and LOQ were set to LOD or LOQ value, respectively. The discrepancy of the frequency of samples below LOD values between water and foodstuffs is relevant.

Table 7. Mean, range (5^{th}-95^{th} percentiles) of LOD values (μg/kg), percentage of samples below the LOD (< LOD) and between LOD and LOQ (< LOQ) for water-based products and food-based products.

Water	Mean[(a)]	Range (5^{th}-95th)	Maximum	< LOD	< LOQ[(a)]
Tap water	0.65	0.01-1.20	1.20	5.3	2.5
Bottled water	0.44	0.02-1.00	5.00	27.5	12.7
Soft drinks	0.41	0.10-0.50	0.50	73.7	0.0
Foodstuffs					
Cereal and cereal products	2.77	1.00-3.00	3.00	94.7	5.3
Sugar and sugar products including chocolate	2.60	1.50-3.00	3.00	68.4	31.6
Fats (vegetable and animal)	Not reported	-	-	-	-
Vegetables	0.82	0.60-1.52	3.03	41.3	41.7
Starchy roots or potatoes	0.81	0.50-1.52	1.52	59.5	39.2
Fruits	0.62	0.20-0.61	1.52	91.0	6.6
Fruit and vegetable juices	0.68	0.60-1.52	1.52	63.6	36.4
Wine	Not reported	-	-	-	-
Other alcoholic beverages	Not reported	-	-	-	-
Meat and meat products	1.01	0.60-2.00	2.00	70.2	25.4
Fish and seafood	0.60	0.60-0.60	0.60	77.3	22.7
Eggs	0.60	0.60-0.60	0.60	100.0	0.0
Milk and dairy based products	1.50	1.50-1.50	1.50	80.0	20.0
Miscellaneous	2.49	0.61-5.00	10.00	13.7	66.1

(a): Percentage of samples above the LOD and below the LOQ

5.5. Occurrence data by food category

Country-specific descriptive statistics of uranium concentrations in tap and bottled waters are shown in Tables 8a and 8b, respectively. France, Germany, Switzerland and UK provided samples to both tap and bottled water, while all other countries contributed to one type only. For tap water, upper-bound mean values of sample measurements collected by EFSA ranged between 0.83 μg/L observed in Germany and UK, to 3.33 μg/L in France. For bottled water, means ranged between 0.72 μg/L in Italy to 8.74 μg/L in France. These values were in line with findings reported in the literature (as shown in Table 3). Results were even more in the same range when focusing on studies conducted in European countries. In the EFSA database, France and Hungary showed slightly higher uranium values than the rest of selected European countries. Values at the 95^{th} percentile were overall below the WHO limit of 15 μg/L in all countries, with the exception of bottled water in France (41.79 μg/L). In Sweden a 95^{th} percentile value equal to 13.60 μg/L was shown.

Table 8a. Descriptive statistics of uranium concentration in tap water (μg/L). The intervals indicate values in the lower- and upper-bound scenarios, respectively. A single value indicates no difference between lower- and upper-bound results.

Country	n	P5	Mean	Median	P95	Maximum
France	642	0.00-0.27	3.12-3.33	0.43-0.71	11.45	112.51
Germany	97	0.50	0.82-0.83	0.50	1.80	10.50
Hungary	25	1.01	2.06	1.90	4.18	4.20
Italy	-	-	-	-	-	-
Portugal	-	-	-	-	-	-
Sweden	255	0.00-1.20	1.79-2.75	0.00-1.20	13.60	40.80
Switzerland	4,423	0.06	2.12	0.73	9.41	92.02
UK	33	0.00-0.78	0.12-0.83	0.00-0.80	0.80	1.69

Table 8b. Descriptive statistics of uranium concentration in bottled waters (μg/L). The intervals indicate values in the lower- and upper-bound scenarios, respectively. A single value indicates no difference between lower- and upper-bound results.

Country	n	P5	Mean	Median	P95	Maximum
France	94	0.24	8.74	1.89	41.79	152.70
Germany	1,224	0.00-0.04	1.08-1.29	0.15-0.50	5.30	35.00
Hungary	--	-	-	-	-	-
Italy	51	0.04	0.72	0.33	2.89	7.15
Portugal	77	0.00	1.03	0.26	6.99	13.90
Sweden	-	-	-	-	-	-
Switzerland	66	0.01	2.54	1.02	7.71	30.35
UK	51	0.00-0.16	3.31-3.32	1.69	10.76	14.86

Uranium concentrations in water-based products and food are detailed in Table 9a and 9b. Tap and bottled waters showed similar averages, medians and 95th percentile values. Overall, higher values were observed in foods, particularly for cereal (lower- and upper-bound means equal to 0.08 and 2.93 μg/kg, respectively) and sugar products (0.63 and 3.96 μg/kg, respectively) compared to waters. The food group 'miscellaneous' showed relatively high uranium concentration values. However, given the low consumption of food belonging to this category, this is likely to have a rather minor impact on total uranium exposure in food. As illustrated in Table 7, high mean values in the upper-bound scenario are partially attributable to the limited amount of information in foodstuffs and to a lack of sensitivity in the analytical method to detect uranium concentrations in food compared to water, as already mentioned in section 5.4. The fact that the vast majority of samples were either below LOD or between LOD and LOQ, raises concerns on the accuracy of uranium concentration values in foodstuffs. Overall, exposure assessment calculations in food groups should be interpreted cautiously. In Table 9b, it is noteworthy that two maximum values are reported for cereals, sugars and fruits and vegetables. In these food groups, the maximum values were equal to the LOQ. As detailed in section 5.4., values between the LOD and LOQ were treated differently in the lower- and upper-bound scenarios.

Table 9a. Descriptive statistics of uranium concentration in water and water-based products (μg/L) according to food categories in the Concise European Food Consumption Database. The interval indicates lower- and upper-bound values while a single value indicates no difference between the two values.

Dietary group	n	P5	Mean	Median	P95	Maximum
Tap water	5,475	0.00-0.08	2.18-2.26	0.66-0.77	9.46	112.51
Bottled water	1,565	0.00-0.02	1.66-1.83	0.36-0.50	7.63	152.70
Soft drinks	57	0.00-0.10	0.52-0.83	0.00-0.50	3.20	5.60

Table 9b. Descriptive statistics of uranium concentration in food products (μg/kg), according to categories in the Concise European Food Consumption Database. All data on foodstuff are from Germany. The interval indicates lower- and upper-bound values, while a single value indicates no difference between the two values.

Dietary group	n	P5	Mean	Median	P95	Maximum
Cereal and cereal products	171	0.00-1.00	0.08-2.93	0.00-3.00	0.50-3.00	3.00-9.00
Sugar and sugar products	38	0.00-1.50	0.63-3.96	0.00-3.00	3.00-9.00	3.00-9.00
Fats (vegetable and animal)	-	-	-	-	-	-
Vegetables	676	0.00-0.60	1.37-2.54	0.61-2.00	5.00-6.00	87.00
Starchy roots or potatoes	79	0.00-0.50	0.55-1.94	0.00-0.60	1.52-5.00	6.00
Fruits	167	0.00-0.20	0.35-1.07	0.00-0.60	1.52-5.00	28.00
Fruit and vegetable juices,	11	0.00-0.60	0.30-1.33	0.00-0.60	1.52-5.00	1.52-5.00
Wine	-	-	-	-	-	-
Other alcoholic beverages	-	-	-	-	-	-
Meat and meat products	67	0.00-0.60	0.46-1.71	0.00-1.00	2.00-5.00	6.30
Fish and seafood	22	0.00-0.60	0.14-0.87	0.00-0.60	0.60-1.80	0.60-1.80
Eggs	17	0.00-0.60	0.00-0.60	0.00-0.60	0.00-0.60	0.00-0.60
Milk and dairy based products	15	0.00-1.50	0.30-2.10	0.00-1.50	1.50-4.50	1.50-4.50
Miscellaneous	124	0.00-1.00	3.70-4.04	0.06-2.00	10.00	25.00

6. Food consumption

As water has been observed to be one of the main dietary sources of exposure to uranium, special attention was given to the consumption of bottled and tap water, and to all water-based beverages (coffee, tea, soft drinks and beer). However, significant uranium levels were also found in solid foods, in particular in leafy vegetables grown on soil with high uranium concentration and in fish and seafood (Kuwahara *et al.*, 1997; Anke *et al.*, 2009). Uranium exposure was thus assessed for all food groups containing uranium. In addition, sub-populations with potentially high intakes of uranium due to differences in the consumption patterns were evaluated. The Concise European Food Consumption Database (EFSA, 2008) provides consumption data for the adult population in European countries. However, the

database currently only provides data on a limited number of food categories and for the adult population.

6.1. EFSA's Concise European Food Consumption Database

The Concise European Food Consumption Database was established by EFSA to support exposure assessments in the EU. Currently 19 countries have provided national food consumption data. To maximize the degree of comparability of dietary estimates, consumption data were aggregated in 15 broad food groups and 29 subcategories. Some Member States provided data only for the broad food groups. The consumption figures for all food groups are complemented by information on the individuals: gender, age and body weight. Main statistics of the data are published on the EFSA website and contain mean consumption, median and standard deviation as well as several low and high percentiles of consumption.

The Concise European Food Consumption Database is intended as a screening tool for exposure assessment as well as the first step on the way to a more comprehensive database. As a screening tool it is possible to assess exposure of individuals on a broad level to a wide variety of substances. It is expected that using conservative assumptions for a lot of substances (e.g. environmental contaminants and food additives) no refinement will be necessary because of no concerns raised. The main limitations of the Concise European Food Consumption Database derive from the broad food categories used and the different methodologies employed for data collection. A guidance document for the use of the data has been published on the EFSA website (EFSA, 2008). Summaries of the food consumption data used in this opinion are given in Tables 10 and 11.

In order to estimate the exposure to uranium, all the 15 broad categories included in the Concise European Food Consumption Database were used. For two food categories consumption data were used at the level of subcategories. For group 7 three sub-groups were evaluated, notably subcategories 7A ("Fruit and vegetable juices"), 7B ("Soft drinks with percentage of fruits lower than nectar, excluding fruit juices") and 7C ("Bottled water"). Also for group 9 three sub-groups were evaluated, subcategories 9A ("Beer and substitutes"), 9B ("Wine and substitutes") and 9C ("Other alcoholic beverages and substitutes"). This choice was motivated by the interest to evaluate all water-based beverages.

It is important to highlight the fact that not all 19 countries provided consumption figures for all broad categories and subcategories. In particular, consumption figures were not available for any of the above mentioned subcategories for Estonia and Finland. These countries were therefore excluded. Consumption of "Bottled water" (subcategory 7C) were not provided by Iceland and Ireland whereas Bulgaria, Estonia and Poland did not report data on "Tap water" (broad category 15). Moreover, it is important to notice that very low tap water consumption figures were reported in Hungary, where a very low percentage of consumers was registered (less than 1 % in the population, data not shown). This explains why the 95th percentile value is lower than the mean.

Data on water consumption in Switzerland were available from three Swiss surveys conducted in 2007 on a total of 83 subjects, comprising of both men and women. Mean and 95th percentile consumption values (g/day) were, respectively, 740 and 1,680 for tap water, 270 and 860 for bottled water, and 820 and 1,740 for the group "Tea, coffee, beer, soft drinks".

Table 10. Mean consumption (g/day) in the adult population in 17 European countries (Annex 3 to EFSA, 2008).

Dietary group	AT	BE	BG	CZ	DE	DK	FR	GB	HU	IE	IS	IT	NL	NO	PL	SE	SK
Tap water	594	114	-	288	71	840	283	202	1	284	670	206	209	312	-	480	224
Bottled water	216	544	52	462	628	65	283	60	137	-	-	330	41	75	159	62	287
Tea, coffee, beer, soft drinks	618	762	320	1054	996	1,225	365	1,194	323	1,158	854	193	1,232	1,035	797	896	682
Cereal and cereal products	330	249	257	274	280	217	317	244	252	227	276	271	220	192	312	291	345
Sugar and sugar products	23	31	40	39	43	43	31	27	39	41	31	19	43	47	57	28	69
Fats (vegetable and animal)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vegetables	211	214	210	131	249	166	210	164	191	244	125	249	193	140	295	118	164
Starchy roots or potatoes	59	98	83	103	122	112	67	109	110	229	79	48	128	133	304	138	96
Fruits	202	108	70	122	198	150	132	98	180	106	71	203	107	119	282	119	116
Fruit and vegetable juices,	144	85	42	34	141	73	57	49	47	34	87	18	70	86	35	87	33
Wine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other alcoholic beverages	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Meat and meat products	186	119	114	187	164	135	202	156	186	148	110	137	152	109	259	150	156
Fish and seafood	16	22	20	19	19	18	37	31	9	24	37	43	13	63	19	34	9
Eggs	5	10	21	20	23	16	18	18	27	20	11	18	15	21	31	14	13
Milk and dairy based products	171	216	169	186	304	386	265	256	265	306	442	212	388	522	181	386	91
Miscellaneous	13	1	13	15	40	5	2	18	17	13	23	5	6	12	7	16	6

Table 11. Values of 95th percentiles (g/day) in the adult population in 17 European countries (Annex 3 to EFSA, 2008).

Dietary group	AT	BE	BG	CZ	DE	DK	FR	GB	HU	IE	IS	IT	NL	NO	PL	SE	SK
Tap water	2,000	750	-	811	197	2,144	964	877	1	1,027	2,060	694	870	900	-	1,514	1,200
Bottled water	1,250	1,625	400	1,500	1,765	343	1,046	357	667	-	-	900	275	326	600	314	1,500
Tea, coffee, beer, soft drinks	1,700	1,916	1,000	2,450	2,296	2,537	976	2,472	883	2,477	2,100	533	2,333	2,196	1,600	1,693	1,900
Cereal and cereal products	686	503	560	551	481	359	546	466	400	395	613	427	393	337	636	503	730
Sugar and sugar products	94	97	155	112	121	100	85	84	93	109	124	53	117	120	144	78	150
Fats (vegetable and animal)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Vegetables	600	550	535	309	497	337	461	361	356	544	360	460	405	321	711	252	530
Starchy roots or potatoes	220	266	345	257	252	272	150	226	250	558	250	126	309	283	708	289	340
Fruits	638	346	355	355	495	431	383	311	468	335	285	459	332	333	840	313	450
Fruit and vegetable juices,	750	375	250	250	574	283	239	223	267	150	500	114	345	304	250	343	250
Wine	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other alcoholic beverages	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Meat and meat products	525	281	333	421	330	258	376	314	343	288	343	264	305	209	680	269	500
Fish and seafood	165	101	150	113	54	54	106	95	67	80	195	122	90	153	150	91	100
Eggs	60	56	120	76	59	43	57	60	74	55	60	43	57	47	150	46	100
Milk and dairy based products	530	583	531	521	807	921	570	560	610	668	1137	435	867	1173	596	802	425
Miscellaneous	80	5	31	33	201	10	3	54	35	47	112	13	23	22	17	59	20

7. Human exposure assessment

7.1. Dietary exposure

Uranium exposure from water and foodstuffs was estimated from the occurrence figures in Tables 9a and 9b and the food consumption figures in Tables 10 and 11. Occurrence values for tap and bottled water were computed separately. The uranium concentration in tap water was used to determine uranium exposure for the category 'Tea, coffee, beer, soft drinks' as tap water is the liquid source of those items. As shown in Table 9b, concentration data in foodstuffs was available from Germany only. Thus, the measured uranium concentration in some 57 samples of soft drinks from Germany was not used, as it was considered to be less reliable. Concentration values for individual food groups were used although considered even less reliable. No data were available for fat, wine and other alcoholic beverages. Country-specific consumption values were obtained from the Concise European Food Consumption Database. An important aspect of the exposure assessment calculation was that country-specific summary values (mean and 95th percentiles) of water-based and food-based groups were determined at the individual level using consumption data in the Concise European Food Consumption Database. Therefore, using data at the individual level, there was no need to identify the (two) most contributing water- or food-groups at the aggregate level, in line with the model specified in the guideline for the use of the database.

Total uranium exposure was calculated by multiplying occurrence values (μg/L for water and μg/kg for foods) by consumption values (g/day), adjusting for the unit discrepancy. Values of individual body weight of participants in the Concise European Food Consumption Database were used to express uranium exposure in μg/kg b.w. per day.

In order to provide summary figures of uranium exposure in Europe, the median of 19 country-specific uranium exposure values calculated for all water-based products and food are reported in Table 12, according to four different exposure scenarios. These scenarios were determined using combinations of average and 95th percentile values of occurrence and consumption figures. Notably, scenario 1 used mean values for dietary consumption in conjunction with water and food mean occurrence values, scenario 2 used 95th percentile consumption and mean occurrence values, scenario 3 used mean consumption and 95th percentile occurrence values and, scenario 4 used 95th percentile consumption and occurrence values. It should be noted that, for exposure scenario 2 and 4, the summary figure for overall water and overall food is not the arithmetic mean of individual dietary components. Both lower- and upper-bound median of the country-specific estimates of uranium exposure are reported in Table 12, as well as the maximum country-specific estimate.

Table 12. Medians of country-specific uranium exposure estimates in water and food sub-groups (μg/kg b.w. per day) according to different exposure scenarios. Lower- and upper-bound values are reported, together with the upper-bound country-specific maximum estimate in parenthesis.

Dietary group	Scenario 1 [(a)]	Scenario 2 [(b)]	Scenario 3 [(c)]	Scenario 4 [(d)]
Tap water	0.009-0.009 (0.026)	0.030-0.030 (0.070)	0.037-0.037 (0.113)	0.130-0.130 (0.302)
Bottled water	0.004-0.004 (0.014)	0.015-0.015 (0.042)	0.017-0.017 (0.064)	0.070-0.070 (0.191)
Tea, coffee, beer, soft drinks	0.025-0.025 (0.037)	0.059-0.059 (0.072)	0.108-0.108 (0.159)	0.258-0.258 (0.314)
Overall water	0.043-0.043 (0.064)	0.082-0.082 (0.118)	0.186-0.186 (0.278)	0.355-0.355 (0.513)
Cereal and cereal products	0.001-0.011 (0.014)	0.001-0.021 (0.031)	0.002-0.011 (0.015)	0.004-0.021 (0.031)
Sugar and sugar products	0.000-0.002 (0.004)	0.001-0.006 (0.009)	0.002-0.005 (0.009)	0.005-0.014 (0.021)
Fats (vegetable and animal)	-	-	-	-
Vegetables	0.004-0.007 (0.011)	0.010-0.018 (0.025)	0.014-0.016 (0.025)	0.036-0.043 (0.060)
Starchy roots or potatoes	0.001-0.003 (0.008)	0.002-0.007 (0.020)	0.002-0.007 (0.022)	0.006-0.019 (0.052)
Fruits	0.001-0.002 (0.004)	0.002-0.006 (0.013)	0.003-0.008 (0.021)	0.008-0.026 (0.061)
Fruit and vegetable juices,	0.000-0.001 (0.003)	0.001-0.005 (0.014)	0.001-0.005 (0.011)	0.006-0.020 (0.054)
Wine	-	-	-	-
Other alcoholic beverages	-	-	-	-
Meat and meat products	0.001-0.004 (0.006)	0.002-0.007 (0.015)	0.004-0.010 (0.018)	0.009-0.021 (0.045)
Fish and seafood	0.000-0.000 (0.001)	0.000-0.001 (0.002)	0.000-0.001 (0.002)	0.001-0.003 (0.005)
Eggs	0.000-0.000 (0.000)	0.000-0.000 (0.001)	0.000-0.000 (0.000)	0.000-0.000 (0.001)
Milk and dairy based products	0.001-0.008 (0.015)	0.003-0.019 (0.034)	0.006-0.017 (0.033)	0.014-0.041 (0.074)
Miscellaneous	0.001-0.001 (0.002)	0.002-0.002 (0.011)	0.002-0.002 (0.006)	0.004-0.004 (0.027)
Overall foodstuffs	0.009-0.040 (0.053)	0.016-0.066 (0.094)	0.036-0.087 (0.122)	0.063-0.143 (0.222)
Overall dietary	0.052-0.085 (0.105)	0.092-0.135 (0.171)	0.222-0.275 (0.364)	0.393-0.452 (0.622)

(a): Uranium exposure obtained multiplying consumption means by occurrence means
(b): Uranium exposure obtained multiplying 95th percentile consumption values by occurrence means
(c): Uranium exposure obtained multiplying consumption means by 95th percentile occurrence values
(d): Uranium exposure obtained multiplying 95th percentile consumption values by 95th percentile occurrence values

Upper-bound uranium exposure estimates in water were equal to 0.043, 0.082, 0.186 and 0.355 μg/kg b.w. per day in the four different scenarios considered. The group "tea, coffee, beer and soft drinks" was consistently the major contributor to uranium exposure. Lower-bound estimates were very similar in water-based groups. Upper-bound uranium exposure estimates for food were 0.040, 0.066, 0.087 and 0.143 μg/kg b.w. per day in the four scenarios, respectively. Major contributors were cereals (0.011 in scenario 1 and 0.021 in scenario 2), vegetables (0.016 in scenario 3 and 0.043 in scenario 4) and milk products (0.017 in scenario 3 and 0.041 in scenario 4). Unlike for water, lower-bound figures were between 2.5 (scenario 3) and 4-fold (scenario 1) lower compared to upper-bound results.

Overall medians of the country-specific lower- and upper-bound uranium exposure estimates were 0.052 and 0.085 μg/kg b.w. per day in scenario 1, 0.092 and 0.135 in scenario 2, 0.222 and 0.275 in scenario 3, and 0.393 and 0.452 in scenario 4. The upper-bound maximum country-specific estimate was 0.622 μg/kg b.w. per day for overall dietary exposure in scenario 4, the most extreme and unlike scenario. This is considered likely only in a locally uranium contaminated area and only for water exposure. Food would be most likely sourced from different less contaminated areas.

In scenario 1, food groups as a whole appeared to contribute about 50 % of total dietary uranium exposure using upper-bound figures, while lower percentages were observed for scenarios 2, 3 and 4. On the contrary, using lower-bound figures, the contribution of foodstuff to total uranium exposure was decidedly lower in scenario 1 (20 %) and 3 (16 %). The difference in the contribution of food and water to total uranium exposure using lower-and upper-bound figures is mainly driven by the large LOD values observed for food groups, particularly for cereals, where only 5.3 % of samples were above the LOD but still below the LOQ. Therefore, particularly in scenario 3, the role of water-based products in total uranium exposure is predominant. Conversely, Anke *et al.* (2009) estimated that "beverages" accounted for 41 % of total uranium exposure from diet.

Using consumption figures from Swiss surveys, upper-bound uranium exposure estimates in water were equal to 0.062, 0.112, 0.259 and 0.467 μg/kg b.w. per day according to the four exposure scenarios, respectively. Tap water and "Tea, coffee, beer and soft drinks" were the major contributors, accounting for 41 % and 44 % of total uranium exposure in scenario 1 and 3, respectively. Lower- and upper-bound estimates were virtually unchanged.

7.2. Specific sub-groups of the population

The infant scenario is based on the German DONALD study (Kersting *et al.*, 1998). In this study, a 3 month old infant was shown to weigh 6.1 kg on average and to consume, at the mean and 95th percentiles, 675 and 917 mL/day of water, respectively. These values resulted from mean and 95th percentile of infant formula intake (780 and 1,060 mL/day, respectively) and a reconstitution ratio of 135 g solid/L of ready-to-eat formula. Uranium exposure estimates are reported in Table 13, separately for tap and bottled waters, according to the same scenarios used for adult exposure (section 7.1.).

For tap water, lower- and upper-bound exposure estimates (in μg/kg b.w. per day) ranged from 0.241 to 0.250 in scenario 1, from 0.328 to 0.340 in scenario 2, and up to values equal to 1.047 and 1.422 in scenario 3 and 4, respectively. Values for bottled water were overall about 20% lower than for tap water, and showed similar pattern over the four scenarios.

Table 13. Uranium exposure estimates (μg/kg b.w. per day) for infants using tap and bottled waters according to different exposure scenarios. The interval indicates lower- and upper-bound values while a single value indicates no difference between the two values.

Type of water	Scenario 1 [(a)]	Scenario 2 [(b)]	Scenario 3 [(c)]	Scenario 4 [(d)]
Tap water	0.241-0.250	0.328-0.340	1.047	1.422
Bottled water	0.184-0.203	0.250-0.275	0.844	1.147

(a): Uranium exposure obtained multiplying consumption means by occurrence means
(b): Uranium exposure obtained multiplying 95th percentile consumption values by occurrence means
(c): Uranium exposure obtained multiplying consumption means by 95th percentile occurrence values
(d): Uranium exposure obtained multiplying 95th percentile consumption values by 95th percentile occurrence values

Applying values consistently with the scenario applied within the Committee on Toxicity (COT) report (COT, 2006), which used different values of infant body weight (4.5 kg) and water consumption (95th percentile value equal to 700 mL/day), resulted in upper-bound estimates equal to 0.285 and 1.187 μg/kg b.w. per day using mean and the 95th percentile values of bottled water, respectively. For tap water, the same values were equal to 0.352 and 1.472 μg/kg b.w. per day.

8. Hazard identification

8.1. Toxicokinetics

Uranium has no known biological function in animals and humans. The focus of this section will be on uranium toxicokinetics *via* the oral route. Data concerning routes of exposure other than oral ingestion (WHO, 2001; ATSDR, 1999) are not directly applicable in the assessment of the fate of dietary uranium.

8.1.1. Absorption

Animal and human data consistently indicate that the systemic availability of uranium after oral intake is very low. The majority (> 95 %) of ingested uranium is not absorbed from the gastrointestinal (GI) tract and it is excreted in the faeces. In humans, absorption of uranium has been shown to range from 0.1 to 6 % of the ingested dose (Wrenn *et al*., 1985; Legget and Harrison, 1995; Zamora *et al*., 2002; 2003). The compound's solubility affects the ease of absorption. Typical GI tract absorption rates for uranium in food and water are about 1-2 % for soluble uranium compounds and only 0.2 % of the oral dose for insoluble uranium compounds (Legget and Harrison, 1995; WHO, 2001). Overall, according to environmental and controlled clinical studies, the central estimates of GI uptake in adult individuals fall in the respective range of 0.3-3.2 % and 1-2.4 % of the total ingested uranium through food and liquids (Legget and Harrison, 1995). A recent investigation in 50 Canadian volunteers (age 13-87 years) chronically ingesting uranium at natural levels in drinking water and food, has provided a median value for GI absorption of 0.9 %, with 78 % of the subjects displaying values below 2 % (Zamora *et al*., 2002). For comparison with animal data, uranium GI uptake in rats has been reported to be < 0.1 % (Wrenn *et al*., 1985; after oral administration of 5.1-25.3 mg uranyl nitrate/kg b.w.), 0.6-2.8 % (La Touche *et al*., 1987; after oral administration of

0.003-45 mg uranium/kg b.w.), 0.06 % (Tracy *et al*., 1992; 91 days at 600 mg uranium/L *via* the drinking water), and 0.38 % (Paquet *et al.*, 2006; acute oral intake of uranyl nitrate). In rabbits uranium GI uptake accounted for 0.06 % (Tracy *et al*., 1992; 91 days at 600 mg uranium/L *via* drinking water) and 0.5-2 % (Harrison and Stather, 1981; Wrenn *et al*., 1985) of the ingested dose. It is likely that part of the differences in GI absorption attributed to interspecies variability could be due to differences in experimental conditions, especially uranium chemical form and ingested doses.

Some factors that influence the absorption of uranium from the gut have been identified experimentally (WHO, 2005). In particular, uranium is more readily taken up if it is in a soluble form (Berlin and Rudell, 1986), under fasting conditions (Sullivan *et al*., 1986; La Touche *et al*., 1987), and/or when it is co-administered with oxidizing agents, e.g., iron$^{(III)}$ ion and quinhydrone (Sullivan *et al*., 1986). There is also some evidence that ingested uranium is better absorbed by neonatal animals than by adult animals. Two-day-old rats fed uranium by gavage had uptakes of 1-7 % (Sullivan and Gorham, 1980), and pigs exposed to uranium on postnatal day 1 accumulated as much as 30 % of the given dose in the skeleton within a week post-exposure (Leggett and Harrison, 1995). There is no direct information on uptake of uranium in human neonates. The International Commission on Radiological Protection (ICRP, 1995) in its "Publication 69" assuming a gastrointestinal absorption fraction of 0.02 (i.e. 2 %) for all age groups and of 0.04 for children aged up to 1 year-old for uranium ingested in relatively stable form. Limited age-specific data for human subjects ≥ 5 years of age suggest that GI uptake may not vary strongly with age (Legget and Harrison, 1995). In human volunteers, no influence on the percentage of uranium GI absorption was exerted by gender, age (> 13 years), duration of exposure, daily total uranium intake (over the range 0.3-570 µg/day) or allocation of intake between food and water (Zamora *et al*., 2002; 2003). In another study (Karpas *et al*., 2005) in 205 individuals living in 134 different households in southern Finland (intake range of 0.03-2,775 µg uranium/day from drinking water), the absorption factor did not statistically differ according to gender, but was higher among younger (< 60 years) than older (≥ 60 years) subjects and among people with a lower exposure (< 100 µg/day) than among those who ingested over 100 µg/day.

8.1.2. Tissue distribution and retention

The absorbed uranium is mainly associated with the erythrocytes in blood. In plasma, it forms a diffusible ionic uranyl-hydrogen carbonate complex ($UO_2HCO_3^+$) in equilibrium with a non diffusible uranyl-albumin complex. Its distribution to body compartments and organs as well as its elimination is independent of the form of the isotope composition (UBA, 2005).

Retained uranium accumulates initially in the kidney tubules and liver, and then in the skeleton, the latter representing the major reservoir for this metal in the body (Li *et al*., 2005). In kidney, accumulation results from the formation of uranium complexes with proteins and phospholipids in the proximal tubule, whereas in bones the uranyl ion replaces calcium in hydroxyapatite (Moss, 1985). The total body burden of uranium in unexposed subjects has been reported to range from 40 to 90 µg, and to be distributed as follows: > 50 % in bone, 20 % in muscle, 15 % in fat, 4 % in the blood and 1-2 % in the lungs, liver and kidneys (Fisenne *et al*., 1988; UBA, 2005).

Recently, the retention of uranium under chronic exposure has been investigated in thirty-five male Sprague Dawley rats exposed during their whole adult life to 40 mg/L uranyl nitrate corresponding to 2.0-2.9 mg uranium/kg b.w. per day (Paquet *et al*., 2006). Tissue

concentrations of uranium were then measured in target and non target tissues at different time-points (32, 95, 186, 312, 368, and 570 days of treatment). Uranium accumulated in most organs, following a non-monotonous pattern, with peak levels achieved at 1-3, 10, and 19 months of continuous exposure depending on the tissue. Between 1 and 3 months, the highest concentrations were found in the large intestine (about 2,200 ng/g tissue) and total gut (about 1,200 ng/g tissue), followed by the teeth (about 650 ng/g tissue), the kidneys (220 and 97 ng/g tissue at 1 and 3 months, respectively), the femurs (25-65 ng/g tissue) and the liver (0.12-2.1 ng/g tissue). By the 10^{th} month of treatment, uranium (in ng/g tissue) had reached levels of about 3,900 in the large intestine wall and of 27 in the liver, and had decreased in teeth and kidneys to about 450 and 60 ng/g tissue, respectively. After 19 month-exposure, uranium concentrations (in ng/g tissue) amounted to 5,500 in the large intestine, 2,100 in the total gut, 750 in teeth, 300 in the kidneys and 100 in the femurs. Uranium was also detected in brain, reaching its peak in the thalamus and hippocampus (up to 54 and 30 ng/g tissue). Besides the brain region specificity, accumulation also displayed significant fluctuations in time. No significant changes in uranium intakes could explain the fluctuations in the individual tissue levels.

Three issues are particularly worthy of consideration in this work. First, uranium can significantly accumulate in non-target tissues such as brain and teeth, the latter containing even higher levels that bone. Second, accumulation of uranium in tissues may not be constant over time during chronic exposure. Third, the comparison of these experimental results with a model prediction based on a reference biokinetic model for uranium in rat that has been validated for acute exposure showed that the accumulation of uranium in target organs after chronic exposure may be overestimated by one to two orders of magnitude. Paquet *et al.* (2006) concluded that "protracted exposure to uranium may induce changes in biokinetic parameters when compared to acute contamination and that calculation of dose resulting from chronic intake of radionuclides may need specific models that are not currently available".

Studies in rats have demonstrated that uranium also enters the brain (Barber *et al.*, 2005; 2007; Paquet *et al.*, 2006), and accumulates in cerebral structures in a regional-dependent fashion (Houpert *et al.*, 2007). Experimentally, uranium has been shown to cross the placental barrier and to enter the foetal tissue (WHO, 2001).

8.1.3. Excretion

Uranium is cleared from the systemic circulation according to a two-phase process. About two thirds of the absorbed fraction of uranium are filtered through the kidney and excreted in the urine within 24 hours (WHO, 2001). The last fraction is excreted over the period of many months (Berlin and Rudell, 1986). Following distribution, uranium is eliminated from various tissues at different rates. The half-life of uranium in the rat kidney is about 15 days and it is considerably longer in the skeleton, e.g., 300 and 5000 days according to a two-compartment model (Wrenn *et al.*, 1985). Another study in rat based on a 10-compartment model showed half-lives of 5-11 and 93-165 days in the kidney and skeleton, respectively (Sontag, 1986). In humans, the half-time in the kidneys has been estimated to be 1-6 days for 99 % of the total renal uranium, and 1,500 days for the remainder (ICRP, 1979). Under conditions of normal daily intake, uranium terminal half-life in the whole human body has been estimated to range between 180 and 360 days (Berlin and Rudell, 1986).

In humans the urinary pathway accounts for approximately 1 % (about 4.4 μg/day) of total uranium excretion (Singh *et al.*, 1990). In continuous uranium exposure through drinking

water, uranium excretion in the urine was estimated to be approximately 0.3 % of the ingested dose (Karpas *et al*., 2005). The variations in uranium excretion rate depend on the pH of the tubular urine, i.e. while alkaline conditions favour excretion, acidic conditions favour accumulation in the tubular wall (Berlin and Rudell, 1986).

In the study carried out by Paquet *et al*. (2006) in rats exposed to 40 mg/L uranyl nitrate (see previous section), urine and faeces were collected separately for 5 days per week during the first two weeks of exposure and thereafter for 2 days every two weeks. Despite a wide inter-individual variability, the urinary excretion of uranium increased with time and peaked (c.a. 200 ng uranium/mL urine) after about 6 months of exposure (n=5), and then decreased to 30 ng uranium/mL urine and remained constant for the following 6 months. The authors inferred that uranium excretion was, at least in part, inversely related to uranium tissue concentration as its maximum excretion occurred concomitantly with a minimum peak of uranium accumulation in the whole body, i.e. after 180 months. This finding would suggest that at this time point, most absorbed uranium was eliminated in the urine either before or after tissue deposition. On the other hand, at 12 months uranium tissue concentrations were low, despite the fact that urinary levels of uranium were also low, thus supporting that a reduced absorption, rather than an increased excretion, contributed to the low accumulation.

8.1.4. Biomarkers of exposure

Human exposure to uranium can be measured by analysis of hair, urine and faeces. Recent uranium ingestion can be assessed by means of analysis of stool samples, given the fast elimination of more than 95 % of ingested unabsorbed uranium through the faecal route. Conversely, the urinary content of uranium is considered a more reliable marker of a past oral exposure. It has been reported that higher uranium levels in urine were present even 10 months after cessation of a long-term elevated exposure via the drinking water (Orloff *et al*., 2004).

The Human Biomonitoring Commission of the German Federal Environment Agency (UBA) in its 2005 Opinion recommended using urine samples collected over a 24h-period for the analysis, and possibly repeating the measurements on consecutive days to overcome the problem of the high intra-individual variability in the daily uranium excretion (UBA, 2005). This Commission also considered the range of 30-60 ng/L uranium in 24-h urine as an orientation level with regard to background exposure, on the basis of examinations performed from 2001 to 2003 in populations groups consisting of a total of 1,518 subjects (mostly students) from the areas of Münster, Halle, Greifswald and Ulm in Germany. In the overall group, the 95th percentile of renal excretion levels was 29.0 ng/L urine, whereas in some subpopulations such value was up to 60 ng/L. A reference value could not be derived by the Human Biomonitoring Commission because of the significant regional variations of uranium urinary concentrations in subjects who had no abnormal history of exposure. A regional dependence of urinary uranium baseline levels has also been reported in 12 non-exposed volunteers from Northern Italy as compared to a larger group of German volunteers and data available from the literature (Bagatti *et al*., 2003).

8.2. Toxicity

In recent years, several international agencies and bodies have thoroughly reviewed the published studies on the acute and chronic toxicity of uranium (ATSDR, 1999; WHO, 1998; 2001; 2005; UBA, 2005). A full account of all toxicological studies will not be provided in

this section. Rather, a summary is presented of the critical studies and the recent relevant studies (from literature searches up to March 2009 available on public databases, e.g. PubMed), specifically addressing the oral route of exposure.

The chemical action of all isotopes and isotopic mixtures of uranium is identical, regardless of the specific activity (i.e. isotope enrichment). The results of the available studies in humans and animals indeed indicate that natural, depleted, and enriched uranium exert the same chemical toxicity (ATSDR, 1999). The experimental studies reviewed in this sub-chapter refer to natural as well as depleted uranium, provided that oral ingestion was the chosen route of administration. The potential radiological health hazards associated with uranium exposure are not addressed and accordingly, studies on enriched uranium are not reviewed.

Toxicity of ingested uranium is directly related to the solubility of the uranium compound as further addressed below. The kidney is recognized as the primary target organ for uranium toxicity both in experimental animals and humans. Renal toxicity is characterised by damage to the proximal convoluted tubules, with possible involvement of the glomerulus at high exposures. To a certain extent, tubular damage appears to be reversible with decreasing exposure. Kidney damage results from the accumulation of uranium in the renal tubular epithelium, where it can cause cell necrosis and atrophy of the tubules, leading to a compromised tubular secretion of organic anions and reabsorption of filtered glucose and amino acids. Nephrotoxicity has been documented by acute, sub-acute, sub-chronic and chronic oral studies in a number of animal species including rats, mice, rabbits and dogs (COT, 2006).

According to animal data, soluble compounds such as uranyl nitrate hexahydrate, uranium hexafluoride, uranyl fluoride, uranium tetrachloride, and uranium pentachloride are the most potent renal toxicants. Insoluble compounds (*e.g.*, uranium tetrafluoride, uranium trioxide, uranium dioxide, uranium peroxide, triuranium octaoxide) display low kidney toxicity, but can cause pulmonary toxicity after being inhaled. Intermediate water-solubility typical of sodium diuranate and ammonium diuranate is associated with a moderate-to-low renal toxicity (ATSDR, 1999).

Besides nephrotoxicity, reproductive and developmental alterations (e.g. decreased pup growth and internal/external malformations), diminished bone growth, genetic damage and neurotoxicity have been documented in animal models after uranium exposure. As yet, however, no conclusive evidence has been provided in this respect for humans.

8.2.1. Acute toxicity

The acute oral LD_{50} has been shown to depend on the specific uranium compound (generally, the higher the solubility of the compound, the greater the toxicity) and to vary widely among animal species, with values ranging from 100 mg/kg b.w. to > 1000 mg/kg b.w. (ATSDR, 1999).

With respect to common laboratory animal species, LD_{50} values for a single oral dose of uranyl acetate have been estimated to be 204 mg/kg b.w. for male Sprague-Dawley rats and 242 mg/kg b.w. for Swiss mice. Toxicity signs included piloerection, a remarkable weight loss and haemorrhages in the eyes, legs and nose (Domingo *et al.*, 1987). The species-related sensitivity to the acute effects of uranium has been ranked as follows: rabbit > rat > guinea-pig > mouse (Orcutt *et al.*, 1949).

8.2.2. Sub-acute toxicity

In early studies (Maynard and Hodge, 1949; US-EPA, 1989) rabbits, rats and dogs were given uranium compounds through the diet for 30 days.

Rabbits (n=6/group, sex not reported) were fed uranyl nitrate hexahydrate at 0, 0.02, 0.1, or 0.5 % in the diet for 30 days (equivalent to 2.8, 14, and 71 mg uranium/kg b.w. per day). Death was observed at the two highest dosages (66 % and 100 % at 14 and at 71 mg uranium/kg b.w. per day, respectively). All treatments caused the body weight to decrease during the first week of exposure, although this effect was only transient in the lowest dose group. After 30-day exposure, all groups except controls displayed renal histopathological alterations, which were ranked as moderate after the two lower level regimens, and as moderately severe at the dose of 71 mg uranium/kg b.w. per day. From this study, a lowest-observed-adverse-effect-level (LOAEL) of 2.8 mg uranium/kg b.w. per day was estimated in rabbits.

In rats undergoing a 30-day feeding trial the highest non-lethal doses for uranyl nitrate hexahydrate, uranyl tetrafluoride and uranium tetrachloride (i.e. soluble uranium compounds) were about 0.5 % in the diet, whereas none of the insoluble uranium compound (uranium dioxide, uranium trioxide, and triuranium octaoxide) caused death at up to the maximum tested dose, i.e. 20 % in the diet (ATSDR, 1999).

In comparison with rabbits, rats and dogs were less sensitive to uranium compounds. LOAELs for uranyl fluoride (UO_2F_2), uranyl dinitrate ($UO_2(NO_3)_2$), and uranium tetrachloride (UCl_4) were 39, 120, and 160 mg uranium/kg b.w. per day for rats, and 7.7, 9.5, and 132 mg uranium/kg b.w. for dogs, respectively (Maynard and Hodge, 1949; ATSDR, 1999).

8.2.3. Sub-chronic and chronic toxicity

In a 91-day toxicity study (Gilman *et al.*, 1998a), male and female Sprague-Dawley rats (n=15) were given uranium as uranyl nitrate hexahydrate *via* the drinking water (background value < 0.001 mg/L) at 0.96, 4.8, 24, 120 or 600 mg/L. The respective daily intakes of uranium were estimated to be 0.06, 0.31, 1.52, 7.54 and 36.73 mg/kg b.w. in males and 0.09, 0.42, 2.01, 9.98 and 53.56 mg/kg b.w. in females. Treatment-induced histopathological lesions were observed in the kidney and liver of either gender and at all dose levels. The kidney was the most affected tissue. In males, renal lesions of tubules (apical nuclear displacement and vesiculation, cytoplasmic vacuolation, and dilation), were observed even in the lowest exposure group and there was a lack of dose-response relationship. Additionally, the ≥ 0.31 mg/kg b.w./treatment in males elicited glomerular adhesions, apical displacement of the proximal tubular epithelial nuclei and cytoplasmic degranulation. In females, renal lesions of glomeruli (capsular sclerosis) and interstitium (reticulin sclerosis), and nuclear vesiculation of the tubular epithelial nuclei were detected in all exposed groups, whereas anisokaryosis were present in all but the 4.8 mg/L group. In females, the glomerular capsular sclerosis and the reticulin sclerosis of the interstitial membranes were considered the most relevant effects because of their non-reversibility. In liver, treatment-related lesions were seen in both sexes at all doses and were generally non-specific nuclear and cytoplasmic changes. The LOAEL was considered to be 0.96 mg of uranyl nitrate hexahydrate per liter of drinking water (average dose equivalent to 0.06 and 0.09 mg uranium/kg b.w. per day for male and female rats, respectively). The different sensitivity of males and females to uranium did not seem to be due to sex-related pharmacokinetic differences, as the levels of uranium in renal tissue did not significantly differ between genders.

In a 91-day-study in male rabbits (n=10), uranyl nitrate hexahydrate was administered in the tap water (background value < 0.001 mg/L) at 0.96, 4.8, 24, 120 or 600 mg/L (estimated daily doses in mg uranium/kg b.w.: 0.05, 0.2, 0.88, 4.82 and 28.7) (Gilman *et al*., 1998b). New Zealand white female rabbits were also exposed for 91 days (4.8, 24, or 600 mg uranium/L). Dose-dependent effects consisted of histopathological changes limited primarily to kidney, e.g., foci of cytoplasmic vacuolation in proximal renal tubular epithelium resting on normal basement membrane, vesiculation and pyknosis of tubular nuclei, where the epithelium was injured prior to any changes in the basement membrane. For males, the LOAEL, based on the nuclear changes in the kidney, was considered to be 0.96 mg of uranyl nitrate hexahydrate per litre (equivalent to 0.05 mg of uranium per kg of body weight per day). The females appeared to be less affected by the exposure regimen, even though their average uranium intake was approximately 50 % greater on a mg/kg b.w. per day basis than that of males. Effects in females included significant tubular nuclear changes in the lowest exposure group, leading to an estimate of the LOAEL of 4.8 mg of uranyl nitrate hexahydrate/L (equivalent to 0.49 mg of uranium per kg of body weight per day). The observed gender-related differences in terms of the type and the degree of the adverse effects were supportive of a different pharmacokinetic profile in males and females, in disagreement with the findings in the rat study by the same authors (Gilman *et al*., 1998a). Noteworthy, the interpretation of the study's results was complicated by the occurrence of *Pasteurella* infection in some of the male rabbits (WHO, 2005; COT, 2006). In a subsequent study (Gilman *et al*., 1998c) aimed at assessing the reversibility of the adverse renal effects, no full or consistent recovery was seen in the top dose animals after a 91-day recovery period.

More recently, administration of uranyl acetate dihydrate via drinking water at 10-40 mg/kg b.w. per day for a 3 month period was found to cause a progressive angiomatose transformation of blood vessels, increased lipid peroxidation and levels of oxidative stress markers in male rat kidney (Linares *et al*., 2006).

Male rats given daily for 9 months drinking water containing 40 mg/L depleted uranium (equivalent to a daily dose of 1 mg/rat) displayed anaemia and renal histopathological lesions but not dysfunction (Berradi *et al*., 2008). Such oral dosing would be equivalent to 2-4 mg/kg b.w. per day, assuming that a male rat's body weight would double from 250 to 500 g between the 3rd and the 12th month of age.

Two-year chronic studies (Maynard and Hodge, 1949) were performed in rats fed uranium as uranyl fluoride, uranyl nitrate hexahydrate, uranium tetrafluoride, and uranium dioxide. The largest daily intakes (in mg uranium/kg b.w. per day) that did not shorten the rat lifespan were 81 for uranyl fluoride, 1130 for uranyl nitrate, 1390 for uranium tetrafluoride, and 1630 mg for uranium dioxide (ATSDR, 1999). In most cases death resulted from renal toxicity.

8.2.4. Reproductive and developmental toxicity

The main results of *in vivo* studies regarding the potential of ingested uranium to exert reproductive and developmental toxicity are summarised in Table 14.

Some investigations in rodents have highlighted a negative impact of repeated ingestion of relatively high doses of uranium on the reproductive function (Arfsten, 2001; Domingo, 2001).

Concerning the male reproductive system, reported adverse effects included testis degeneration and depletion of germ cells (Maynard *et al*., 1953), testicular lesions, necrosis of spermatocytes and spermatogonia, reduced testis weight (Malenchenko *et al*., 1978),

decreased male fertility and spermatid number per testis with few histopathological effect on the seminiferous tubules and interstitium, such as focal atrophy, binucleated cells and vacuolization of Leydig cells (Llobet *et al*., 1991; Linares *et al*., 2005).

Maternal toxicity, embryolethality, foeto-toxicity, and teratogenic effects have been observed in mice fed uranyl acetate dihydrate at doses between 5 and 50 mg/kg b.w. per day (corresponding to 2.8 and 28 mg uranium/kg b.w. per day), respectively (Domingo *et al*., 1989a, 1989b; Paternain *et al*., 1989). A decrease in litter size was recorded at weaning when female mice were fed doses as high as 28 mg uranium/kg b.w. per day from the 13th day of pregnancy until weaning (Domingo *et al*., 1989a). A 10-fold lower LOAEL, i.e. 2.8 mg uranium/kg b.w. per day, was derived for maternal and foetal toxicity when maternal exposure occurred during organogenesis (Domingo *et al*., 1989b). Additionally, postnatal growth and development were affected in mouse pups whose dams had been ingesting 2.8 mg uranium/kg b.w. per day for 14 days prior to mating, and throughout gestation and lactation (Paternain *et al*., 1989). Conversely, a similar maternal treatment in rats (continual ingestion before mating, plus gestation and lactation) with uranyl acetate dihydrate at doses up to 80 mg/kg b.w. per day through the drinking water failed to produce any significant adverse effect on postnatal development and offspring behaviour (Sánchez *et al*., 2006).

More recently, three studies have addressed the effects of ingested uranium, given as uranyl nitrate hexahydrate, on the mouse female reproductive system. The no-observed-adverse-effect-level (NOAEL) for qualitative (but not quantitative) changes in murine oocytes in a subchronic oral study (49 days; Feugier *et al*., 2008) was 10 mg uranium/L of drinking water, corresponding to a daily dose of 1.9 mg/kg b.w. Non-dose dependent disturbances in ovarian folliculogenesis were found in dams and their female offspring three months after a 15 week pre-gestational treatment with ≥ 1.25 mg uranium/kg b.w. per day (Arnault *et al*., 2008).

Another recent study (Raymond-Whish *et al*., 2007) has suggested that ingestion of low levels of uranium can result in estrogen-like effects in mice. Intact, ovariectomized, or pregnant mice (n=5-10 per experimental group) were exposed to uranium nitrate hexahydrated at 0.5 μg/L to 28 mg/L in drinking water. Effects indicative of estrogenic responses included the selective reduction of primary follicles, increased uterine weight, greater uterine luminal epithelial cell height, accelerated vaginal opening, and persistent presence of cornified vaginal cells in exposed mice. These responses were antagonized by the antiestrogenic compound ICI 182,780. The daily water intake and the doses expressed on a kg b.w. per day basis were not recorded.

The authors also noted that dams consuming water containing 2.5, 12.5 or 60 μg/L uranium for 30 days before mating and during gestation displayed a significant reduction of small primary follicles, in comparison with their respective controls. Primordial follicle number was significantly reduced in the ovaries of pups whose dams had drunk water containing either the lowest or the highest uranium test concentration, e.g. 0.5 or 60 μg/L, but not with the two intermediate doses. To assess the impact of uranium on the female reproductive tract in the absence of endogenous estrogen, ovariectomized mice were dosed with 60, 600, or 6000 μg/L uranium for 30 days. Uterine weights were significantly increased only in the mice exposed to the lowest dosage, in comparison with both controls and other uranium-treated groups. No changes were observed in ovary-intact, age-matched mice that drank uranium containing water (Raymond-Whish *et al*., 2007).

In summary, the study by Raymond-Whish and co-workers (2007) has reported alterations in the ovarian follicle populations in mouse dams and their female offspring after gestational

exposure to environmentally relevant levels of uranium, that is 0.5-12.5 μg/L in the drinking water. Assuming an average body weight of 20 g and a daily water consumption of 5-10 ml per animal during pregnancy, the Panel on Contaminants in the Food Chain (CONTAM Panel) estimated that a LOAEL of 0.5 μg/L drinking water would correspond to a 0.125-0.250 μg uranium/kg b.w. per day for the oral route.

The CONTAM Panel noted that no dose-response relationships were found for the effects reported either in dams or in pups (Raymond-Whish *et al*., 2007). It is also worth noting that none of the most recent experimental works on uranium toxicity to the female reproductive tract has provided evidence for such a relationship (Arnault *et al*., 2008; Feugier *et al*., 2008), and the LOAELs from these studies were much higher, e.g. 1.25 and 3.9 mg/kg b.w. per day. Furthermore, the 0.5 μg/L LOAEL from the Raymond-Whish study even falls below the LOD of uranium in water as assessed by kinetic phosphorescence analysis < 2 μg/L.

Overall, the current evidence does not support that uranium can significantly affect fertility, general reproductive parameters or offspring development at concentrations that are relevant to environmentally-exposed humans. The CONTAM Panel concluded that the reproduction system is not the most sensitive target for uranium toxicity based on recent animal data together with the lack of evidence in humans. The CONTAM Panel considers nephrotoxicity as the most relevant toxicity endpoint for animals and humans.

Table 14. Summary of the main reproductive and developmental effects of uranium (U) in oral rodent studies.

Species/Gender	Uranium Compound	Oral treatment (mg/kg-d) (a)	Effect	LOAEL (mg/kg-d) (a)	NOAEL (mg/kg-d) (a)	Reference
Rat Male	Uranyl nitrate hexahydrate	0.1 % (diet) for 12 months	Severe degeneration in the testes and depletion of germ cells		N/A	Maynard *et al.*, 1953
Rat Male	Uranyl nitrate hexahydrate	0.07 % (diet) for 16 weeks	↓ testes weight, testicular lesions, necrosis of spermatocytes and spermatogonia		N/A	Malenchenko *et al.*, 1978
Swiss mouse Male	Uranyl nitrate dihydrate	10, 20, 40, 80 (drinking water) for 64 days before mating	↑ Leydig cells vacuolization (only highest dose). ↓ pregnancy rate at all doses (not dose dependent) of untreated females mated for 4 days with treated males	80 10	40	Llobet *et al.*, 1991
Sprague Dawley Rat Male	Uranyl nitrate dihydrate	10, 20, 40 (drinking water) for 3 months before mating	↓ spermatid number per testis (not dose-dependent) ↓ pregnancy rate of control females mated with pre-treated males (not dose-dependent).			Linares *et al.*, 2005

Abbreviations: GD: gestational day, PND: postnatal day, mg/kg-d: mg/kg b.w. per day
(a): Unless otherwise stated

Table 14. (*Cont.*) Summary of the main reproductive and developmental effects of uranium (U) in oral rodent studies.

Species/Gender	Uranium Compound	Oral treatment (mg/kg-d) [(a)]	Effect	LOAEL (mg/kg-d) [(a)]	NOAEL (mg/kg-d) [(a)]	Reference
Rat Both genders	Uranyl nitrate hexahydrate	2 % (diet) for 1 day (about 460 mg/kg)	↓ Reproductive success in the following 7 months: ↓ (12 %) number of total pups born and ↓ (7 %) litter size			Maynard and Hodge, 1949
Rat Both genders	Uranyl nitrate hexahydrate	2 % (diet) for 2 years (about 470 mg/kg)	↓ number of litters, ↓ litter size, associated with ↓ food consumption, and ↓ weight gain			Maynard and Hodge, 1949
Swiss mouse Female	Uranyl nitrate dihydrate	0.05, 0.5, 5, 50 GD13 – PND21	At weaning significant ↓ litter size, ↓viability and ↓ lactation indices only at the highest dose. No effects on sex ratios, litter size, pup growth (up to 5 mg/kg)	50 (28 mg as U)	5 (2.8 mg as U)	Domingo *et al*., 1989a
Swiss mouse Female	Uranyl acetate dihydrate	5, 10, 25, 50 (gavage), GD 6-15 (organogenesis)	On GD18: at all doses maternal toxicity (↓weight gain, ↓food intake, ↑ relative liver weight) No embryolethality at any dose Dose-related fetotoxicity (↓ fetal growth) and teratogenicity at 25 and 50 mg/kg.	5 (2.8 mg as U) 5 (2.8 mg as U)		Domingo *et al*., 1989b
Swiss mouse Both genders	Uranyl acetate dihydrate	5, 10, 25 (gavage) Females: for 14 days before mating, during gestation and lactation Males: for 60 days before mating	Embryolethality at 25 mg/kg/day ↑ pup lethality at birth and at PND 4 ↓ Postnatal growth at all dosages No adverse effects on fertility	25 (14 mg as U) 25 (14 mg as U) 5 (2.8 mg as U)		Paternain *et al*., 1989

Abbreviations: GD: gestational day, PND: postnatal day, mg/kg-d: mg/kg b.w. per day
(a): Unless otherwise stated

Table 14. (*Cont.*) Summary of the main reproductive and developmental effects of uranium (U) in oral rodent studies.

Species/Gender	Uranium Compound	Oral treatment (mg/kg-d) [(a)]	Effect	LOAEL (mg/kg-d) [(a)]	NOAEL (mg/kg-d) [(a)]	Reference
Sprague-Dawley Rat Female	Uranyl acetate dihydrate	0, 40, 80 (drinking water) for 4 weeks before mating, during gestation and lactation	No significant dose-related adverse effects on postnatal development and offspring behaviour			Sánchez *et al*., 2006
Mouse Female	Uranyl nitrate hexahydrated	0.5 µg/L - 28 mg/L 0.5-12.5 µg/L water for 30 days before mating and during gestation	Estrogenic effects ↓ small primary follicles (dams) ↓ primordial follicle numbers (female pups) at 0.5 or 60 µg/L (not dose dependent).	2.5 µg/L water 0.5 µg/L water	0.5 µg/L water	Raymond-Wish *et al*., 2007
C57BlxCBA Mouse Female	Uranyl nitrate	5, 50, 400 mg/L drinking water (1.25, 12.5, 100 mg U/kg-day) for 15 weeks before mating	Disturbances in ovarian folliculogenesis (non dose-related) - End of treatment: ↓ number of large antral follicles (dams) - 3 months after treatment: ↑ number of secondary and early preantral follicles (dams) ↓ number of large antral follicles (female pups)	1.25		Arnault *et al*., 2008
Hybrid B6CBAF1Mouse Female	Uranyl nitrate hexahydrated	10, 20, 40 mg/L drinking water (1.9, 3.9, and 6.9 mg U/kg-day) Continual for 49 days	End of treatment: no change in number of ovulated oocytes, significant (non dose-dependent) ↑ number of oocytes with altered morphology (Absence of the 1st polar body or abnormal perivitelline space) at doses ≥20 mg/L water.	3.9	1.9	Feugier *et al*., 2008

Abbreviations: GD: gestational day, PND: postnatal day, mg/kg-d: mg/kg b.w. per day
(a): Unless otherwise stated

8.2.5. Other effects

Neurotoxicity

Early studies in rats have documented the appearance of tremors and acute cholinergic toxicity upon high (11-717 mg/kg b.w.) and acute oral exposure to uranyl acetate (Domingo *et al*., 1987). More recently, uranium given chronically to male rats as uranyl nitrate through drinking water (40 mg/L, corresponding to a daily intake of 4-15 mg/kg b.w.) has been found to perturb brain acetylcholinesterase activity and monoamine metabolism in discrete brain areas at different time-points during exposure (1.5, 6 and/or 9 months) (Bussy *et al*., 2006). Other rodent studies have reported effects of uranium on memory (4 % enriched but not depleted uranium for 1.5 months through drinking water; Houpert *et al*., 2005), activity and sleep (40 mg uranyl nitrate/L drinking water for 90 days, Lestaevel *et al*., 2005).

Genotoxicity

Some *in vitro* experiments in mammalian cells are suggestive of a genotoxic potential for uranium. Uranyl nitrate at 10-300 µM caused cytotoxicity and genotoxicity, as assessed by increased frequencies of micronuclei, sister chromatid exchanges and chromosomal aberrations, in Chinese hamster ovary cells (Lin *et al*., 1993; WHO, 2005). The genotoxic effects were suggested to be mediated by the binding of uranyl nitrate to DNA. Chromosomal aberrations have also been reported in male mouse germ cells exposed to enriched uranyl fluoride, most likely as a result of its radioactive properties (Hu and Zhu, 1990). More recently, Stearns *et al*. (2005) have reported a mutagenic effect of 200 µM depleted uranium uranyl acetate in XRCC1-deficient Chinese hamster ovary (CHO) EM9 cells.

Carcinogenicity

As yet, no controlled carcinogenicity studies have been performed in rodents ingesting soluble or insoluble uranium compounds. Because of uranium radioactive properties, a risk for carcinogenicity cannot be ruled out (ATSDR, 1999).

8.3. Observations in humans

8.3.1. Acute intoxication

Data reporting human death due to uranium poisoning are lacking. There are a few cases of accidentally or deliberately high intake of uranium in humans described in the literature; in all cases the subjects suffered acute kidney function impairment (Lu and Zhao, 1990; Pavlakis *et al*., 1996). Based on previous calculations reported by Just and Emler (1984), McGuire (1991) roughly estimated the uranium dose (presumably systemic dose) for 50 % lethality in humans at 114 mg in a 70 kg person. Considering a gastrointestinal uptake of 1-2 % (Wrenn *et al*., 1985; Zamora *et al*., 2002), Kathren and Burklin (2008) suggested that 5 g can be provisionally considered the acute oral LD_{50} for uranium in humans.

8.3.2. Long-term effects

In this chapter, only epidemiological studies on humans exposed to natural uranium from water and food will be considered. Effects produced by depleted uranium and radiation activity do not fall under the scope of this opinion and therefore they will not be discussed further.

8.3.2.1. Effects on kidney

Mao *et al*. (1995) performed a study on 100 people (aged 18-84 years) from 3 different Canadian regions consuming drinking water with uranium content up to 50 μg/L uranium. The mean uranium concentration in water was 0.71 μg/L in the control group (range, 0.48-0.74 μg/L), and 20 μg/L (range, < 0.1-48 μg/L) respectively 15 μg/L (< 0.1-50 μg/L) in the other two groups, which were considered as high exposure groups. The association between uranium concentration in water and microalbuminuria was investigated. The cumulative exposure index was calculated for each subject 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. There was no significant relationship between the urine albumin or serum creatinine and the uranium concentration in water. A statistically significant association (P=0.03) was found between urine albumin (measured as mg/mmol creatinine) and the uranium cumulative exposure index. However, urine albumin level was in most subjects within the normal clinical range.

In another human study from Canada (Zamora *et al*., 1998), long-term ingestion of uranium at the levels of uranium found in some groundwater supplies was reported to affect the kidney function, as assessed by urinary biochemical biomarkers. Subjects (males aged 14-56 years and females aged 13-87) were assigned to either a low-exposure group (n=20) or a high-exposure (n=30) group depending on whether their drinking water contained < 1 μg uranium/L (total daily intake from all sources: 0.004-0.2 μg/ kg b.w.), or 2-781 μg /L (total daily intake from all sources: 0.058-8.5 μg/ kg b.w.). Total uranium intake from both water and food, averaged over the 3-day study period, was used as the marker for uranium exposure. In the high exposure group, the percentage of uranium intake from water varied between 31 and 98 %, whereas in the low exposure group from 1 to 9 %. Years of residence ranged 1-33 years and 3-59 years in the low and high-exposure groups, respectively. The following kidney function indicators were measured: glucose, creatinine, protein, and β_2-microglobulin (BMG). The markers for cell toxicity studied were alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), lactate dehydrogenase (LDH), and N-acetyl-β-D-glucosaminidase (NAG).

Urinary glucose was significantly increased in the high exposure group (males, females and pooled data) and positively correlated with total daily uranium intake. Increases in ALP and BMG correlated with total uranium intake for pooled data only. Creatinine and protein, the indicators for glomerular injury, were not significantly affected nor was their urinary excretion correlated to uranium intake. The authors also concluded that glucose, creatinine, and total protein data taken together suggest that at the levels of uranium intake of 2 to 410 μg/day among males and 2 to 570 μg /day for females (corresponding approximately to 0.004-8.5 μg/ kg b.w. per day), the segment of the nephron most at risk to injury is the proximal tubule (Zamora *et al*., 1998).

In a Finnish study (Kurttio *et al*., 2002) on 325 persons aged 15-83 (mean age, 52 years) who had used drilled wells for drinking water (uranium content in range of 0.001-1920 μg/L, median of 28 μg/L, daily intake from drinking water 0.000007-52 μg/kg body weight) for 1-34 years, no changes in glomerular function have been observed on the basis of creatinine excretion and urinary albumin. As indicators of renal proximal tubule function, BMG, glucose, calcium and phosphate ions in urine were measured. A positive correlation was found between urinary uranium and increased fractional excretion of calcium and phosphate in urine. Calcium excretion also positively correlated with uranium in the drinking water. Changes in renal tubular function were significant at uranium concentrations in drinking water exceeding

300 μg/L. The correlation between renal toxicity and urinary uranium was higher than that between renal toxicity and content of uranium in water. Cumulative intake was not correlated with toxicity possibly supporting that short-term exposure is more critical for renal adverse effects (Kurttio *et al*., 2002). The most damaged part of the nephron was the proximal tubule, rather than the glomerulus.

A second study (Kurttio *et al*., 2006) was conducted as an extension of the investigations presented in Kurttio *et al*. (2002), with the aim to further evaluate the long-term exposure to uranium from drinking water, focusing on parameters reflecting possible cytotoxicity and tissue damage to the kidneys. The study population (95 men and 98 women aged 18-81 years) was a subset of subjects from the previous study who used the same drilled-wells as source of drinking water for an average of 16 years (range, 5-40 years). Median uranium concentration in drinking water was 25 μg/L (interquartile range, 5-148 μg/L; maximum, 1,500 μg/L). Data for dietary intake of uranium were not available in this study. The following parameters were measured in kidneys: NAG, ALP, LDH, GGT as indicators of cytotoxicity, α-glutathione-*S*-transferase (GST) in urine, calcium, phosphate, glucose and creatinine in both urine and serum, and serum cystatin C as indicators of effects on renal proximal tubules. In addition, supine blood pressure was measured. Urine, hair, and nail samples were analysed for uranium content.

Indicators of cytotoxicity and kidney function did not show evidence of renal damage. No statistically significant correlation with uranium in urine, water, hair, or toenails was found for all measured kidney toxicity indicators. Uranium exposure was associated with higher diastolic and systolic blood pressures, but the effect was small and no clear hypertension was observed. This study failed to confirm the correlation between urinary uranium and increased fractional excretion of calcium and phosphate in urine as reported in the first study. Cumulative uranium intake was significantly associated with increased glucose excretion in urine (R^2=0.21; P=0.02), an effect observed also by Zamora *et al*. (1998), but not by Kurttio *et al.* in 2002. The authors concluded that continuous uranium intake from drinking water, at the levels presented in this study, did not produce cytotoxic effects on kidneys in humans. (Kurttio *et al*., 2006).

In a case report on 7 family members (aged 3, 5, 7, 9, 12, 34 and 37 years) consuming water from a private well containing uranium at levels of 866-1160 μg/L (two independent measurements), the youngest one presented the highest BMG excretion rate (90 μg/mmol creatinine) as a marker of nephrotoxicity and the highest uranium concentration in urine (6.2 μg/L). This child stayed most of the time at home and a high proportion of its dietary intake consisted of infant formula prepared with well water. In the other family members the BMG excretion rate was normal (< 40 μg/mmol creatinine). Three months after cessation of well water consumption the youngest child's urinary BMG excretion rate decreased to 52 μg/mmol creatinine (Magdo *et al*., 2007). This case report highlights the particular sensitivity of young children to uranium exposure determined by the large amount of water they consume relative to their body mass, and their developmental immaturity.

Extrapolations of the animal studies and data for acute intoxications in humans revealed a nephrotoxic threshold limit for chronic low-level exposure of about 3 μg of uranium per gram of kidney (Kathren and Burklin, 2008).

8.3.2.2. Effects on bones

Bone is considered a critical organ for the concentration of many uranium compounds but relatively little is known about bone effects of ingested uranium in humans (Neuman *et al*., 1948, Adams and Spoor, 1974). Kurttio *et al*. (2005) studied a cohort of 146 men and 142 women (26-83 years of age), who for an average of 13 years (range, 1-34 years) had used drinking water originating from wells with high uranium concentrations (median, 27 μg/L; range, 0.001-1,920 μg/L). The study population was a subset from a previous study by Kurttio *et al*. (2002) presented above in section 8.3.2.1. The median daily uranium intake from water was 36 μg (maximum, 4128 μg) and of cumulative intake 0.12 g (0.01-0.33 g).

The authors suggested that elevation of carboxy-terminal telopeptide (CTx) (p=0.05) used as an indicator of bone resorption as well as osteocalcin (p=0.19) could be associated with increased uranium exposure in men, but a similar relationship was not found in women.

8.3.2.3. Other effects

There are no data for neurological effects in humans caused by natural uranium. Moreover, there are no reported cases of cancer in humans as a result of exposure to natural uranium from water and food.

8.3.2.4. Conclusions

Correlations have been found between uranium exposure in humans and various biomarkers of renal toxicity (albumin, glucose, ALP, calcium, phosphate, and BMG) and indicators of bone formation (CTx and osteocalcin). Most of the epidemiological studies have already been discussed in the previous risk assessments of uranium in drinking water (UBA, 2005; Konietzka *et al*., 2005; Svensson *et al*., 2005; WHO, 2005; COT, 2006). The second study of Kurttio *et al*. (2006) failed to confirm the effects on calcium and phosphate excretion observed in the first study but supported the results of other authors who found an association between uranium and increased urinary glucose. Furthermore, there was a slight association between blood pressure and uranium exposure. The case report of Magdo *et al*. (2007) confirms renal effects of uranium and highlights the possible higher exposure and higher sensitivity of young children to uranium. The study of Kurttio *et al*. (2005) suggests that in addition to kidneys, bone may be another target for uranium toxicity. However, nephrotoxicity is the most evident effect associated with long term uranium exposure in humans. Due to deficiencies in study design and data reporting in the epidemiological studies, the CONTAM Panel concluded that none of these studies can be used for deriving a tolerable daily intake (TDI) for uranium.

9. Health based guidance values

The US-EPA (1989) has derived a reference dose (RfD) for uranium (soluble salts) of 3 μg/kg b.w. per day from the LOAEL of 0.02 mg/kg uranyl nitrate hexahydrate in food (corresponding to 2.8 mg uranium/kg b.w. per day) for initial body weight loss and moderate nephrotoxicity in a 30-day dietary study in rabbits (Maynard and Hodge, 1949; see section 8.2.2.).

The WHO has established a TDI for uranium of 0.6 μg/kg b.w. per day (WHO, 1998; 2004), based on the LOAEL for uranium nephrotoxicity from a 91-day study in male rats of 0.96 mg/L of uranyl nitrate hexahydrate, which is equivalent to 0.06 mg uranium/kg b.w. per day

(Gilman *et al.*, 1998a; see section 8.2.3.). An UF of 100 was applied, representing factors of 10 for inter-species extrapolation and for inter-individual variation. No further adjustments were made to account for data extrapolation from a LOAEL to a NOAEL or from a sub-chronic to a chronic exposure, on the grounds of biokinetic considerations and the minimal degree of the observed renal injury. In rat kidney, the uranium biological half-life is approximately 15 days. This suggests that in this tissue steady-state concentrations are reached within a 3 month exposure (WHO, 1998).

The Agency for Toxic Substances and Disease Registry (ATSDR) set a minimal risk level (MRL) for the intermediate-duration (15-364 days) uranium ingestion at 2 μg/kg b.w. per day (ATSDR, 1999), based on the LOAEL of 0.05 mg uranium/kg b.w. per day for nephrotoxicity in a 91-day sub-chronic study with uranyl nitrate hexahydrate in rabbits (Gilman *et al*., 1998b; see section 8.2.3.). An UF of 30 was applied to this LOAEL (3 for using the LOAEL and 10 for human variability). Because of the high susceptibility of the rabbit to uranium toxicity, no additional factor was applied to allow for interspecies variation.

Based on the evaluation of the experimental studies that have been published since the above assessments, the CONTAM Panel has come to the conclusion that there is no clear evidence supporting that uranium can cause adverse effects at doses below those that were shown to induce kidney toxicity (0.06 mg/kg b.w. per day for 91 days) (Gilman *et al.*, 1998a; 1998b). Therefore, the CONTAM Panel considers the sub-chronic study by Gilman *et al.* (1998a) in male rats as the key study for establishing a TDI and takes the LOAEL of 0.06 mg/kg b.w. per day for uranium nephrotoxicity as the reference point.

After reviewing the available toxicokinetic studies in animals and humans, the CONTAM Panel noted that the apparent species-related difference in the absorption would be within the 10 default interspecies UF. In 2005, Konietzka *et al.* proposed that the uranium WHO TDI should be reduced to 0.1-0.2 μg/kg b.w./day (three- to six-fold reduction of the WHO TDI), considering the five-fold difference in the GI absorption between humans (about 1.5 %) and rabbits or rats (about 0.3 %). In addition, a further default UF factor of 50-100 (for inter- and intra-species differences and for LOAEL to NOAEL extrapolation) was applied to the estimated absorbed uranium dose in the rabbit from the Gilman *et al*. (1998b) study.

On the grounds of biokinetic considerations and the minimal degree of the observed renal injury, the CONTAM Panel agreed that no further adjustments should be made to account for data extrapolation from a LOAEL to a NOAEL or from a sub-chronic to a chronic exposure. Therefore, the CONTAM Panel decided to endorse the 1998 WHO TDI for soluble uranium of 0.6 μg/kg b.w. per day, applying an overall UF of 100 for inter- and intra-species differences to the LOAEL of 0.06 mg/kg b.w. per day for nephrotoxicity in male rats after sub-chronic exposure (Gilman *et al*., 1998a).

10. Risk characterization

The CONTAM Panel assessed whether the dietary exposure to uranium in foodstuffs and water (tap and bottled) and water-based drinks would pose a health risk to consumers in Europe. Different exposure scenarios were calculated for the general population, high consumers in naturally contaminated areas and infants (see chapter 7.1).

Using individual values of participants' body weight in the EFSA Concise European Food Consumption Database, it was estimated that the median overall lower- and upper-bound dietary exposure to uranium across European countries is between 0.050 and 0.085 μg/kg b.w.

per day. This figure comprises around 0.04 μg/kg b.w. per day from water (tap and bottled) and water-based products (tea, coffee, beer and soft drinks) and 0.009-0.040 μg/kg b.w. per day via other foodstuffs, according to whether lower- or upper-bound occurrence values were used, respectively. For high consumers the median country-specific overall dietary exposure to uranium was estimated to be between 0.09 and 0.14 μg/kg b.w. per day, 0.082 μg/kg b.w. per day coming from water and water-based products and 0.016-0.066 μg/kg b.w. per day via foodstuffs. These different dietary exposure estimates are all below the TDI of 0.60 μg/kg b.w. per day.

Two specific sub-groups of the population were looked at in more detail. As a very conservative scenario, it can be assumed that the population of some local communities with high uranium concentrations in their water supply can be exposed at the 95th percentile concentration level for life-time. At the same time there might be high consumers of water among these sub-populations at the 95th percentile consumption level. In such a situation, water could contribute 0.36 μg/kg b.w. per day as a median across the countries studied, and a country maximum of 0.51 μg/kg b.w. per day. Contribution from food is not considered likely at the 95th percentile concentration level of uranium at the same time, but more likely at the mean concentration level of 0.040 μg/kg b.w. per day and possibly 0.066 μg/kg b.w. per day in a high consumption scenario. Thus, also in such a situation the TDI would not be exceeded.

The CONTAM Panel noted that the exposure of infants fed with infant formula reconstituted with water containing uranium at the mean and the 95th percentile concentration levels may be up to 3 times higher than the exposure of adults on the body weight basis, for both mean and 95th percentile consumption values.

11. Uncertainty

The evaluation of the inherent uncertainties in the assessment of exposure to natural uranium has been performed following the guidance of the Opinion of the Scientific Committee related to Uncertainties in Dietary Exposure Assessment (EFSA, 2006). In addition, the report on "Characterizing and Communicating Uncertainty in Exposure Assessment" by the WHO/IPCS has been considered (WHO/IPCS, 2008).

According to the guidance provided by the EFSA opinion (EFSA, 2006) the following sources of uncertainties have been considered: assessment objectives, exposure scenario, exposure model, and model input (parameters).

11.1. Assessment objectives

The objectives of the assessment were defined in the terms of reference and the CONTAM Panel assessed the new occurrence data collected by EFSA on the levels of uranium in water and water based products as well as in food. This opinion focuses on the chemical toxicity of uranium. Additionally, the radiological risk will be addressed by the Group of Experts established under Article 31 of the EURATOM Treaty under the Directorate-General for Energy and Transport.

11.2. Exposures scenarios/Exposure model

In response to the request from EFSA to selected countries, data on uranium concentration in tap water, bottled water and water-based drinks from eight countries were submitted to EFSA.

Food data were only available from one Member State. Some data were also obtained directly from scientific publications submitted to EFSA.

Occurrence data on uranium in foodstuffs were submitted only by Germany and thus, these data cannot be considered to be representative for food on the EU market or for any individual food group. Further, they do not cover all food groups leaving gaps in the coverage. The food results should therefore be seen as indicative only and are associated with a large uncertainty resulting in an underestimation of the exposure. However, extrapolation of such data to the whole EU creates further uncertainty that may overall lead to either over- or underestimation of exposure to uranium in food.

The initial exposure calculations were based on mean data for uranium occurrence and consumption. Scenarios for high consumers were estimated as well as scenarios combining high occurrence values and mean consumption values. Thus, the exposure scenarios cover all possible options, from average to highest possible exposure estimates within the general population. In addition, a scenario for people drinking/consuming high amounts of water (high consumers) from highly contaminated local sources was also considered. However, it is uncertain about how realistic such a scenario is even for a limited number of extreme consumers.

Uranium exposure for infants was based on lower- and upper-bound occurrence values and mean and high consumption of infant formula prepared with both bottled and tap water. There is an uncertainty associated with the likelihood of the highest exposure situation for infants occurring in practice. It should also be considered that absorption is believed to be more effective in infants than in adults, possibly leading to a higher internal dose.

For the general population the main source of uranium exposure is via the diet, while inhalation and dermal contact are relevant in specific cases such as occupational exposure and at wartimes. Non-dietary exposure pathways were not considered in the exposure assessment.

The CONTAM Panel did not include an exposure assessment for depleted uranium, since such a scenario would apply just to specific war sites where depleted uranium munitions have been used.

11.3. Model input (parameters)

There are no prescribed official analytical methods for the determination of uranium neither in tap and bottled water nor in foodstuffs. This fact may add analytical uncertainty, given that the sensitivity of radiological methods seems to be lower than chemically-based methods. This might not be true for water where the sensitivity was sufficient as indicated by the high ratio of detects vs. non-detects, but for food the ratio was reversed with many results below the LOD. This has a considerable impact on the calculation of upper-bound values and may have introduced uncertainties in the overall estimate. However, since lower-bound estimates were also provided the impact can be quantified. Upper-bound exposure was estimated to be between 15 to 66 % higher than lower bound estimates with the high exposure scenarios being at the lower end. Overall, the impact was thus small for the exposure estimation.

Some results were expressed in radiological activity units for ^{238}U rather than in mass units. The conversion to a mass unit introduces some uncertainty. Similar conversion formulas were not applied for ^{234}U and ^{235}U since their mass contribution can be considered negligible.

The use of information from the EFSA Concise European Food Consumption Database to estimate general food consumption in the population introduces uncertainty because of the

food group aggregation. In particular there is variation in the recording of water consumption between the countries in the database. Because of the many countries providing information to the database there is no reliance on individual countries only and thus the uncertainty is reduced.

11.4. Other uncertainties

The CONTAM Panel used the TDI as established by the WHO in 1998, although noted the inherent uncertainties in using animal data to derive health based guidance values. However, the CONTAM Panel acknowledged the in-built uncertainty factor to be sufficiently conservative.

There is some uncertainty related to the key rat sub-chronic study (Gilman *et al*., 1998a), which was used to derive the TDI, due to the lack of a dose-response relationship for the kidney histopathological changes and the lack of clinical chemistry data reflecting kidney function. In addition, only a LOAEL (not a NOAEL) for renal effects could be derived from this study.

11.5. Summary of uncertainties

In Table 15, a summary of the uncertainty evaluation is presented, highlighting the main sources of uncertainty and indicating an estimate of whether the respective source of uncertainty might have led to an over- or underestimation of the exposure or the resulting risk.

Table 15. Summary of qualitative evaluation of the impact of uncertainties on the risk assessment of the dietary exposure of uranium.

Sources of uncertainty	Direction [(a)]
Uncertainty in analytical results	-/+
Extrapolation of occurrence data from one European country to whole Europe	-/+
Lack of representative food results	-
Influence of non-detects on the exposure estimation (using the upper-bound approach in the risk characterization)	+
Variation in the recording of water consumption between the countries in the Concise European Food Consumption Database	-
Conservatism of the exposure scenarios	+
Use of a conversion from activity to mass units	-/+
Limitations in the dataset establishing the health based guidance value	-/+

(a): + = uncertainty with potential to cause overestimation of exposure/risk
- = uncertainty with potential to cause underestimation of exposure/risk

The CONTAM Panel considered the impact of the uncertainties on the risk assessment of exposure to uranium from food and water consumption and concluded that its assessment of the risk is likely to be conservative in the high exposure scenarios – i.e. more likely to overestimate than to underestimate the risk. However, the lack of representative food results might have led to an underestimation in the average exposure scenario.

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

Occurrence/exposure

- Uranium (U) is a silvery-white metal occurring in a number of minerals such as uraninite, carnotite and pitchblende. Uranium is also a naturally occurring radioactive element. Uranium can be present in water, air, food and feed in varying concentrations through leaching from natural deposits such as soil or rocks, emission from nuclear industry, dissolution in fertilizers and combustion of coal and other fuels. It has not biological function in human nutrition.
- The occurrence data reported in the literature indicate that the uranium level in water varies with the type of water, geological origin, and anthropogenic uranium emissions, although this was not confirmed by the data submitted to the European Food Safety Authority (EFSA).
- Limited occurrence data on uranium in food (i.e. from Germany only) were available, indicating that water may contribute about 50 % of the total uranium exposure in the average exposure scenario. Larger proportions of water contribution were observed in all the other exposure scenarios.
- For adults, overall country-specific lower- and upper-bound uranium exposure estimates varied between 0.05 and 0.28 μg/kg body weight (b.w.) per day considering different exposure scenarios. When high local concentrations occur together with a high consumption, the lower- and upper-bound uranium exposure estimates varied between 0.39 to 0.45 μg/kg b.w. per day.
- For infants, the exposure scenario included mean and high consumption of infant formula reconstituted with water containing both average and high levels of uranium. The lower- and upper-bound uranium exposure estimates varied between 0.18 and 1.42 μg/kg b.w. per day, for either bottled or tap water.

Hazard identification and characterization

- The bioavailability of uranium after oral intake is relatively low. Depending on the doses and solubility, uranium gastrointestinal absorption can range 0.1-6 % or 0.06-2.8 % of the ingested dose in humans and rats, respectively. There is indication from animal studies that ingested uranium is more efficiently absorbed in neonates than in adult individuals. About one third of the absorbed uranium is retained in the body, initially in the kidney and liver, then redistributed to the skeleton.
- The kidney is recognized as the primary target organ for uranium toxicity both in experimental animals and humans. Renal toxicity is characterised by damage to the proximal convoluted tubules, with possible involvement of the glomerulus at high exposures. Reproductive and developmental alterations (e.g. decreased pup growth and internal/external malformations), diminished bone growth and neurotoxicity have also been documented at higher doses in animal models.

- Epidemiological studies in adult individuals exposed to natural uranium from water and food have reported some correlations between exposure and various biomarkers of renal toxicity. Long-term uranium exposure may also increase the bone turnover and the blood pressure. Due to deficiencies in study design and data reporting in these epidemiological studies, the Panel on Contaminants in the Food Chain (CONTAM Panel) concluded that none of these studies can be used for deriving a tolerable daily intake (TDI) for uranium.
- The lowest-observed-adverse-effect-level (LOAEL) of 0.06 mg/kg b.w. per day was identified for nephrotoxicity in a sub-chronic study in male rats (Gilman *et al*., 1998a). The CONTAM Panel decided to endorse the World Health Organization (WHO) TDI for soluble uranium of 0.6 μg/kg b.w. per day in which the default uncertainty factor (UF) for inter- and intra-species differences of 100 was applied to the LOAEL of 60 μg/kg b.w. per day. No further adjustment was considered necessary to extrapolate a LOAEL to a no-observed-adverse-effect-level (NOAEL) or from a sub-chronic to a chronic exposure, on the ground of biokinetic considerations and the minimal degree of the observed renal effects.

Risk characterization

- The uranium dietary exposure estimates for the general population and high consumers across European countries are below the TDI of 0.6 μg/kg b.w. per day. In specific local situations e.g. drinking water with high uranium concentrations the exposure estimates are close to the TDI.
- The CONTAM Panel noted, however, that for infants fed with infant formula reconstituted with water containing uranium at the mean and the 95th percentile concentration levels, the exposure may be up to 3 times higher than the uranium exposure of adults on the body weight basis, for both mean and 95th percentile consumption values. The CONTAM Panel concluded that such exposure in infants should be avoided.

RECOMMENDATIONS

- There is a need for more detailed data on uranium concentrations in food at the European level to improve the accuracy of the exposure estimates.
- Controlled chronic animal studies addressing dose-response relationships for uranium adverse effects are needed to overcome some uncertainties and limitations associated with the currently available data.

REFERENCES

Adams N and Spoor NL, 1974. Kidney and bone retention functions in the human metabolism of uranium. Phys. Med. Biol. 19, 460-471.

Anke M, Seeber O, Müller R., Schäfer U and Zerull J, 2009. Uranium transfer in the food chain from soil to plants, animals and man. Chem. Erde-Geochem. 69, 75-90.

Alirezazadeh N and Garshasbi H, 2003. A survey of natural uranium concentrations in drinking water supplies in Iran. Iran. J. Radiat. Res. 1, 139-142.

Arfsten DP, 2001. A review of the effects of uranium and depleted uranium exposure on reproduction and fetal development. Toxicol. Ind. Health 17, 180-191.

Arnault E, Doussau M, Pesty A, Gouget B, Van der Meeren A, Fouchet P and Lefevre B, 2008. Natural uranium disturbs mouse foliculogenesis in vivo and oocyte meiosis in vitro. Toxicology 247, 80-87.

ATSDR, 1990. Agency for Toxic Substances and Disease Registry. Toxicological profile for uranium. U.S. Department of health and human services. Public Health Service. Report TP-90-29, Atlanta, USA.

ATSDR, 1999. Agency for Toxic Substances and Disease Registry. Toxicological profile for uranium. U.S. Department of health and human services. Public Health Service.

Bagatti D, Cantone MC, Giussani A, Veronese I, Roth P, Werne E and Hoellriegl V, 2003. Regional dependence of urinary uranium baseline levels in non-exposed subjects with particular reference to volunteers from Northern Italy. J. Environ. Radioact. 65, 357-364.

Barber DS, Ehrich MF and Jortner BS, 2005. The effect of stress on the temporal and regional distribution of uranium in rat brain after acute uranyl acetate exposure. J. Toxicol. Environ. Health A. 68, 99-111.

Berlin M and Rudell B, 1986. Uranium, in Handbook on the Toxicology of Metals, Vol. II, 2nd Ed., L. Friberg, G. Nordberg, and V. Vouk, eds. Amsterdam: Elsevier. p. 623-637.

Berradi H, Bertho JM, Dudoignon N, Mazur A, Grandcolas L, Baudelin C, Grison S, Voisin P, Gourmelon P and Dublineau I, 2008. Renal anemia induced by chronic ingestion of depleted uranium in rats. Toxicol. Sci. 103, 397-348.

BfR, 2005. Uran in Mineralwasser. Bei Erwachsenen geringe Mengen tolerierbar, Wasser für Säulingsnahrung sollte uranfrei sein. Stellungnahme Nr. 024/2005 des BfR vom 13 Mai 2005. http://www.bfr.bund.de/cm/208/uran_in_mineralwasser.pdf

BfR, 2007. BfR empfiehlt die Ableitung eines europäischen Höchstwertes für Uran in Trink- und Mineralwasser. Gemeinsame Stellungnahme Nr. 020/2007 des BfS und des BfR vom 5 April 2007. (in German).

http://www.bfr.bund.de/cm/208/bfr_empfiehlt_die_ableitung_eines_europaeischen_hoechstwertes_fuer_uran_in_trink_und_mineralwasser.pdf

Bussy C, Lestaevel P, Dhieux B, Amourette C, Paquet F, Gourmelon P and Houpert P, 2006. Chronic ingestion of uranyl nitrate perturbs acetylcholinesterase activity and monoamine metabolism in male rat brain. Neurotoxicol. 27, 245-252.

BVL, 2006. Berichte zur Lebensmittelsicherheit. Bundesweiter Überwachungsplan 2006. http://www.bvl.bund.de/cln_027/DE/01__Lebensmittel/00__doks__download/05__BUEp__dokumente/BUEp__Bericht__2006,templateId=raw,property=publicationFile.pdf/BUEp_Bericht_2006.pdf

COT, 2006. COT statement on uranium levels in water used to reconstitute infant formula. Committee on toxicity of chemicals in food, consumer products and the environment.

Desideri D, Roselli C, Assunta Meli M, Feduzi L, Rongoni A and Saetta D, 2007. Radioactivity measurements and radiation dose evaluation in tap waters of Central Italy. Mol. Nutr. Food Res. 51, 1182-1188.

D'Ilio S, Violante N, Senoforte O and Petrucci F, 2007. Determination of depleted uranium in fish. Validation of a confirmation method by dynamix reaction cell ICP-MS (DRC-ICP-MS). Anal. Chim. Acta. 597, 195-202.

Domingo JL, 2001. Reproductive and developmental toxicity of natural and depleted uranium: a review. Reprod. Toxicol. 15, 603-609.

Domingo JL, Llobet JM, Tomas JM and Corbella J, 1987. Acute toxicity of uranium in rats and mice. Bull. Environ. Contam. Toxicol. 39, 168-174.

Domingo JL, Ortega A, Paternain JL, Corbella J, 1989a. Evaluation of the perinatal and postnatal effects of uranium in mice upon oral administration. J. Arch Environ. Health 44, 395-398.

Domingo JL, Paternain JL, Llobet JM, Corbella J, 1989b. The developmental toxicity of uranium in mice. Toxicology 55, 143-152.

EFSA (European Food Safety Authority), 2006. Opinion of the Scientific Committee related to Uncertainties in Dietary Exposure Assessment. http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178620763403.htm

EFSA, 2008. Concise European Food Consumption Database. http://www.efsa.europa.eu/EFSA/ScientificPanels/DATEX/efsa_locale-1178620753812_ConciseEuropeanConsumptionDatabase.htm

Feugier A, Frelon S, Gourmelon P and Claraz M, 2008. Alteration of mouse oocyte quality after a subchronic exposure to depleted uranium. Reprod. Toxicol. 26, 273-277.

Fisenne IM, PM Perry and Harley NH, 1988. Uranium in humans. Rad. Prot. Dosim. 24, 127-131.

Frengstad B, Skrede AK, Banks D, Krog JR and Siewers U, 2000. The chemistry of Norwegian groundwaters: III. The distribution of trace elements in 476 crystalline bedrock groundwaters, as analysed by ICP-MS techniques. Sci. Total Environ. 246, 21-40.

FSA, 2004. Uranium-238 in the 2001 Total Diet Study. Food Survey Information Sheet 56/04. Food Standard Agency, UK. http://www.food.gov.uk/science/surveillance/fsis2004branch/fsis5604.

Gilman AP, Villeneuve DC, Secours VE, Yagminas AP, Tracy BL, Quinn JM, Valli VE, Willes RJ and Moss MA, 1998a. Uranyl nitrate: 28-day and 91-day toxicity studies in the Sprague-Dawley rat. Toxicol. Sci. 41, 117-128.

Gilman AP, Villeneuve DC, Secours VE, Yagminas AP, Tracy BL, Quinn JM, Valli VE, Willes RJ and Moss MA, 1998b. Uranyl nitrate: 91-day toxicity studies in the New Zealand white rabbit. Toxicol. Sci. 41, 129-137.

Gilman AP, Moss MA, Villeneuve DC, Secours VE, Yagminas AP, Tracy BL, Quinn JM, Long G and, Valli VE, 1998c. Uranyl nitrate: 91-day exposure and recovery studies in the male New Zealand white rabbit. Toxicol. Sci. 41, 138-151.

Gorman-Lewis D, Burns PC and Fein JB, 2008. Review of uranyl mineral solubility measurements. J. Chem. Thermodynamics 40, 335-352.

Harper RM and Kantar C, 2008. Ecotoxicology: Uranium. Jorgensen SE and Fath BD (eds.). 1st Edition, Elsevier B.V., Oxford, pp 3662-3665.

Harrison JD and Stather JW, 1981. The gastrointestinal absorption of protoactinium, uranium and neptunium in the hamster. Rad. Res. 88, 47-55.

Herranz M, Abelairas A and Legarda F, 1997. Uranium contents and associated effective doses in drinking water from Biscay (Spain). Appl. Radiat. Isot. 48, 857-861.

Hou X and Roos P, 2008. Review: Critical comparison of radiometric and mass spectrometric methods for the determination of radionuclides in environmental, biological and nuclear waste samples. Anal. Chim. Acta 608, 105-139.

Houpert P, Lestaevel P, Bussy C, Paquet F and Gourmelon P, 2005. Enriched but not depleted uranium affects central nervous system in long-term exposed rat. Neurotoxicology 26, 1015-1020.

Houpert P, Frelon S, Monleau M, Bussy C, Chazel V and Paquet F, 2007. Heterogeneous accumulation of uranium in the brain of rats. Radiat. Prot. Dosim. 127, 86-89.

Hu QY and Zhu SP, 1990. Induction of chromosomal-aberrations in male-mouse germ-cells by uranyl fluoride containing enriched uranium. Mutat. Res. 244, 209-214.

Huikuri P, Salonen L and Hämäläinen K, 2001. Occurrence of Uranium in Finnish Bedrock Water and Its Removal with a Strongly Basic Anion-Exchange Resin. Radiochem. 43, 482-486.

ICRP, 1979. Limits on Intakes of Radionuclides by Workers, Part 1. ICRP Publication 30. International Commission on Radiological Protection, Annals of the ICRP 2 (Nos. 3/4), Elmsford, N.Y.: Pergamon Press.

ICRP, 1995. Age-Dependent Doses to Members of the Public from Intake of Radionuclides, Part 3. ICRP Publication 69. International Commission on Radiological Protection. Annals of the ICRP 25 (No 1), Pergamon Press.

Jia G, Torri G, Sansone U, Innocenzi P, Rosamilia S, Di Lullo A and Gaudino S, 2006. Concentrations and characteristics of uranium isotopes in drinking waters collected in Italy and the Balcan regions and their radiological impact on the public. In: Radioactivity in the Environment. By V. Valković Ed. Vol 8. pp. 223-234.

Just RA and Emler VS, 1984. Generic report on health effects for U.S. gaseous diffusion plants. Report K/D-5050-Sect.8-Pt. 1, Martin Marietta Energy Systems. U.S. Department of Energy Oak Ridge Gaseous Diffusion Plant, Oak Ridge, TN.

Karpas Z, Paz-Tal O, Lorber A, Salonen L, Komulainen H, Auvinen A, Saha H and Kurttio P, 2005. Urine, hair, and nails as indicators for ingestion of uranium in drinking water. Health Phys. 88, 229-242.

Kathren RL and Burklin RK, 2008. Acute chemical toxicity of uranium. Health Phys. 94, 179-179.

Katsoyiannis IA, Hug SJ, Ammann A, Zikoudi A and Hatziliontos C, 2007. Arsenic specification and uranium concentrations in drinking water supply wells in Northern Greece: Correlations with redox indicative parameters and implications for groundwater treatment. Sci. Total Environ. 383, 128-140.

Kawabata Y, Yamamoto M, Aparin V, Ko S, Shiraishi M, Nagai M and Katayama Y, 2006. Uranium pollution of water in the western part of Uzbekistan. J. Radioanal. Nuclear Chem. 270, 137-141.

Kersting M, Alexy U, Sichert Hellert W, Manz F and Schoch G, 1998. Measured consumption of commercial infant food products in German infants: results from the DONALD study. Dortmund Nutritional and Anthropometrical Longitudinally Designed. J. Pediatr. Gastroeneterol. Nutr. 27, 547-552.

Konietzka R, Dieter HH and Voss JU, 2005. Vorschlag für eine gesundheitlichen Leitwert für Uran in Trinkwasser. Umweltmed. Forsch. Prax. 10, 133-143.

Kozlowska B, Walencik A, Dorda J and Przylibski TA, 2007. Uranium, radium and 40K isotopes in bottled mineral waters from Outer Carpathians, Poland. Radiat. Meas. 42, 1380-1386.

Kumar M, Singh S and Mahajan RK, 2006. Trace level determination of U, Zn, Cd, Pb and Cu in drinking water samples. Environ. Monit. Assess. 112, 283-292.

Kumar SA, Shenoy NS, Pandey S, Souderajan S and Venkateswaran G, 2008. Direct determination of uranium in seawater by laser fluorimetry. Talanta 77, 422-426.

Kurttio P, Auvinen A, Salonen L, Saha H, Pekkanen J, Makelainen I, Vaisanen SB, Penttila IM and Komulainen H, 2002. Renal effects of uranium in drinking water. Environ. Health Persp. 110, 337-342.

Kurttio P, Komulainen H, Leino A, Salonen L, Auvinen A and Saha H, 2005. Bone as a possible target of chemical toxicity of natural uranium in drinking water. Environ. Health Persp. 113, 68-72.

Kurttio P, Salonen L, Ilus T, Pekkanen J, Pukkala E and Aivinen A, 2006. Well radio radioactivity and risk of cancers of the urinary organs. Environ. Res. 102, 333-338.

Kuwahara C, Koyama K and Sugiyama H, 1997. Estimation of daily uranium ingestion by urban residents in Japan. J. Radioanal. Nucl. Chem. 220, 161-165.

La Touche YD, Willis DL and Dawydiak OI, 1987. Absorption and biokinetics of U in rats following an oral administration of uranyl nitrate solution. Health Phys. 53, 147-162.

Leggett RW and Harrison JD, 1995. Fractional absorption of ingested uranium in humans. Health Phys. 68, 484-498.

Lestaevel P, Bussy C, Paquet, Dhieux B, Clarencon D, Houpert P and Gourmelon P, 2005. Changes in sleep-wake cycle after chronic exposure to uranium in rats. Neurotoxicol. Teratol. 27, 835-840.

Li WB, Roth P, Wahl W, Oeh U, Höllriegl V and Paretzke HG, 2005. Biokinetic modeling of uranium in man after injection and ingestion. Radiat. Environ. Biophys. 44, 29-40.

Lin RH, Wu LJ, Lee CH and Lin-Shiau SY, 1993. Cytogenetic toxicity of uranyl nitrate in Chinese hamster ovary cells. Mutat. Res. 319, 197-203.

Linares V, Albina ML, Bellés M, Mayayoc E, Sánchez DJ, Domingo JL, 2005. Combined action of uranium and stress in the rat II. Effects on male reproduction. Toxicol. Lett. 158, 186-195.

Linares V, Bellés M, Albina ML, Sirvent JJ, Sánchez DJ and Domingo JL, 2006. Assessment of the pro-oxidant activity of uranium in kidney and testis of rats. Toxicol. Lett. 167, 152-161.

Llobet JM, Sirvent JJ, Ortega A and Domingo JL, 1991. Influence of chronic exposure to uranium on male reproduction in mice. Fundam. Appl. Toxicol. 16, 821-829.

Lu S and Zhao FY, 1990. Nephrotoxic limit and annual limit on intake for natural uranium. Health Phys. 58, 619-623.

Magdo SH, Forman J, Graber N, Newman B, Klein K, Satlin L, Amler RW, Winston JA and Landrigan PJ, 2007. Grand Rounds: Nephrotoxicity in a young child exposed to uranium from contaminated well water. Environ. Health Persp. 115, 1237-1241.

Malenchenko AF, Barkun NA and Guseva GF, 1978. Effect of uranium on the induction and course of experimental autoimmune orchitis and thyroiditis. J. Hyg. Epidemiol. Microbiol. Immuno. 22, 268-277.

Mao Y, Desmueles M, Scaubel D, Bérubé D, Dyck R, Brule D and Thomas B, 1995. Inorganic components of drinking water and microalbuminuria. Environ. Res. 71, 135-140.

May CC, Worsfold PJ and Keith-Roach MJ, 2008. Analytical techniques for speciation analysis of aqueous long-lived radionuclides in environmental matrices. TRAC-Trend Anal. Chem. 27, 160-168.

Maynard EA and Hodge HC, 1949. Studies of the toxicity of various uranium compounds when fed to experimental animals. In: The Pharmacology and Toxicology of Uranium Compounds. Nations Nuclear Energy Service. Division VI, Vol. I, C. Voegtlin and H.C. Hodge, Ed. McGraw Hill, New York, NY. p. 309-376.

Maynard EA, Downs WL and Hodge HC, 1953. Oral toxicity of uranium compounds. In *Pharmacology and Toxicology of Uranium Volume 3*. Edited by: Voegtlin C, Hodge HC. New York: McGraw Hill; 1221-1369.

McGuire SA, 1991. Chemical toxicity of uranium hexafluoride compared to acute effects of radiation. Report NUREG-1391. U.S. Nuclear Regulatory Commission, Washington, DC.

Miller AC and McClain D, 2007. A review of Depleted Uranium biological effects: *in vitro* and *in vivo* studies. Rev. Environ Health 22, 75-89.

Milvy P and Cothem RC, 1991. Scientific background for the development of regulations for radionuclides in drinking water. In: Radon, Radium and Uranium in Drinking Water. Cothern CR and Roberts PA (eds.). Lewis, Mich. pp. 1-16.

Misra NL, Dhara S and Singh Mudher KD, 2006. Uranium determination in seawater by total reflection X-ray fluorescence spectrometry. Spectrochim. Acta Part B 61, 1166-1169.

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

Neuman WF, Neuman MW, Main ER and Mulryan BJ, 1948. The deposition of uranium in bone III. The effect of diet. J. Biol. Chem. 175, 715-719.

Neves O and Matias MJ, 2008. Assessment of groundwater quality and concentration problems ascribed to an abandoned uranium mine (Cunha Baixa region, Central Portugal). Environ. Geol. 53, 1799-1810.

NCRP, 1975. National Council on Radiological Protection. Natural background radiation in the United States. Report 45, Bethesda, MD, USA.

NRC, 2000. United States Nuclear Regulatory Commission (USNRC). Title 10 of the Code of Federal Regulations. http://www.nrc.gov/reading-rm/doc-collections/cfr/

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

Orcutt JA, 1949. The toxicology of compounds of uranium following application to the skin. Voegtlin K and Hodge HC (eds.). New York: McGraw-Hill. Vol. 1, pp. 376-414.

Orloff KG, Mistry K, Sharp P, Metcalf S, Marino R, Shelly T, Melaro E, Donohoe AM and Jones RL, 2004. Human exposure to uranium in groundwater. Env. Res. 94, 319-326.

Paquet F, Houpert P, Blanchardon E, Delissen O, Maubert C, Dhieux B, Moreels AM, Frelon S, Voisin Ph and Gourmelon P, 2006. Accumulation and distribution of uranium in rats after chronic exposure by ingestion. Health Phys. 90, 139-147.

Parrish RR, Hortswood M, Arnason JG, Chenery S, Brewer T, Lloyd NS and Carpenter DO, 2008. Depleted uranium contamination by inhalation exposure and its detection after ~ 20 years: implications for human health assessment. Sci. Tot. Environ. 390, 58-68.

Paternain JL, Domingo JL, Ortega A and Llobet JM, 1989. The effects of uranium on reproduction, gestation and postnatal survival in mice. Ecotox. Environ. Saf. 17, 291-296.

Pavlakis N, Pollock CA, McLean G and Bartrop R, 1996. Deliberate overdose of uranium: Toxicity and treatment. Nephron. 72, 313-317.

Pawlak Z and Rabiega G, 2002. Comparison of ICP-MS and radiochemical techniques for total uranium in environmental water samples. Environ. Sci. Technol. 36, 5395-5398.

Pfenning G, Klewe-Nebenius H and Seelmann-Eggebert W, 1998. Chart of the Nuclides. 6th edition revised reprint. Forschungszentrum Karlsruhe.

Prasada Rao T, Metilda P and Gladis JM, 2008. Review: Preconcentration techniques for uranium (VI) and thorium (IV) prior to analytical determination - an overview. Talanta 68, 1047-1064.

Priest ND, 2001. Toxicity of depleted uranium. Lancet 357, 244-246.

Raymond-Whish S, Mayer LP, O'Neal T, Martínez A, Sellers MA, Christian PJ, Marion SL, Begay C, Propper CR, Hoyer PB and Dyer CA, 2007. Drinking Water with Uranium below the U.S. EPA Water Standard Causes Estrogen Receptor–Dependent Responses in Female Mice. Environ. Health Persp. 115, 1711-1716.

Ribera D, Labrot F, Tisnerat G and Narbenne JF, 1996. Uranium in the Environment: occurrence, transfer, and biological effects. Rev. Environ. Contam. Toxicol. 146, 53-89.

RIFE, 2007. Radioactivity in Food and the Environment. Food Standards Agency, UK. http://www.food.gov.uk/science/surveillance/radiosurv/rife13

Sadeghi S, Mohammadzadeh D and Yamini Y, 2003. Solid-phase extraction–spectrophotometric determination of uranium(VI) in natural waters. Anal. Bioanal. Chem. 375, 698-702.

Sadeghi S and Sheikhzadeh E, 2009. Solid phase extraction using silica gel modified with murexide for preconcentration of uranium (VI) ions from water samples. J. Haz. Mat. 163, 861-868.

Sánchez J, Bellés M, Albina ML, Gómez M, Linares V and Domingo JL, 2006. Exposure of pregnant rats to uranium and restraint stress: effects on postnatal development and behaviour of the offspring. Toxicology 228, 323-332.

Schnug E, Steckel H and Haneklaus S, 2005. Contribution of uranium in drinking water to the daily uranium intake of humans - a case study from Northern Germany, Landbauforschung Völkenrode 55, 227-236.

Sheppard MI, 1980. The environmental behaviour of uranium and thorium. Whiteshell Nuclear Research Establishment, Atromica energy of Canda, Pinawa, Manitoba. Technical Report AECL-6795.

Sheppard SC, Sheppard MI, Gallerand M-O and Sanipelli B, 2005. Derivation of ecotoxicity thresholds for uranium. J. Environ. Radioact. 79, 55-83.

Singh NP, Burleigh DP, Ruth HM and Wrenn ME, 1990. Daily uranium intake in Utah resident from food and drinking water, Health Phys. 59, 333-337.

Singh J, Singh H, Singh S and Bajwa BS, 2008. Estimation of uranium and radon concentration in some drinking water samples. Radiat. Meas. 43, Supplement 1, 523-526.

Sontag W, 1986. Multicompartment kinetic models for the metabolism of americium, plutonium and uranium in rats. Human Toxicol. 5, 163-173.

Stearns DM, Yazzie M, Bradley AS, Coryell VH, Shelley JT, Ashby A, Asplund CS and Lantz RC, 2005. Uranyl acetate induces hprt mutations and uranium-DNA adducts in Chinese hamster ovary EM9 cells. Mutagenesis 20, 417-423.

Sullivan MF and Gorham LS, 1980. Absorption of Actinide Elements from the Gastrointestinal tract of Neonatal Animals. Health Phys. 38, 173-185.

Sullivan MF, Ruemmler PS, Ryan JL and Buschbom RL, 1986. Influence of oxidizing or reducing agents on gastrointestinal absorption of U, Pu, Am, Cm and Pm by rats. Health Phys. 50, 223-232.

Svensson K, Darnerud PO and Skerfving S, 2005. A Risk Assessment of Uranium in Drinking Water. National Food Administration. Sweden. http://www.slv.se

Tagami K and Uchida S, 2007. Rapid uranium preconcentration and separation method from fresh water samples for total U and $^{235}U/^{238}U$ ratio measurements by ICP-MS. Anal. Chim. Acta 592, 101-105.

Tracy BL, Quinn JM, Lahey J, Gilman AP, Mancuso K, Yagminas AP and Villeneuve DC, 1992. Absorption and retention of uranium from drinking water by rats and rabbits. Health Phys. 62, 65-73.

UBA, 2005. Uranium and Human Biomonitoring Opinion of the Human Biomonitoring Commission of the German Federal Environment Agency. Bundesgesundheitsblatt – Gesundheitsforschung – Gesundheitsschutz 48(7), 822-827. http://www.umweltdaten.de/gesundheit-e/monitor/Uranium-in-urine.pdf

Unsworth ER, Cook JM and Hill SJ, 2001. Determination of uranium and thorium in natural waters with a high matrix concentration using solid-phase extraction inductively coupled plasma mass spectrometry. Anal. Chim. Acta 442, 141-146.

US-EPA, 1986. Environmental Radiation Data. Report 42. April-June 1985. NTIS PB166311.

US-EPA, 1989. U.S. Environmental Protection Agency. *Integrated Risk Information System (IRIS) on Uranium, Soluble Salts*. National Center for Environmental Assessment, Office of Research and Development, Washington, DC. 1999. http://www.epa.gov/iris/subst/0421.htm

US-EPA, 1990. Occurrence and exposure assessment for uranium in public drinking water supplies. Report prepared by Wade Miller Associates, Inc. for the Office of Drinking Water, US Environmental Protection Agency, 26 April 1990.

US-EPA, 1991. Review of RSC analysis. Report prepared by Wade Miller Associates, Inc. for the US Environmental Protection Agency, 9 May 1991.

US-EPA, 1994. EPA METHOD 200.8. Determination of trace elements in waters and wastes by inductively coupled plasma - mass spectrometry. Revision 5.4. Environmental monitoring systems laboratory office of research and development. U.S. Environmental Protection Agency. Cincinnati, Ohio 45268.

US-EPA, 1999. EPA METHOD 908.0. Uranium in drinking water-radiochemical method. Revision 2.0. U.S. Environmental Protection Agency.

US-EPA, 2003. Drinking water contaminants. Accessed on 20 January 2009. http://www.epa.gov/safewater/contaminants/index.html#rads.

Vesterbacka P, Mäkeläinen I and Arvela H, 2005. Natural radioactivity in drinking water in private wells in Finland. Radiat. Prot. Dosim. 113, 223-232.

Vesterbacka P, 2005. ^{238}U series radionuclides in Finnish groundwaters-based drinking water and effective doses. Academic Dissertation. University of Helsinki.

Wallner G, Wagner R and Katzlberger C, 2008. Natural radionuclides in Austrian mineral water and their sequential measurement by fast methods. J. Environ. Radioact. 99, 1090-1094.

WHO, 1998. Guidelines for Drinking-Water Quality - Second Edition - Volume 2 – Health Criteria and Other Supporting Information – Addendum.

WHO, 2001. Depleted uranium: sources, exposure and health effects. Department of Protection of the Human Environment. World Health Organization. Geneva. WHO/SDE/PHE/01.1. http://www.who.int/ionizing_radiation/pub_meet/ir_pub/en/

WHO, 2004. Guidelines for drinking-water quality – Third Edition. Geneva, Switzerland: WHO.

WHO, 2005. Uranium in Drinking Water. Background Document for development of WHO guidelines for Drinking Water Quality. WHO/SDE/03.04/118.

WHO/IPCS, 2008. World Health Organization/International Programme on Chemical Safety. Part 1: guidance document on characterizing and communicating uncertainty in exposure assessment. http://www.who.int/ipcs/methods/harmonization/areas/draftundertainty.pdf

Wrenn ME, Durbin PW, Howard B, Lipsztein J, Rundo J, Still ET and Willis DL, 1985. Metabolism of ingested U and Ra. Health Phys. 48, 601-633.

Zamora ML, Tracy BL, Zielinski JM, Meyerhof DP and Moss MA, 1998. Chronic ingestion of uranium in drinking water: a study of kidney bioeffects in humans. Toxicol. Sci. 43, 68-77.

Zamora ML, Zielinski JM, Meyerhof D and Tracy B, 2002. Gastrointestinal absorption of uranium in humans. Health Phys. 83, 35-45.

Zamora ML, Zielinski JM, Meyerhof D, Moodie G, Falcomer R and Tracy B, 2003. Uranium gastrointestinal absorption: the F1 factor in humans. Rad. Prot. Dosim. 105, 55-60.

ABBREVIATIONS

ALP	Alkaline phosphatase
ATSDR	Agency for Toxic Substances and Disease Registry
BfR	German Federal Institute for Risk Assessment
BMG	β_2-microglobulin
Bq	Becquerel
BVL	German Federal Office of Consumer Protection and Food Safety
b.w.	Body weight
Ci	Curie
CTx	Carboxy-terminal telopeptide
CONTAM Panel	Panel on Contaminants in the Food Chain
COT	Committee on Toxicity
DNA	Deoxyribonucleic acid
DM	Dry matter
DONALD study	Dortmund Nutritional and Anthropometric Longitudinally Designed Study
DU	Depleted uranium
EFSA	European Food Safety Authority
EU	European Union
EURATOM	European Atomic Energy Community
FSA	UK Food Standards Agency
GD	Gestational day
GDMS	Glow discharge mass spectrometry
GGT	γ-glutamyl transferase
GI	Gastrointestinal
GST	α-glutathione-S-transferase
ICP-MS	Inductively coupled plasma mass spectrometry
ICRP	International Committee on Radiological Protection
LD_{50}	Lethal dose – the dose required to kill half the members of a tested animal population
LDH	Lactate dehydrogenase
LOAEL	Lowest-observed-adverse-effect-level
LOD	Limit of detection

LOQ	Limit of quantification
MRL	Minimal risk level
MS	Mass spectrometry
NAG	N-acetyl-γ-D-glucosaminidase
NOAEL	No-observed-adverse-effect level
Pb	Lead
PhD	Doctor of Philosophy
PND	Postnatal day
RfD	Reference dose
RIFE	Radioactivity in Food and the Environment (UK report)
SIMS	Secondary ion mass spectrometry
SPE	Solid phase extraction
TDI	Tolerable daily intake
TIMS	Thermal ionization mass spectrometry
TXRF	Total reflection X-Ray fluorescence spectrometry
U	Uranium
UBA	German Federal Environment Agency
UF	Uncertainty factor
UK	United Kingdom
USA	United States of America
US-EPA	United States Environmental Protection Agency
WHO	World Health Organization
XRF	X-Ray Fluorescence spectrometry