AGENCE FRANÇAISE
DE SÉCURITÉ SANITAIRE
DES ALIMENTS

Maisons-Alfort, 13 January 2010

OPINION

of the French Food Safety Agency on the determination of a quality requirement for the mass concentration of uranium in water intended for human consumption

THE DIRECTOR GENERAL

Summary of the request:

On 4 December 2008, the French Food Safety Agency (AFSSA) received a request from the Directorate General for Health (DGS) for an Opinion on the determination of a quality requirement for the mass concentration of uranium in water intended for human consumption, based on its chemical toxicity and an assessment of the health risks associated with situations in which this concentration is exceeded.

Background:

Considering the guideline value of 15 µg/L for uranium proposed by the World Health Organisation in 2004;

Considering the Opinion of the European Food Safety Authority (EFSA) of 25 March 2009[1] on the "maximum tolerable intake of natural uranium from foodstuffs, particularly natural mineral waters".

Method of expert assessment:

Based on the collective expert assessment done by the 'Non-compliance' working group, whose report was approved by the Scientific panel on 'Water' (consulted on 7 July and 3 November 2009) and the Scientific panel on 'Physical and Chemical Residues and Contaminants' (consulted on 20 November 2009), AFSSA has reached the following conclusions:

Rationale:

1- Origins and sources of contamination

Uranium (U) is the heaviest naturally-occurring element on Earth. It is found in many minerals, of which the most commonly exploited are:

- carnotite ($K_2(UO_2)_2(VO_4)_2$, 3 H_2O)
- uraninite and pitchblende (UO_2)
- coffinite ($U(SiO_4)_{1-x}(OH)_{4x}$)

It has 14 isotopes, all radioactive, of which only three are of natural origin: ^{234}U, ^{235}U and ^{238}U, and which emit alpha and gamma radiation as they decay. The isotope ^{235}U is fissile when

[1] EFSA – European Food Safety Authority (2009). Scientific Opinion of the Panel on Contaminants in the Food Chain in response to a request from the German Federal Institute for Risk Assessment (BfR) on uranium in foodstuffs, in particular mineral water. *The EFSA Journal* 1018, 1-59 (2009).

27-31, avenue
du Général Leclerc
94701
Maisons-Alfort cedex
Tel 01 49 77 13 50
Fax 01 49 77 26 13
www.AFSSA.fr

REPUBLIQUE
FRANÇAISE

bombarded with neutrons, a property which has led to the development of the nuclear industry. Depleted uranium is a by-product of the nuclear industry and comes mainly from plants enriching natural uranium into ^{235}U in order to produce fuel for nuclear reactors. It can be distinguished from natural uranium by its different isotopic composition, including a lower concentration of ^{235}U, which is about 0.2 to 0.3% instead of 0.72% in natural uranium. As a general rule, the signature of an artificial source of uranium is given by a $^{235}U/^{238}U$ isotopic ratio different from 0.72%.

Table 1 shows the isotopic composition by mass of uranium according to its degree of enrichment (depleted, natural and enriched uranium) for the three isotopes.

Table 1: isotopic composition by mass and activity of uranium according to its degree of enrichment

	Depleted uranium		**Natural uranium**		**Enriched uranium**	
	Mass (%)	Activity (%)	Mass (%)	Activity (%)	Mass (%)	Activity (%)
^{234}U	0.0013	19	0.0056	49	0.022	80
^{235}U	0.3	2	0.72	2	3.25	4
^{238}U	99.6987	79	99.28	49	96.73	16
Overall Activity (kBq/g)	16		25		63	

Because of its strong affinity for oxygen, uranium is found in nature as oxides, oxyanions or oxycations and with valence states of +2, +3, +4, +5, or more commonly in the hexavalent state as the uranyl ion, UO_2^{2+}. Under reductive conditions the oxidation state is valence +4 and uranium's solubility in this form is low.
Uranium is also found in soluble (uranium trioxide, uranyl chloride, uranyl nitrate) and relatively insoluble forms (uranium dioxide, triuranium octocide).

Contamination of raw water is due mainly to the natural alteration of rock and soil, with concentrations being very unevenly distributed. In addition to these geological sources, contamination also comes from industrial activities:

- exploitation of uranium deposits and, to a lesser extent, leaching resulting from industrial processes related to the nuclear fuel cycle;
- combustion of coal which contains non-negligible quantities of natural radionuclides, including uranium;
- agricultural use of large amounts of natural phosphates containing high levels of radionuclides;
- military use of depleted uranium, which can lead to blast sites being enriched in fine particles of $UO_{2(s)}$.
- civil use of depleted uranium such as for ballast in aircraft.

Thus uranium is redistributed in all environmental compartments. It is highly mobile, except when adsorbed on metal oxy-hydroxides. It is found in very low concentrations in river water (0.02 to 6 ppb) and the oceans (3 ppb). However, uranium found in the soil remains partially available. It may therefore be transferred to plants (especially root vegetables), including those intended for food, and the food chain.

2- Review of national legislation relating to the radiological quality of water intended for human consumption

The French Public Health Code, in its Articles R 1321-1 to R 1321-68 and the texts implementing them, only focuses on the radiological quality of water intended for human consumption, excluding natural mineral water. The procedures for controlling and managing the health risk associated with the presence of radionuclides were established by the Ministerial Order of 12 May 2004[2] and the Circular of 13 June 2007[3].

The methodology for the radiological analysis of water intended for human consumption is summarised in the Annex.

3- Treatments for reducing uranium content in water

Coagulation with aluminium sulfate or ferric chloride can achieve respectively an 80 and 95% reduction in uranium content, subject to optimal pH conditions and a coagulant dose specific to this element. However, less than 20% will be eliminated if pre-polymerised aluminium salts are used.
A reduction of more than 95% can be obtained when the water is decarbonated with lime (or soda) and from selective adsorption on metal oxy-hydroxides (especially MnO_2).
Filtration on anion exchange resin is effective (WHO, 2005).
Membrane processes used for nanofiltration or reverse osmosis demineralisation are also effective (Raff *et al.*, 1999; Favre-Réguillon *et al.*, 2008).

4- Analytical methods

There are several analytical techniques for determining the concentration or measuring the activities of the different uranium isotopes in water.
Only the relevant analytical methods are described here.

4.1- Total element analysis

In a gravimetric analysis, the measurement result is a concentration expressed as a ratio of mass to volume (e.g. milligrams per litre or micrograms per litre).

It can be achieved using the following techniques:

- flameless atomic absorption,
- ICP-AES,
- ICP-MS which, in addition to total uranium content, enables the isotopic composition to be determined.

These last two techniques are included in the standard analytical protocols.

Standard: **NF M60-805-2** of February 2003: Nuclear energy - Measurement of radioactivity in the environment - Water - Part 2: measurement of the concentration of uranium in water by inductively-coupled plasma atomic emission spectroscopy.

Standard: **NF M60-805-4** of December 2005: Nuclear energy - Measurement of radioactivity in the environment - Water - Part 4: uranium measurement in water using inductively coupled plasma mass spectrometry.

4.2- Analysis of the radioactivity emitted

[2] Ministerial Order of 12 May 2004 establishing the procedures for controlling the radiological quality of water intended for human consumption
[3] Circular of 13 June 2007 on the control and management of the health risk associated with the presence of radionuclides in water intended for human consumption, with the exception of bottled water and natural mineral water

With the isotopic analysis of a sample, the results are expressed in Becquerel per litre.

4.2.1- Measuring overall emissions

- Measurement of total alpha emissions: as uranium 235 and 234 are both alpha emitters, they are included, among others, in this measurement.

Standard: **NF M60-801** of September 2004: Nuclear energy - Measurement of radioactivity in the environment - Water - Measurement of alpha activity index in terms of plutonium 239 equivalent in low salted water.

- **Measurement of** total beta emissions: this is not suited to monitoring uranium content in water.

4.2.2- Measuring specific emissions for radionuclides

Standard: **NF M60-805-5** of December 2005: Nuclear energy - Measurement of radioactivity in the environment - Water - Part 5: measurement of the activity and concentration of uranium in water by alpha spectrometry.

Based on the activities of the different uranium isotopes measured, the corresponding uranium mass can be calculated, given that the mass due to uranium 238 will predominate in the end result.

4.3- Limits of detection and quantitation – Analytical uncertainties

The Ministerial Order of 17 September 2003 on analytical methods for water samples and their performance characteristics specifies that, in the case of uranium 234 and 238, the limit of detection must not exceed 0.005 Bq/L.

The data on limits of quantitation in uranium mass concentration provided by the French Institute for Radiological Protection and Nuclear Safety (IRSN) are as follows:

- By alpha spectrometry: 0.5 µg/L
- By ICP-AES: <10 -70 µg/L
- By quadrupole ICP-MS: 0.01 µg/L

5- Exposure assessment

Exposure to uranium may be via respiratory or oral route.

5.1- Intake through air, excluding occupational exposure

This is negligible, approximately one nanogram per day according to the WHO (2004).

5.2- Uranium contamination of food and drinking water

5.2.1- Data on uranium contamination of food (excluding water)

There are no national data on uranium contamination of food that would enable the daily dietary intake (excluding water) to be estimated.

Anke *et al.* (2009) have shown that wild and cultivated plants in the immediate vicinity of uranium waste storage sites contain levels of uranium eight times higher than plants located away from these sites. Leafy plants accumulate more uranium than tubers, the thick parts of stems, fruits

and seeds which store less. Asparagus (50 µg uranium/kg dry matter [DM]) and mushrooms (100 µg uranium/kg DM) exhibit high levels of uranium.
Some foods such as margarine, honey and pearl barley generally have low levels of uranium (concentrations between 0.8 and 1.9 µg uranium/kg DM).

Generally, foods of animal origin are less contaminated by uranium than foods of plant origin, although high concentrations may be found in shellfish and fish (Ribera *et al.*, 1996; WHO, 2001; Anke *et al.*, 2009).

In its Opinion of 25 March 2009 on the maximum tolerable intake of natural uranium from foodstuffs, the European Food Safety Authority (EFSA) determined daily intake levels of uranium from foodstuffs (excluding water) from German data alone. The food groups most contaminated by uranium are cereals (0.08-2.93 µg uranium/kg on average), sugar, sugar products (0.63-3.96 µg uranium/kg on average) and vegetables (1.37-2.54 µg uranium/kg on average).

5.2.2- Data on uranium contamination of water in France

There are several types of data on uranium contamination of water intended for human consumption in France.

5.2.2.1- IRSN data

In its report DEI/STEME no. 2008-08, the IRSN stated that 760 uranium concentration values are available for the period 2004 to 2007 from the IRSN's Department for sample processing and metrology for the environment (STEME).
These results are not representative of the radiological quality of all water distributed in France, as they are merely analyses conducted by the IRSN for calculating the TID, i.e. they are only carried out when the guideline values for total alpha activity and/or total residual beta activity (approximately 4% of the national total for radioactivity analyses carried out on water intended for human consumption) are exceeded.

Figure 1 shows uranium mass concentrations below 15 µg/L in the water supply as well as the distribution of uranium mass concentrations above 15 µg/L.

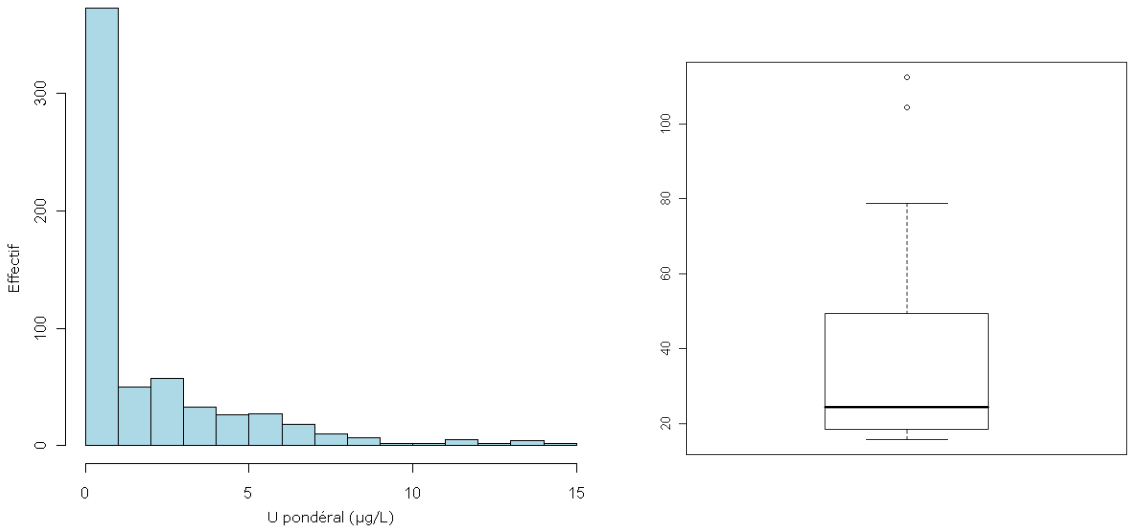


Figure 1: Histogram of uranium mass concentrations below 15 µg/L and box plot of uranium mass concentrations (µg/L) above 15 µg/L in the water supply (in English, "U pondéral" is "mass concentration in uranium" and "Effectif" is "number of values")

Twenty-four of these values (n = 642) are above the WHO guideline value of 15 µg/L. The samples concerned represent isolated cases.

Considering all the available data, the median value is 0.71 µg/L and the 95th percentile is 11.44 µg/L.

Figure 2 shows uranium mass concentrations below 15 µg/L as well as the distribution of uranium mass concentrations above 15 µg/L in mineral or thermal waters.

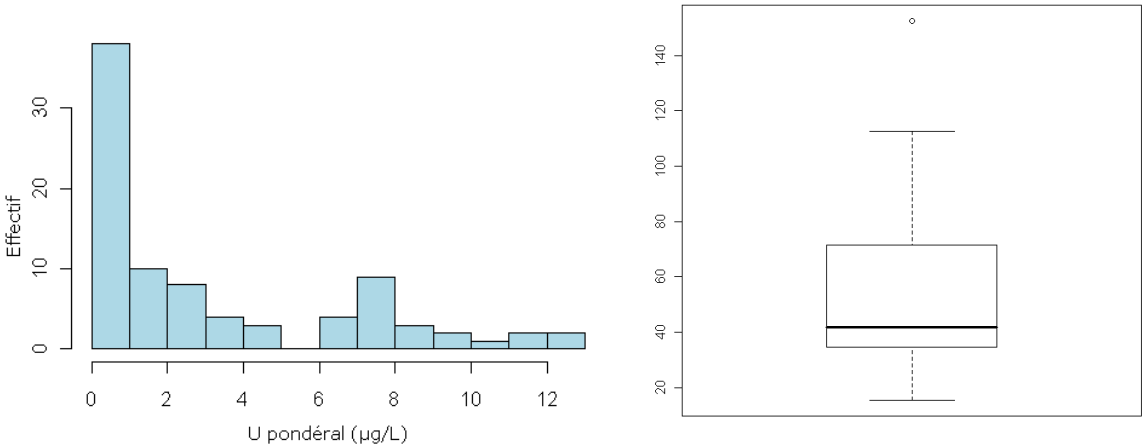


Figure 2: Histogram of uranium mass concentrations below 15 µg/L and box plot of uranium mass concentrations (µg/L) above 15 µg/L in mineral or thermal waters (in English, "U pondéral" is "mass concentration in uranium" and "Effectif" is "number of values")

Nine of these values (n = 95) are above the WHO guideline value of 15 µg/L. The samples concerned all come from the same French *département*.
Considering all the available data, the median value is 1.92 µg/L and the 95th percentile is 38.07 µg/L. The maximum value is 152.7 µg/L.
The analysed water could have come from either the resource (untreated water) or the finished commercial product. Consequently, these results are not representative of the quality of the water as consumed.

5.2.2.2- SISE-Eaux data (DDASS-DRASS-Ministry for Health)

The results from the SISE-Eaux (Health & Environment Information System – Water) database relate to uranium content (^{234}U, ^{235}U and ^{238}U) expressed in Bq/L measured in water leaving the treatment and production plant (TTP) between January 2000 and December 2008.
Insofar as there are no health inspections for uranium, except where it exceeds the guideline values for total alpha activity and/or total residual beta activity, the results for uranium from the processed data in the SISE-Eaux database are not representative of the quality of all water distributed in France.

To convert activity concentrations (Bq/L) to mass concentrations (µg/L), the following formula[4] was applied for a given sample:

$$[U\ (\mu g/L)] = 0.00434\ [^{234}U\ (Bq/L)] + 12.5\ [^{235}U\ (Bq/L)] + 80.37\ [^{238}U\ (Bq/L)]$$

The results below a limit of quantitation (LoQ) were estimated as LoQ/2. At the national level, 711 results are available from the database, relating to 44 French *départements*. Figure 3 shows the cumulative frequencies from the results in the SISE-Eaux database in the TTPs according to the uranium mass concentration.

[4] 1 Bq/L ^{234}U is equivalent to 0.00434 µg/L ^{234}U; 1 Bq/L ^{235}U is equivalent to 12.5 µg/L ^{235}U and 1 Bq/L ^{238}U is equivalent to 80.37 µg/L ^{238}U

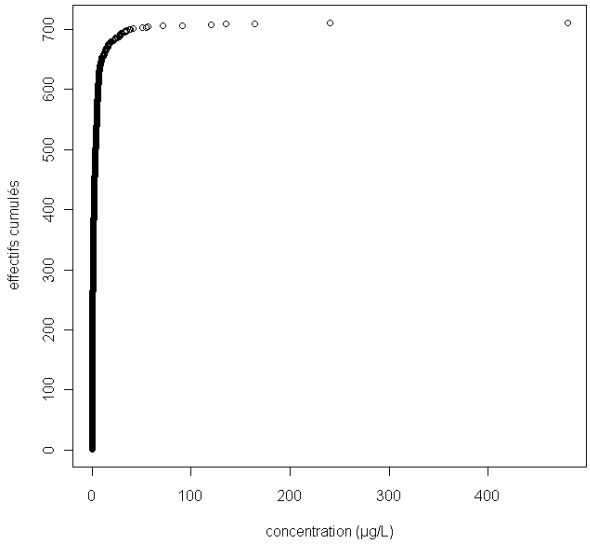


Figure 3: cumulative number of values from the results observed in the SISE-Eaux database in the TTPs according to the uranium mass concentration (in English, "effectifs cumulés" is "cumulative number")

Table 2 below gives some percentiles of the distribution of results observed in the SISE-Eaux database between January 2000 and December 2008 measured in water leaving the treatment plant.

Table 2: Percentiles of the distribution of contamination of water intended for human consumption (SISE-Eaux 2000-2008 – type of plant: leaving the treatment plant)

Percentile of the distribution	5%	25%	50%	75%	95%
Concentration	0.15 µg/L	0.40 µg/L	1.37 µg/L	4.42 µg/L	18.57 µg/L

Forty-three of the 711 results available are above the WHO guideline value (2004) of 15 µg/L. The results concerned are isolated cases.

5.2.2.3- Data from AFSSA's Laboratory for study and research on hydrology, relating to natural mineral water (2008)

The data on contamination of natural mineral water come from processed data resulting from an investigation conducted by the Laboratory for study and research on hydrology in 2008. Seventy-three natural mineral waters were analysed with 18 quantized values for uranium. Only two of the natural mineral waters had levels of uranium mass concentration higher than the WHO guideline value (2004) of 15 µg/L. Figure 4 shows the results of this investigation.

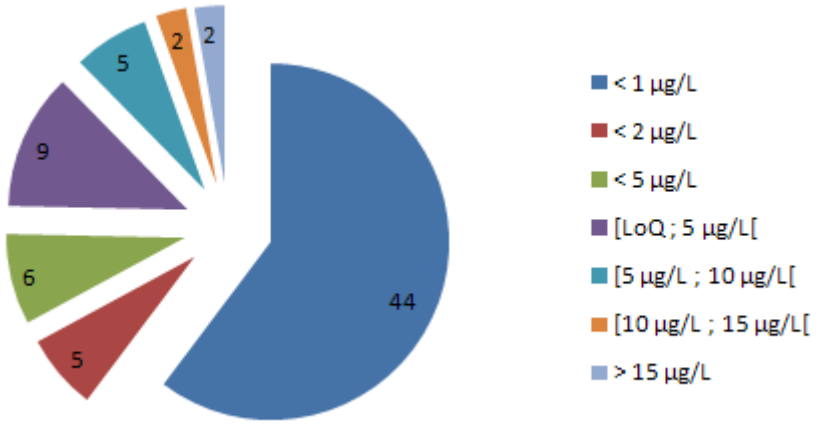


Figure 4: Distribution of classes of uranium mass concentration in natural mineral water (AFSSA's Laboratory for study and research on hydrology, 2008)

5.3- Share of total uranium exposure due to exposure through water

In its Opinion of 25 March 2009 relating to the "maximum tolerable intake of natural uranium from foodstuffs, particularly natural mineral waters", EFSA estimated the daily dietary intake of natural uranium.
The consumption data come from the European food consumption database (EFSA's Concise European Food Consumption Database, 2008).
The contamination data were cross-matched with the consumption data in order to estimate daily intakes of natural uranium.
For intakes related to consumption of tea, coffee, beer and other soft drinks, the consumption data were cross-matched with data on contamination of water intended for human consumption.
Four exposure scenarios were selected by EFSA to take into account the variability of contamination and consumption data:

- mean contamination and mean consumption (scenario 1),
- mean contamination and 95th percentile of the consumption distribution (scenario 2),
- 95th percentile of the contamination distribution and mean consumption (scenario 3),
- 95th percentile of the contamination distribution and 95th percentile of the consumption distribution (scenario 4).

The results are shown in Table 3.

Table 3: Medians of estimated uranium exposure values (µg/kg b.w./d) for ingestion of water and food under four scenarios (from EFSA, 2009)

	Scenario 1		Scenario 2		Scenario 3		Scenario 4	
	Lower bound[5]	Upper bound[6]	Lower bound	Upper bound	Lower bound	Upper bound	Lower bound	Upper bound
Tap water	0.009	0.009	0.03	0.03	0.037	0.037	0.13	0.13
Bottled water	0.004	0.004	0.015	0.015	0.017	0.017	0.07	0.07
Tea, coffee, beer, soft drinks	0.025	0.025	0.059	0.059	0.108	0.108	0.258	0.258
Total water	0.043	0.043	0.082	0.082	0.186	0.186	0.355	0.355
Total food	0.009	0.04	0.016	0.066	0.036	0.087	0.063	0.143
Total dietary exposure	0.052	0.085	0.092	0.135	0.222	0.275	0.393	0.452
% Total water / Total dietary exposure	83%	50%	89%	61%	84%	68%	90%	78%

The share of total uranium exposure due to exposure through water therefore varies between 50% and 90% depending on the scenario and assumptions about the processing of censored contamination data. Given the lack of national data on food contamination, the working group chose a proportion of 80% of total uranium exposure as being due to exposure through water, an approach also used by the WHO in 2004 which considers that this choice is supported by the low daily intakes of uranium from food (between 1 and 4 µg/d). This percentage is fairly representative of the assessment of exposure in EFSA's Opinion of 25 March 2009.

6- Effects on health

EFSA received a request from the German BfR for an Opinion relating to the maximum tolerable intake of natural uranium from foodstuffs, particularly natural mineral waters, that would not pose a health risk to consumers in Europe. This Opinion of 25 March 2009 relates to the chemical toxicity of natural uranium. The assessment of the radiological risks of natural uranium has been entrusted to the 'Article 31 group of experts' from the European Atomic Energy Community (EURATOM).

6.1- Metabolism of uranium

Gastrointestinal absorption of uranium by ingestion is relatively low (< 5% of the ingested dose) in both adult animals and adult humans.
The International Commission on Radiological Protection (ICRP 100, 2006) indicates that the value of 2% is used for the fractional gastrointestinal absorption of soluble forms of uranium, and 0.2% for insoluble forms. According to animal studies, ingested uranium is absorbed more efficiently in newborns than in adults. No data are available for humans, however, this specificity was taken into account by the International Commission on Radiological Protection (ICRP 69, 1995) in its risk assessment. The fractional gastrointestinal absorption may be increased depending on dietary conditions (Sullivan *et al.*, 1986).
Regardless of the route of exposure, uranium is distributed through the body in the bloodstream and is rapidly absorbed by certain tissues or excreted in urine.
Approximately one third of the absorbed uranium is retained by the body 10 days after administration, initially in the kidney and liver, before being redistributed in the skeleton. Uranium is thus likely to accumulate in the body.
The ICRP considers that a typical distribution after exposure to environmental uranium is 90 µg, with 66% contained in the skeleton, 16% in the liver, 8% in the kidneys and 10% in other tissue.
After ingestion, the non-absorbed uranium is excreted in faeces and the absorbed part is excreted in urine.

[5] Results of contamination lower than the limit of detection (LoD) were counted as being equal to 0 and results between the LoD and the limit of quantitation (LoQ) were counted as being equal to the LoD.
[6] Results of contamination lower than the LoD were counted as being equal to the LoD and results between the LoD and the LoQ were counted as being equal to the LoQ.

6.2- Effects on health of depleted and natural uranium

In this section, only data on sub-chronic and chronic toxicity have been examined with administration in drinking water. There is no difference between the chemical toxicity of natural uranium and that of depleted uranium. Therefore, the toxicological and epidemiological data for both natural and depleted uranium have been taken into account for characterising the chemical toxicity of uranium.

6.2.1- Renal toxicity

Due to the tropism of uranium, the kidneys, and more specifically the proximal convoluted tubules, are recognised as being the major target organs.
Exposure to high doses of uranium (greater than 100 mg/kg b.w.) causes severe kidney disease affecting the proximal tubules and glomerular structures in animals (Domingo *et al.*, 1987).
Table 4 gives the results of animal studies on sub-chronic and chronic renal toxicity from administration via drinking water. In particular, the study by Gilman *et al.* (1998a) is reported as it is most frequently used as a pivotal study in the establishment of toxicological reference values for natural uranium on an international level. A review of the literature enables the data cited in the EFSA Opinion to be consolidated with those of Donnadieu-Claraz *et al.* (2007), Tissandié *et al.* (2007), Souidi *et al.* (2005), Taulan *et al.* (2004) and Ortega *et al.* (1989).

Epidemiological data from adult individuals exposed to natural uranium through drinking water have shown associations between exposure and various biomarkers of renal function (Mao *et al.*, 1995; Limson-Zamora, 1998; Kurttio *et al.*, 2002; Magdo *et al.*, 2007).
However, because of the methodological shortcomings of these studies, the epidemiological data on the renal toxicity of natural uranium do not enable a chronic toxicological reference value to be established.

6.2.2- Toxicity for reproduction and development

In its Opinion of 25 March 2009, EFSA summarises the main oral studies in rodents relating to the effects of uranium on reproduction and development. Table 5 lists the studies among these which concern the administration of natural or depleted uranium via drinking water. A review of the literature enables the data used by EFSA to be consolidated with those from the papers of Albina *et al.* (2007); Linares *et al.* (2007); Grignard *et al.* (2008) and Kundt *et al.* (2009).

The effects on fertility reported in animals occur at uranium doses higher than those relating to renal effects.

A single study tested concentrations of uranium below 100 µg/L in drinking water administered to animals (Raymond-Whish *et al.*, 2007). However, the methodology and results are questionable.

6.2.3- Toxicity to the central nervous system

Table 6 gives the results of sub-chronic and chronic toxicity studies on the central nervous system (CNS) following the administration of depleted or natural uranium in the drinking water of animals.

The effects on the central nervous system (mainly cognitive) reported in animals occur at uranium doses higher than those relating to renal effects.

6.2.4- Toxicity to bone

Kurttio *et al.* (2005) have shown the effects of depleted or natural uranium on bone growth. There are no studies available on toxicity to bone in animal models following oral administration (there are however data on administration via muscle implantation). The concentration tested was 40 mg/L, and is therefore higher than the threshold values in water intended for human consumption.

6.2.5- Other effects

Table 7 gives the results of animal studies of sub-chronic and chronic toxicity with administration via drinking water for other effects than on the kidneys, central nervous system, bone, reproduction and development, such as altered metabolism of vitamin D.

6.2.6- Genotoxicity and mutagenesis

In its Opinion of 25 March 2009 relating to uranium from foodstuffs, particularly natural mineral waters, EFSA reports on the results of the few *in vitro* studies that suggest the genotoxic potential of uranium. In the present state of the knowledge, there are no data on *in vivo* genotoxicity or mutagenesis.

6.2.7- Carcinogenicity

To date, no carcinogenicity studies have been conducted in rodents with ingestion of uranium in soluble or insoluble form. This report relates to the chemical toxicity of natural uranium and does not deal with its radiological toxicity.

6.3- Review

The epidemiological data cannot be used as pivotal studies for determining toxicological reference values given that no causality has yet been established.

The available animal data indicate that renal effects may be proposed as critical effects for establishing toxicological reference values. For these effects, a single study was carried out with a broad spectrum of doses which examines the deleterious effects: that of Gilman *et al.* (1998a).

Effects on other physiological systems (reproductive system, CNS, bones) have been reported but with higher uranium doses.

Finally, the study of Gilman *et al.* (1998a) was adopted by AFSSA's 'Non-compliance' working group as a pivotal study for the establishment of the chronic toxicological reference value for natural uranium.

Table 4: Sub-chronic and chronic renal toxicity studies with uranium in drinking water administered to animals

Animal model	Physico-chemical form	Concentration in water	Exposure dose	Exposure time	Threshold dose	Biological effects	References
Adult rat	Uranyl nitrate	40 mg/L	2 mg/kg b.w./d	9 months	LOAEL: 2 mg/kg b.w./d	**Histological lesions** Glomerular and tubulo-interstitial lesions and increased iron accumulation **Molecular effects** Iron metabolism	Berradi *et al.* 2008
Adult rat	Uranyl nitrate	40 mg/L	2 mg/kg b.w./d	6, 9, 12, 18 months	LOAEL: 2 mg/kg b.w./d	**Histological lesions** Increased number of vesicles with dense granular inclusions containing iron	Donnadieu-Claraz *et al.* 2007
Adult rat	Uranyl nitrate	40 mg/L	2 mg/kg b.w./d	9 months	LOAEL: 2 mg/kg b.w./d	**Molecular effects** Reduced mRNA levels of nuclear receptors and Vitamin D target genes	Tissandié *et al.* 2007
Adult rat	Uranyl acetate	200; 400; 800 mg/L	10; 20; 40 mg/kg b.w./d	3 months	LOAEL: 10 mg/kg b.w./d	**Molecular effects** Increase in pro-oxidant molecules	Linares *et al.* 2006
Adult rat	Uranyl nitrate	40 mg/L	2 mg/kg b.w./d	9 months	LOAEL: 2 mg/kg b.w./d	**Molecular effects** Increased mRNA levels of nuclear receptors and cytochrome P450	Souidi *et al.* 2005
Adult mouse	Uranyl nitrate	80; 160 mg/L	16; 32 mg/kg b.w./d	4 months	LOAEL: 16 mg/kg b.w./d	**Molecular effects** Genes involved in oxidative stress, ion transport and biosynthesis	Taulan *et al.* 2004
Adult rabbit	Uranyl nitrate	0.96; 4.8; 24; 120; 600 mg/L	0.09; 0.45; 2.25; 11; 56 mg/kg b.w./d	3 months	LOAEL: 0.09 mg/kg b.w./d	**Histological lesions** Changes to the renal tubule	Gilman *et al.* 1998b
Adult rat	Uranyl nitrate	0.96; 4.8; 24; 120; 600 mg/L	0.06; 0.3; 1.5; 7.5; 37,5 mg/kg b.w./d	4 weeks, 3 months	LOAEL: 0.06 mg/kg b.w./d	**Histological lesions** Glomerular and tubulo-interstitial lesions	Gilman *et al.* 1998a
Post-weaning rat	Uranyl acetate	6.25; 12.5; 25; 50 mg/L	2; 4; 8; 16 mg/kg b.w./d	4 weeks	NOAEL: 8 mg/kg b.w./d	**Histological lesions** Tubular lesions at 1 week and glomerular and tubulo-interstitial lesions at 52 weeks	Ortega *et al.* 1989

Table 5: Sub-chronic and chronic toxicity studies on reproduction and development with uranium in drinking water administered to animals

Animal model	Physico-chemical form	Concentration in water	Exposure dose	Exposure time	Threshold dose	Biological effects	References
Adult mouse	Uranyl nitrate	20; 40; 80 mg/L	2.5; 5; 10 mg/kg b.w./d	40 days	LOAEL: 2.5 mg/kg b.w./d	**Quality of oocytes** No change in the number of ovulated oocytes but increase in oocyte dysmorphism	Kundt *et al.* 2009
Adult mouse	Uranyl nitrate	10; 20; 40 mg/L	1.9; 3.8; 7.6 mg/kg b.w./d	49 days	NOAEL: 1.9 mg/kg b.w./d	**Quality of oocytes** No change in the number of oocytes but increase in anomalies	Feugier *et al.* 2008
Adult rat	Uranyl nitrate	40 mg/L	2 mg/kg b.w./d	9 months	NOAEL: > 2 mg/kg b.w./d	**Hormonal level** No effect on levels of testosterone or 17β-estradiol	Grignard *et al.* 2008
Adult mouse	Uranyl nitrate	5; 50; 400 mg/L	1.25; 12.5; 100 mg/kg b.w./d	3 months	LOAEL: 1.25 mg/kg b.w./d	**Female fertility** Change in size of ovarian follicles	Arnault *et al.* 2008
In utero mouse	Uranyl nitrate	5; 50; 400 mg/L	1.25; 12.5; 100 mg/kg b.w./d	+ 3 months after intoxication	LOAEL: 1.25 mg/kg b.w./d	**Female fertility** Change in size of ovarian follicles	Arnault *et al.* 2008
Immature mouse	Uranyl nitrate	0.5; 2.5; 12.5; 60 mg/L	0.06; 0.31; 1.56; 7.5 mg/kg b.w./d	30 days	LOAEL: 0.06 mg/kg b.w./d	**Female fertility** Change in size of ovarian follicles	Raymond-Whish *et al.* 2007
In utero mouse	Uranyl nitrate	0.5; 2.5; 12.5; 60 mg/L	0.06; 0.31; 1.56; 7.5 mg/kg b.w./d	30 days before mating and through gestation	NOAEL: 0.31 mg/kg b.w./d	**Female fertility** Change in size of ovarian follicles	Raymond-Whish *et al.* 2007
Adult rat	Uranyl acetate	200; 400; 800 mg/L	10; 20; 40 mg/kg b.w./d	3 months	LOAEL: 10 mg/kg b.w./d	**Molecular effects** Increase in pro-oxidant molecules	Linares *et al.* 2007
In utero rat	Uranyl acetate	200; 400; 800 mg/L	10; 20; 40 mg/kg b.w./d	14th day of gestation	NOAEL: 20 mg/kg b.w./d	**Gestation parameters** Increase in the mass of the gravid uterus	Albina *et al.* 2005
Adult rat	Uranyl acetate	200; 400; 800 mg/L	10; 20; 40 mg/kg b.w./d	3 months	LOAEL: 10 mg/kg b.w./d	**Fertility** Reduction in the rate of pregnancy and reduction in the number of spermatids **Histological lesions** Some interstitial and tubular changes	Linares *et al.* 2005
Adult mouse	Uranyl acetate	80; 160; 320; 640 mg/L	10; 20; 40; 80 mg/kg b.w./d	2 months	**Fertility** LOAEL: 10 mg/kg b.w./d **Histology** NOAEL: 40 mg/kg b.w./d	**Fertility** Reduction in the rate of pregnancy **Histological lesions** Interstitial and tubular changes at the highest dose	Llobet *et al.* 1991

Table 6: Sub-chronic and chronic toxicity studies on the effects on the central nervous system with uranium in drinking water administered to animals

Animal model	Physico-chemical form	Concentration in water	Exposure dose	Exposure time	Threshold dose	Biological effects	References
Adult rat	Uranyl nitrate	40 mg/L	2 mg/kg b.w./d	9 months	LOAEL: 2 mg/kg b.w./d	**Molecular effects** Increase in anti-oxidant molecules	Lestaevel *et al.* 2009
Adult rat	Uranyl nitrate	40 mg/L	2 mg/kg b.w./d	9 months	LOAEL: 2 mg/kg b.w./d	**Molecular effects** Genes involved in the metabolism of cholesterol in the CNS	Racine *et al.* 2009
Adult rat	Uranyl acetate	200; 400; 800 mg/L	10; 20; 40 mg/kg b.w./d	3 months	LOAEL: 10 mg/kg b.w./d	**Molecular effects** Increase in pro-oxidant molecules	Linares *et al.* 2006
In utero rat	Uranyl acetate	800; 1600 mg/L	40; 80 mg/kg b.w./d	3 months	NOAEL: 40 mg/kg b.w./d	**Cognitive effects** Mild memory impairment	Sanchez *et al.* 2006
In utero rat	Uranyl acetate	200; 400; 800 mg/L	10; 20; 40 mg/kg b.w./d	3 months	NOAEL: 10 mg/kg b.w./d	**Cognitive effects** Mild memory impairment	Albina *et al.* 2005
Adult rat	Uranyl nitrate	40 mg/L	2 mg/kg b.w./d	1, 5, 6, 9 months	LOAEL: 2 mg/kg b.w./d	**Neurotransmitters** Reduction in the levels of neurotransmitters in the brain	Bussy *et al.* 2006
Adult rat	Uranyl acetate	75; 150 mg/L	25; 50 mg/kg b.w./d	2 weeks or 6 months	NOAEL: 25 mg/kg b.w./d	**Cognitive effects** Locomotion **Molecular effects** Increase in pro-oxidant molecules	Briner *et al.* 2005

Table 7: Sub-chronic and chronic toxicity studies on other effects with uranium in drinking water administered to animals

Animal model	Physico-chemical form	Concentration in water	Exposure dose	Exposure time	Threshold dose	Biological effects	References
Adult rat	Uranyl nitrate	40 mg/L	2 mg/kg b.w./d	3, 6, 9 months	LOAEL: 2 mg/kg b.w./d	**Population of immune-defence cells** Change in the number of mast cells, neutrophils and macrophages in the intestinal wall **Synthesis of nitric oxide** inhibition	Dublineau *et al.* 2007
Adult rat	Uranyl nitrate	40 mg/L	2 mg/kg b.w./d	6, 9 months	> 2 mg/kg b.w./d	**Functions of Peyer's patches** No effect	Dublineau *et al.* 2006
Adult rat	Uranyl nitrate	40 mg/L	2 mg/kg b.w./d	9 months	LOAEL: 2 mg/kg b.w./d	**Antivitamin effects** Reduction in the level of plasma vitamin D	Tissandié *et al.* 2007

7- Toxicological reference values

WHO (2004)

The pivotal study adopted by the WHO for establishing the tolerable daily intake of uranium was a three-month study in Sprague Dawley rats (Gilman *et al.*, 1998a). Groups of 15 male rats and 15 female rats were exposed via drinking water to uranyl nitrate at concentrations of 0; 0.96; 4.8; 24; 120; 600 mg UN/L (equivalent to uranium doses of < 0.0001; 0.06; 0.31; 1.52; 7.54; 36.73 mg/kg b.w./d for males and doses of < 0.0001; 0.09; 0.42; 2.01; 9.98 and 53.56 mg/kg b.w./d for females). Histopathological changes were observed mainly in the liver and kidneys, with kidneys being the most affected. In males the renal effects observed were nuclear vesiculation and cytoplasmic vacuolation of tubular cells, as well as renal tubular dilation. Other significant effects were reported above a dose of 0.31 mg/kg b.w./d in males: glomerular sclerosis, apical displacement of the proximal tubular epithelial nuclei and cytoplasmic degranulation. In females, the renal changes observed were nuclear vesiculation of the tubular epithelial nuclei (at all doses) and anisokaryosis (at all doses from 0.42 mg/kg b.w./d). The most significant changes in females were however capsular sclerosis of glomeruli and reticulin sclerosis of the interstitial membranes. These changes occurred at all doses and are considered to be 'irreparable lesions'. Taking the renal lesions of the proximal convoluted tubule as a critical effect, an LOAEL of 0.06 mg/kg b.w./d was defined for males (equivalent to 0.09 mg/kg b.w./d for females). The reason for this difference in sensitivity between males and females is not clear, but it does not seem to be due to pharmaco-kinetic differences, as the accumulation of uranium in kidney tissue did not differ significantly between the two sexes at all doses and the females received a larger time-weighted average dose than the males. By applying a safety factor of 100 (10 for inter-species uncertainty and 10 for intra-species variability), the WHO established a TDI of **0.6 µg/kg b.w./d**. Because of uranium's short half-life in the kidney (approximately 15 days) and the minimal renal effects reported, the WHO did not consider it necessary to apply an additional safety factor, which might have been expected due to the use of an LOAEL rather than an NOAEL. Indeed, epidemiological studies do not show any exacerbation of nephrotoxic effects following continuous exposure.

Health Canada (2001)

The toxicological reference value for uranium established by Health Canada was the same as that of the WHO in 2004, i.e. **0.6 µg/kg b.w./d**.

ATSDR (1999)

The pivotal study used by the ATSDR to establish a toxicological reference value for the oral route was that of Gilman *et al.* (1998b). This "intermediate MRL" covers the risk of chronic exposure.

Groups of New Zealand rabbits (10 per sex per dose) were exposed to uranyl nitrate in drinking water for three months at concentrations of 0; 0.96; 4.8; 24; 120; 600 mg UN/L (equivalent to uranium doses of < 0.001; 0.05; 0.20; 0.88; 4.82 and 28.70 mg/kg b.w./d) for males and 0; 4.8; 24 and 600 mg UN/L (equivalent to uranium doses of < 0.001; 0.49; 1.32 and 43.02 mg/kg b.w./d) for females. During the study, four males contracted a *Pasteurella multocida* infection and were excluded from the study. Two other males in the most highly exposed group died prematurely (mucoid enteritis and acute renal disease). Two others were removed from the study due to obstruction of the gastrointestinal tract by a hairball. An LOAEL of 0.05 mg/kg b.w./d was adopted on the basis of renal effects. The following effects were reported in males at this dose: cytoplasmic vacuolation, anisokaryosis, nuclear vesiculation, pycnosis, dilation, tubular atrophy and reticulin sclerosis. An uncertainty factor of 30 was applied (3 because an LOAEL was used and 10 for intra-species variability). The TRV ultimately adopted by the ATSDR was **2 µg/kg b.w./d** ("intermediate MRL").

US EPA (1998)

The pivotal study used by the US EPA to establish a chronic toxicological reference value for the non-carcinogenic effects was that of Gilman *et al.* (1998a). Like the WHO, the US EPA identified an LOAEL of 0.06 mg U/kg/d for renal effects in male rats. After applying an uncertainty factor of 3 for inter-species extrapolation, 10 for intra-species variability, 1 for the use of a sub-chronic study and 3 for the use of an LOAEL, the EPA ultimately adopted a TRV (RfD) of **0.6 µg/kg/d**.

OEHHA (2001)
The OEHHA used the study by Gilman *et al.* (1998a) to establish a chronic toxicological reference value for the non-carcinogenic effects based on the LOAEL of 0.06 mg/kg/d. By applying an uncertainty factor of 3000 (3 for using an LOAEL, 100 for the inter- and intra-species uncertainty and 10 for the use of a sub-chronic study), the TRV thus calculated was **0.02 µg/kg/d**.

The OEHHA equated these results with a study conducted by Health Canada in 1998 in which the renal effects associated with exposure to uranium were studied in individuals living in Kitigan Zibi (a village in Quebec). The village is supplied by water from wells contaminated with uranium at levels of 10 to 1418 µg/L. Exposure to uranium was measured by assaying uranium excreted in urine. The effects on renal function were determined by analysing the urine samples for a great variety of parameters and enzymes, including volume, specific gravity, γGT (gamma-glutamyltransferase) and β2M (beta-2-microglobulin). The data show that exposure relating to urinary excretion of uranium below 12 µg/d has no effect on levels of urinary β2M.
This dose of 12 µg/d was therefore adopted as an exposure level that corresponds to a no observed effect level (NOEL). Applying an uncertainty factor of 10 to take into account the intra-species variability led to a dose of 1.2 µg/d, which supports the experimental data.

In conclusion, the toxicological reference values proposed by various organisations are summarised in Table 8.

Table 8: Summary of toxicological reference values proposed by different organisations.

Source	TRV	LOAEL (µg/kg b.w./d)	Uncertainty factor	TRV value (µg/kg b.w./d)	Study	Population	Effect
US EPA (1998)	RfD	60	3 inter-species 10 intra-species 3 LOAEL	0.6	Gilman *et al.* (1998a)	Rats	Renal effects
ATSDR (1999)	Intermediate MRL	50	3 LOAEL 10 intra-species	2	Gilman *et al.* (1998b)	Rabbits	Renal effects
Health Canada (2003)	TDI	60	10 inter-species 10 intra-species	0.6	Gilman *et al.* (1998a)	Rats	Renal effects
OEHHA (2001)	-	60	10 inter-species 10 intra-species 10 sub-chronic studies 3 LOAEL	0.02	Gilman *et al.* (1998a)	Rats	Renal effects
WHO (2005)	TDI	60	10 inter-species 10 intra-species	0.6	Gilman *et al.* (1998a)	Rats	Renal effects

Review: The ATSDR's TRV was not adopted by AFSSA's 'Non-compliance' working group due to the abnormally high morbidity and mortality reported in the control group of male animals. The TRV of the OEHHA was not selected because of its high safety factor of 3000, which seems to overstate the uncertainty. Finally, AFSSA adopted the WHO's TDI of **0.6 µg/kg b.w./d**. This TRV was also adopted by EFSA in its Opinion of 25 March 2009.

8- Reference values in water

With regard to water from the public distribution system, uranium mass concentration does not feature in the Ministerial Order of 11 January 2007 on thresholds and quality references for raw water and water intended for human consumption.
Several recommendations and parameter values can be found in the literature. These values are summarised in Table 9.

Table 9: Reference values for uranium mass concentration in drinking water proposed by different organisations

Source	Toxicological reference value	% of the TRV attributed to drinking water	Individual body weight (kg)	Daily water consumption	Threshold value in water
US EPA (2000)	0.6 µg/kg b.w./d	80%	70	2 L/d	20 µg/L but value at **30 µg/L** after 'cost/benefit' consideration
OEHHA (2001)	0.02 µg/kg b.w./d	40%	70	2 L/d	0.3 µg/L but value at **0.5 µg/L** based on radiological effects
Health Canada (2003)	0.6 µg/kg b.w./d	35%	70	1.5 L/d	10 µg/L but value at **20 µg/L** after 'cost/benefit' consideration
WHO (2004)	0.6 µg/kg b.w./d	80%	60	2 L/d	**15 µg/L**

AFSSA suggests adopting the WHO's provisional threshold value of 15 µg/L in water, established in 2004. This proposal should be reconsidered if new toxicological or exposure data (particularly concerning food) should emerge that changes the evidence currently available.

9- Comparison of daily intake with the share of the tolerable daily intake from water

In the absence of estimates of daily uranium intake from foodstuffs (excluding water), the estimated intake for different concentrations of uranium, in water intended for human consumption, is compared with the share of the tolerable daily intake from water.

The following assumptions have been made:

- the approach taken in 2004 by the WHO led to the share of the tolerable daily intake from water being defined and rounded to 30 µg/d (for a 60 kg individual and allocating 80% of the TRV of 0.6 µg/kg b.w./d to exposure to water);
- drinking water intakes are calculated for adults on the basis of hypothesised water consumption of 2 L/d per individual, which is representative of water consumption of the highest consumers.

Figure 5 gives the intake of natural uranium from water for an increasing concentration in water intended for human consumption, considering an adult individual consuming 2 L/d of water.

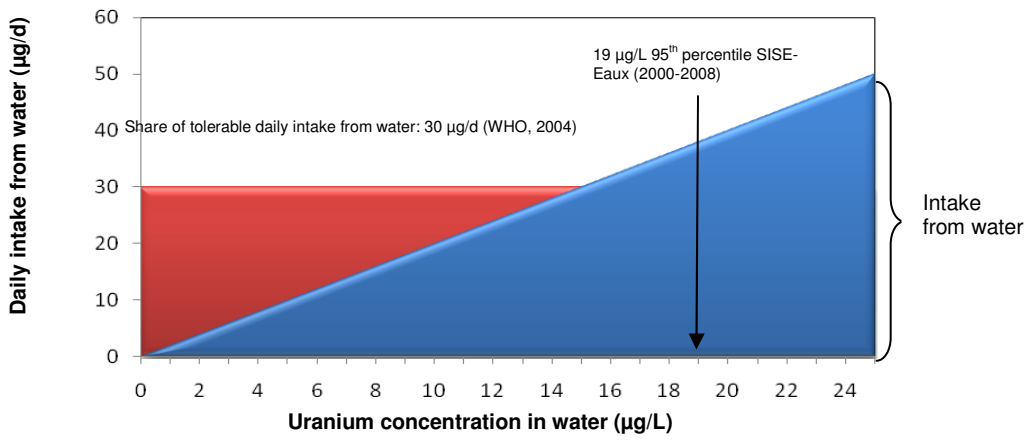


Figure 5: Uranium intake from water for an increasing concentration – adult individual consuming 2 L/d of water.

It thus appears that at the concentration of 19 µg/L of natural uranium in drinking water (95th percentile of the estimated uranium mass concentrations based on the results of specific activity of uranium isotopes entered into the SISE-Eaux database between 2000 and 2008), the intake from water is higher than the share of the tolerable daily intake from water of 30 µg/d for an adult individual.

Nevertheless, the results for uranium above 15 µg/L, which come from processed data from the SISE-Eaux database, are isolated cases and are not representative of the quality of all the water distributed in France, since these measurements are only taken for health inspections if the guideline values are exceeded for total alpha activity and/or total residual beta activity.

Conclusions and recommendations:

The French Food Safety Agency

- considers that:
  - the toxicological data available for establishing the toxicological reference value are limited,
  - considering a toxicological reference value of 0.6 µg/kg b.w./d, exposure due to water at 80% of total exposure, and water consumption of 2 L/d for a 60 kg individual (approach adopted by the WHO in 2004), a quality requirement for uranium in water intended for human consumption could be set at 15 µg/L,
  - consequently long-term consumption of water with a concentration exceeding 15 µg/L does not seem, in the current state of knowledge, to be acceptable for consumer health;
- notes that the 95th percentile of available values, based on data from the SISE-Eaux base, is close to 19 µg/L;
- recommends:
  - conducting analysis campaigns to obtain data on uranium contamination in foodstuffs, in order to estimate the exposure of the French population from total diet,
  - consolidating data on the chemical toxicity of uranium, particularly by commissioning chronic toxicity studies in animals;
- reiterates that there are treatment methods available to reduce the concentration of uranium in water intended for human consumption that could be implemented in the event of contamination of the resource.

The Director General

Marc MORTUREUX

Keywords: natural uranium, water intended for human consumption

List of abbreviations

AFSSA	*Agence française de la sécurité sanitaire des aliments* (French Food Safety Agency)
ATSDR	United States Agency for Toxic Substances and Disease Registry
BfR	*Bundesinstitut für Risikobewertung* (German Federal Institute for Risk Assessment)
CNS	Central Nervous System
DGS	*Direction Générale de la Santé* (French Directorate General for Health)
DM	Dry Matter
EFSA	European Food Safety Authority
ICP-AES	Inductively Coupled Plasma-Absorption Emission Spectroscopy
ICP-MS	Inductively Coupled Plasma Mass Spectrometry Tolerable Daily Intake
ICRP	International Commission on Radiological Protection
IRSN	*Institut de Radioprotection et de Sureté Nucléaire* (French Institute for Radiological Protection and Nuclear Safety)
LERH	AFSSA's Laboratory for study and research on hydrology
LO(A)EL	Lowest Observed (Adverse) Effect Level
LoD	Limit of Detection
LoQ	Limit of Quantitation
MRL	Minimum Risk Level
NO(A)EL	No Observed (Adverse) Effect Level
OEHHA	Office of Environmental Health Hazard Assessment (California, USA)
RfD	Reference Dose
SISE-Eaux	*Système d'Information Santé Environnement – Eaux* (Health & Environment Information System – Water)
STEME	Service de Traitement des Echantillons et de Métrologie pour l'Environnement (IRSN's Department for sample processing and metrology for the environment)
TDI	Tolerable Daily Intake
TID	Total Indicative Dose
TRV	Toxicological Reference Value
TTP	Treatment and Production Plant
UDI	Distribution Unit
WHO	World Health Organization

Bibliography

Albina ML, Bellés M, Linares V, Sánchez DJ, Domingo JL. Restraint stress does not enhance the uranium-induced developmental and behavioral effects in the offspring of uranium-exposed male rats. *Toxicology.* 215: 69-79 (2005).

Anke, M., Seeber, O., Müller, R., Schäfer, U., Zerull, J. Uranium transfer in the food chain from soil to plants, animals and man Chemie der Erde - *Geochemistry*, 69 (SUPPL.), pp. 75-90. (2009)

Arnault E, Doussau M, Pesty A, Gouget B, Van der Meeren A, Fouchet P, Lefèvre B. Natural uranium disturbs mouse folliculogenesis in vivo and oocyte meiosis in vitro. *Toxicology.* 247: 80-87 (2008).

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

Berradi H, Bertho JM, Dudoignon N, Mazur A, Grandcolas L, Baudelin C, Grison S, Voisin P, Gourmelon P, Dublineau I. Renal anemia induced by chronic ingestion of depleted uranium in rats. *Toxicol Sci.* 103: 397-408 (2008).

Briner W, Murray J Effects of short-term and long-term depleted uranium exposure on open-field behavior and brain lipid oxidation in rats. *Neurotoxicol Teratol.* 27: 135-144 (2005).

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

Domingo, J.L., Llobet, J.M., Tomas, J.M., Corbella, J. Acute toxicity of uranium in rats and mice. *Bulletin of Environmental Contamination and Toxicology*, 39 (1), pp. 168-174(1987).

Donnadieu-Claraz M, Bonnehorgne M, Dhieux B, Maubert C, Cheynet M, Paquet F, Gourmelon P. Chronic exposure to uranium leads to iron accumulation in rat kidney cells. *Radiat Res.* 167: 454-464 (2007).

Dublineau I, Grandcolas L, Grison S, Baudelin C, Paquet F, Voisin P, Aigueperse J, Gourmelon P. Modifications of inflammatory pathways in rat intestine following chronic ingestion of depleted uranium. *Toxicol Sci.* 98: 458-468 (2007).

Dublineau I, Grison S, Grandcolas L, Baudelin C, Tessier C, Suhard D, Frelon S, Cossonnet C, Claraz M, Ritt J, Paquet P, Voisin P, Gourmelon P. Absorption, accumulation and biological effects of depleted uranium in Peyer's patches of rats. *Toxicology.* 227: 227-239 (2006).

EFSA – European Food Safety Authority (2009). 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* 1018, 1-59 (2009).

Favre-Réguillon, A., Lebuzit, G., Murat, D., Foos, J., Mansour, C., Draye, M. Selective removal of dissolved uranium in drinking water by nanofiltration. *Water Research*, 42 (4-5), pp. 1160-1166 (2008).

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

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

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

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

Grignard E, Gueguen Y, Grison S, Lobaccaro JM, Gourmelon P, Souidi M. Contamination with depleted or enriched uranium differently affects steroidogenesis metabolism in rat. *Int J Toxicol.* 27: 323-328 (2008).

International Commission on Radiological Protection. Human alimentary tract model for radiological protection. ICRP Publication 100, Elsevier, Oxford (2006).

International Commission on Radiological Protection. Age-dependent doses to members of the public from intake of radionuclides: Part 3 Ingestion dose coefficients, Ann. ICRP 25, 1. ICRP publication 69 (1995).

Institut National de santé Publique du Québec. Fiche “uranium” du groupe scientifique sur l’eau. Juillet 2003.

Kundt MS, Martinez-Taibo C, Muhlmann MC, Furnari JC. Uranium in drinking water: effects on mouse oocyte quality. *Health Phys.* 96: 568-574 (2009).

Kurttio, P., Auvinen, A., Salonen, L., Saha, H., Pekkanen, J., Mäkeläinen, I., Väisänen, S.B., Penttilä, I.M., Komulainen, H. Renal effects of uranium in drinking water. *Environmental Health Perspectives*, 110 (4), pp. 337-342 (2002).

Kurttio, P., Komulainen, H., Leino, A., Salonen, L., Auvinen, A., Saha, H. Bone as a possible target of chemical toxicity of natural uranium in drinking water. *Environmental Health Perspectives*, 113 (1), pp. 68-72 (2005).

Lestaevel P, Romero E, Dhieux B, Ben Soussan H, Berradi H, Dublineau I, Voisin P, Gourmelon P. Different pattern of brain pro-/anti-oxidant activity between depleted and enriched uranium in chronically exposed rats. *Toxicology.* 258: 1-9 (2009).

Limson Zamora, M., Tracy, B.L., Zielinski, J.M., Meyerhof, D.P., Moss, M.A. Chronic ingestion of uranium in drinking water: A study of kidney bioeffects in humans. *Toxicological Sciences*, 43 (1), pp. 68-77 (1998).

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

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

Linares V, Sánchez DJ, Bellés M, Albina L, Gómez M, Domingo JL. Pro-oxidant effects in the brain of rats concurrently exposed to uranium and stress. *Toxicology*. 236: 82-91 (2007).

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

Magdo, H.S., Forman, J., Graber, N., Newman, B., Klein, K., Satlin, L., Amler, R.W., Winston, J.A., Landrigan, P.J. Grand rounds: Nephrotoxicity in a young child exposed to uranium from contaminated well water. *Environmental Health Perspectives*, 115 (8), pp. 1237-1241 (2007).

Mao, Y., Desmeules, M., Schaubel, D., Bérubé, D., Dyck, R., Brulé, D., Thomas, B. Inorganic components of drinking water and microalbuminuria. *Environmental Research*, 71 (2), pp. 135-140 (1995).

OEHHA – Office of Environmental Health Hazard Assessment. Public Health Goals for chemicals in drinking water – Uranium. 37 pp (2001).

Ortega A, Domingo JL, Llobet JM, Tomás JM, Paternain JL. Evaluation of the oral toxicity of uranium in a 4-week drinking-water study in rats. *Bull Environ Contam Toxicol.* 42: 935-941 (1989).

Racine R, Gueguen Y, Gourmelon P, Veyssiere G, Souidi M. Modifications of the expression of genes involved in cerebral cholesterol metabolism in the rat following chronic ingestion of depleted uranium. *J Mol Neurosci.* 38: 159-165 (2009).

Raff, O., Wilken, R.-D. Removal of dissolved uranium by nanofiltration. *Desalination*, 122 (2-3), pp. 147-150 (1999).

Raymond-Whish S, Mayer LP, O'Neal T, Martinez A, Sellers MA, Christian PJ, Marion SL, Begay C, Propper CR, Hoyer PB, Dyer CA. Drinking water with uranium below the U.S. EPA water standard causes estrogen receptor-dependent responses in female mice. *Environ Health Perspect.* 115: 1711-1716 (2007).

Ribera, D., Labrot, F., Tisnerat, G., Narbonne, J.F. Uranium in the environment: occurrence, transfer, and biological effects. Reviews *of environmental contamination and toxicology*, 146, pp. 53-89 (1996).

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

Souidi M, Gueguen Y, Linard C, Dudoignon N, Grison S, Baudelin C, Marquette C, Gourmelon P, Aigueperse J, Dublineau I. In vivo effects of chronic contamination with depleted uranium on CYP3A and associated nuclear receptors PXR and CAR in the rat. *Toxicology*. 214: 113-122 (2005).

Sullivan, M.F., Ruemmler, P.S., Ryan, J.L., Buschbom, R.L. Influence of oxidizing or reducing agents on gastrointestinal absorption of U, Pu, Am, Cm and Pm by rats. *Health Physics*, 50 (2), pp. 223-232 (1986).

Taulan M, Paquet F, Maubert C, Delissen O, Demaille J, Romey MC. Renal toxicogenomic response to chronic uranyl nitrate insult in mice. *Environ Health Perspect.* 112: 1628-1635 (2004).

Tissandié E, Guéguen Y, Lobaccaro JM, Grandcolas L, Voisin P, Aigueperse J, Gourmelon P, Souidi M. In vivo effects of chronic contamination with depleted uranium on vitamin D3 metabolism in rat. *Biochim Biophys Acta.* 1770: 266-272 (2007).

US EPA. Radionuclides notice of data availability technical support document. US EPA Office of Groundwater and Drinking Water in collaboration with US EPA Office of Indoor Air and Radiation and United States Geological Survey (2000).

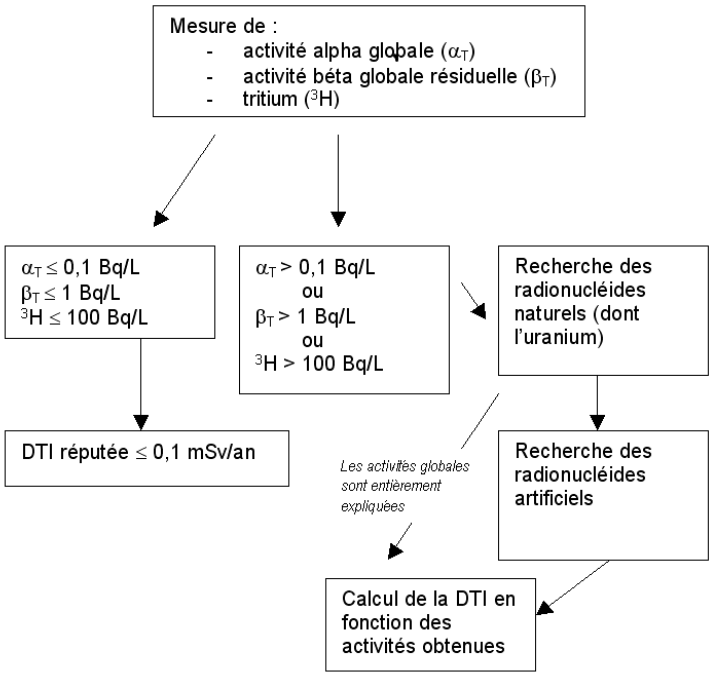
WHO. Depleted uranium: sources, exposure and health effects. Department of Protection of the Human Environment. World Health Organization. Geneva (2001). WHO/SDE/PHE/01.1. http://www.who.int/ionizing_radiation/pub_meet/ir_pub/en/

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

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

Annex

Methodology for analysing radioactivity in water intended for human consumption



FRANCAIS	ANGLAIS
Mesure de : - activité alpha globale (α_T) - activité beta globale résiduelle (β_T) - tritium (^3H)	Mesurement of: - total alpha activity (α_T) - total residual beta activity (β_T) - tritium (^3H)
$\alpha_T \leq 0,1$ Bq/L $\beta_T \leq 1$ Bq/L $^3H \leq 100$ Bq/L	$\alpha_T \leq 0.1$ Bq/L $\beta_T \leq 1$ Bq/L $^3H \leq 100$ Bq/L
$\alpha_T > 0,1$ Bq/L ou $\beta_T > 1$ Bq/L ou $^3H > 100$ Bq/L	$\alpha_T > 0.1$ Bq/L or $\beta_T > 1$ Bq/L or $^3H > 100$ Bq/L
Recherche des radionucléides naturels (dont l'uranium)	Screening for natural radionuclides (including uranium)
DTI réputée ≤ 0,1 mSv/an	TID considered to be ≤ 0.1 mSv/year
Les activités globales sont entièrement expliquées	Total activity fully explained
Recherche des radionucléides artificiels	Screening for artificial radionuclides
Calcul de la DTI en fonction des activités obtenues	Calculation of TID depending on activities obtained