

**COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT**

**URANIUM LEVELS IN NATURAL MINERAL WATER AND USE TO RECONSTITUTE INFANT FORMULA**

**Introduction**

1. Uranium is a metallic element which is ubiquitous in the environment. It occurs in rocks, soil, air, food and water. Where present in water, this tends to be the major source of intake. Due to dissolution from mineral deposits, in particular granite, ground waters contain higher levels of uranium than surface waters, although the level will vary considerably depending on the local geology.
2. The critical toxic effect of uranium is nephrotoxicity. The WHO has derived a Tolerable Daily Intake (TDI) for soluble uranium based on protecting against this endpoint, as a basis to setting a "guideline value" for acceptable levels of uranium in drinking water.
3. The Food Standards Agency currently advises that natural mineral waters may not be suitable for use in reconstituting infant formula because of higher levels of dissolved minerals than other forms of drinking water. Agency advice is to use drinking (tap) water for this purpose, or bottled water that meets the criteria for drinking water. However, Council Directive 80/777/EEC permits Member States to adopt special provisions to enable manufacturers to indicate on labels the suitability of a natural mineral water for the feeding of infants.
4. Although the UK is yet to allow such claims, natural mineral waters produced in some other Member States already carry the statement "suitable for infant feeding" on their labels. A natural mineral water officially recognised by a Member State can be freely marketed across the EU and so be legally sold in the UK.
5. New legislation is in preparation that will amend the Natural Mineral Water, Spring Water and Bottled Drinking Water Regulations 1999 to allow natural mineral waters recognised in the UK to make claims for their suitability for infant feeding. On the advice of the COMA Panel on Maternal and Infant Nutrition, it is intended that natural mineral waters that meet essentially the limits required for tap water will be allowed to use the prescribed wording indicating their suitability for infant feeding. The legislation will protect consumers by indicating which natural mineral water is suitable for the preparation of infant feed.

6. There are currently no regulatory limits for uranium in mineral water, spring water or bottled drinking water, or in tap water. The FSA published a survey of levels of uranium in bottled waters in 2004. FSA intake estimates by formula fed infants indicate that the use of some natural mineral waters to reconstitute infant formula would lead to an exceedance of the WHO TDI for uranium by the infant. The purpose of this paper is to seek the COT's opinion on the public health implications from uranium of using natural mineral waters to reconstitute infant formula.

## **Background**

7. Uranium is a 'heavy' metal which occurs naturally in the environment in a number of valence states (+2, +3, +4, +5 and +6), but most commonly in the hexavalent form in association with oxygen as the uranyl ion ( $\text{UO}_2^+$ ). Uranium occurs at low levels in foods and occurs at variable levels in drinking water depending on the nature of the water (e.g. surface or ground water) and the local geology, i.e. the presence of granite and other mineral deposits which contain uranium. Where it is present in drinking water this tends to be the major source of intake. Intake of uranium from the air would normally be extremely low. Uranium has no known nutritional function.

8. Naturally occurring uranium consists of 3 different radionuclides,  $^{234}\text{U}$ ,  $^{235}\text{U}$  and  $^{238}\text{U}$ , with more than 99% being  $^{238}\text{U}$ . It is weakly radioactive, and therefore contributes to the radioactivity of natural mineral waters and other waters and foods. The radiological safety of bottled waters has been considered elsewhere, with the conclusion that the consumption of bottled water is unlikely to add significantly to the average annual background radiation dose received by the UK population. The radiological aspects of uranium will not be considered further in this paper.

9. EC legislation on natural mineral water, spring water and bottled drinking water is currently implemented in the UK by the Natural Mineral Water, Spring Water and Bottled Drinking Water Regulations 1999 (S.I. 1999/1540) (as amended). Natural mineral water is water originating in an underground water table or deposit, which emerges from a spring tapped at one or more natural or bore exits. It is characterised by its consistent chemical and microbiological composition, which distinguishes it from other drinking water, and may not be treated in any way that alters these properties.

10. Spring water also originates in an underground water source and must meet with most of the requirements that apply to natural mineral water, but it must also comply with the physical, chemical and microbiological parameters laid down for drinking water. Bottled drinking water is simply drinking water from a variety of sources which is bottled, and is neither spring water nor natural mineral water. There are currently no limits on uranium for any type of bottled water, or for tap water.

## **Toxicity of uranium**

11. The toxicity of uranium has been considered by the WHO in the setting of a TDI and a guideline value for levels in drinking water. Members are referred to the WHO background document attached at Annex A. The following paragraphs provide a summary only of the key toxicological issues.

### ***Absorption, distribution, metabolism and excretion***

12. Gastrointestinal absorption of soluble uranium is 1-2% in humans. Absorbed uranium tends to accumulate in the kidneys and the skeleton, particularly the skeleton, where the uranyl ion replaces calcium in hydroxyapatite. Uranium is excreted in the urine and faeces, with approximately 1% excreted via the urine. The overall elimination half-life of uranium in humans has been estimated to be 180-360 days.

### ***Sub-acute, sub-chronic and chronic toxicity***

13. The critical toxicological effect of uranium is nephrotoxicity, with damage occurring principally to the proximal convoluted tubules. There is some evidence that uranium inhibits both sodium transport-dependent and sodium transport-independent ATP utilisation and inhibition of mitochondrial oxidative phosphorylation in the renal proximal tubules.

14. Nephrotoxicity has been observed in acute, sub-acute, subchronic and chronic oral studies in rats, mice, rabbits and dogs. Nephritis has been reported to occur in humans following high level exposure to uranium.

15. Early studies, with some limited histopathology, in which rats, dogs and rabbits were fed high doses of uranium compounds for periods ranging from 30 days to 2 years, showed renal toxicity in each species. The lowest dose tested was equivalent to 2.8 mg/kg bw/day uranium in a 30-day study in rabbits, at which “modest” renal damage was described. It was observed that in longer term studies in rats and dogs, the renal effects tended to be identifiable within 30 days of the start of treatment (cited also by EPA, 1989).

16. More recent studies, conducted to modern standards, have been conducted in New Zealand white rabbits and Sprague-Dawley rats for a maximum of 91 days. The lowest dose tested was 0.96 mg/L uranyl nitrate hexahydrate in the drinking water, equivalent to 0.06 mg/kg bw.day uranium in male rats, 0.09 mg/kg bw/day uranium in female rats and 0.05 mg/kg bw/day uranium in rabbits. Adverse effects were observed at all doses in the rabbits but the interpretation of the findings in this study was complicated by the occurrence of *Pasteurella* infection. However, in the rats, treatment related lesions were observed in the kidney and liver in all treated dose groups of both sexes. Effects in the kidney were, in males, nuclear vesiculation, cytoplasmic vacuolation and tubular dilation at all treated dose levels and at doses of 0.31 mg/kg bw/day uranium and above glomerular adhesions, apical

displacement of the proximal tubular epithelial nuclei and cytoplasmic degranulation. In females the kidney effects were nuclear vesiculation of the tubular epithelial nuclei, capsular sclerosis of glomeruli and reticulin sclerosis of the interstitial membranes at all treatment doses, and anisokaryosis in all but one mid-dose group. The WHO report states that the authors of the study considered the capsular sclerosis of the glomeruli and the reticulin sclerosis of the interstitial membranes in the kidneys of females to be particularly important as these were considered to be non-reversible effects. The liver effects included non-specific nuclear and cytoplasmic changes.

17. Additional studies are available which have tested higher doses. For example, in a study to investigate the reversibility of the renal effects of uranium, groups of male New Zealand white rabbits were given doses of uranyl nitrate hexahydrate equivalent to 0, 1.36 or 40.98 mg/kg bw/day uranium in the drinking water for 91 days followed by a recovery period of 91 days. Renal tubular injury, with degenerative nuclear changes, cytoplasmic vacuolation and tubular dilation, was observed in the high dose group. These effects had not completely or consistently recovered after the 91-day recovery period. 'Minor' histopathological changes were also observed in the liver and aorta.

18. A number of studies of human populations have been conducted in areas of Canada in which the drinking water naturally contains high levels of uranium. Although uranium levels in these populations have not been linked to overt kidney disease, correlations have been shown between uranium exposure and various biomarkers of renal toxicity. Clinical studies in 324 persons exposed to levels of uranium in drinking water up to 700 µg/L showed a trend of increasing β-2-microglobulin excretion. In another study in 100 people with drinking water containing mean uranium levels up to 19.6 µg/L, a statistically significant association was demonstrated between 'uranium cumulative index', calculated based on the level of uranium, the level of consumption of the water and the length of time living at the current residence, and levels of urine albumin. In a further study of two groups, one with uranium levels in drinking water of <1 µg/L and one with 2-781 µg/L, a correlation was found with levels of alkaline phosphatase and β-2-microglobulin. In addition, in a study in Finland in a population exposed to an average concentration of 28 µg/L uranium in well water, uranium level was associated with increased fractional excretion of calcium. Urinary uranium level was associated with increased fractional excretion of calcium, phosphate and glucose.

### ***Reproductive and developmental toxicity***

19. Reproductive and developmental toxicity have been observed in studies with uranium. For example, in a study in Swiss mice administered uranium as uranium acetate dihydrate by gavage on days 6-15 of gestation, fetotoxicity was observed at all doses tested, with effects including reduced fetal body weight and length, increased incidence of stunted fetuses per litter, and increased incidence of internal and external malformations. Maternal effects included a dose-dependent decrease in food consumption and

decrease in body weight. The lowest dose tested (LOAEL) was equivalent to 2.8 mg/kg bw/day uranium.

20. In a study of the effects of uranium (as uranyl acetate dihydrate) on reproduction, gestation and postnatal survival, male mice were administered uranium via the diet for 60 days prior to mating, and females for 14 days prior to pregnancy and until weaning of pups. No treatment related effects on mating or fertility were observed at any dose (up to an equivalent of 14 mg/kg bw/day uranium). Increased embryoletality was observed at the highest dose and pup growth and development were affected in the highest dose group. Increased pup mortality was increased in the mid-dose group (5.6 mg/kg bw/day uranium). No effects were observed in the low dose group (2.8 mg/kg bw/day uranium).

### ***Mutagenicity and carcinogenicity***

21. Uranyl nitrate produced a dose-related increase in micronuclei and sister chromatid exchanges in an *in vitro* study in Chinese hamster ovary cells (concentrations tested: 0.01-0.3 mmol/L uranyl nitrate). Chromosomal aberrations were induced in male mouse germ cells following injection of enriched uranyl fluoride into mouse testes, although this effect may have been produced by the radioactivity of the test compound.

22. Carcinogenicity data appear to be limited, although it is reported that no carcinogenic effects have been observed in animals exposed orally to uranium compounds.

### **Derivation of the WHO TDI**

23. The WHO considered nephrotoxicity to be the most sensitive adverse effect, and derived a TDI for soluble uranium based on the lowest available LOAEL of 0.06 mg/kg bw/day uranium from the male rats in the 91-day study described in paragraph 16. A total uncertainty factor of 100 was applied, incorporating factors of 10 for inter-species variation and 10 for inter-individual variation. The resulting TDI was 0.6 µg/kg bw/day.

24. It was considered that an additional factor for LOAEL to NOAEL extrapolation was not required as the histopathological changes observed at the LOAEL were considered to be of minor severity. It was also considered that no additional factor was required for subchronic to chronic extrapolation as the limited, older chronic studies indicated that the appearance of histopathological changes occurred within 30 days and these did not appear to further progress, and the half-life of uranium in the kidney is 15 days.

25. The WHO also established a provisional "guideline value" level for uranium in drinking water. Following consideration of uranium levels in food, 80% of the TDI was allocated to intake from drinking water. The provisional guideline value was then based on the assumption that a 60 kg adult consumes 2 L/day water. The current provisional guideline value is 15 µg/L.

## Exposure assessment

26. The results of an FSA survey of uranium contents of bottled waters published in 2004 are in Annex B. 170 samples of bottled water were analysed. Of these, 118 samples, representing 55 brands (there was multiple sampling), are identifiable as natural mineral waters. All of the waters sampled contained levels of uranium within the WHO guideline value for uranium in drinking water.

27. Several methods for estimating potential intakes of water by formula-fed infants have previously been used in COT evaluations and those of other bodies. These have typically assumed a reference bodyweight for an infant and a fluid intake for an infant of that body weight. Recent intake calculations by EFSA and SCF have used a body weight of 4.5 kg and a consumption of 700 mL formula/day, which has been considered to represent the highest ratio between intake and bodyweight in infants (SCF, 2002; EFSA, 2005). This method has been used here to estimate potential infant exposures to uranium.

28. Table 1 lists the mineral water samples for which the measured uranium levels could lead to an exceedance of either the total TDI (17 samples, representing 5 mineral water brands on sale in the UK at the time of survey) or the proportion of the TDI allocated to drinking water by the WHO (in total, 23 samples, representing 6 mineral water brands).

Table 1: Mineral waters sampled with levels of uranium which may potentially lead to the WHO TDI being exceeded by infants.

Product	Total uranium content ( $\mu\text{g/L}$ )*	Intake (based on mean level measured) ( $\mu\text{g/kg bw/day}$ )	Exceedance of total TDI	Exceedance of proportion of TDI allocated by WHO to drinking water (80%)
Caffe nero	$13 \pm 2.6$	2.02	x 3.4	x 4.2
Caffe nero	$12 \pm 2.4$	1.87	x 3.1	x 3.9
Radnor hills	$11 \pm 2.2$	1.71	x 2.9	x 3.6
Radnor hills	$7.8 \pm 1.6$	1.21	x 2.0	x 2.5
San Pellegrino	$7.8 \pm 1.56$	1.21	x 2.0	x 2.5
San Pellegrino	$8.6 \pm 1.72$	1.34	x 2.2	x 2.8
San Pellegrino	$8.1 \pm 1.62$	1.26	x 2.1	x 2.6
San Pellegrino	$7 \pm 1.4$	1.09	x 1.8	x 2.3
San Pellegrino	$7.4 \pm 1.48$	1.15	x 1.9	x 2.4

San Pellegrino	7.2 ± 1.4	1.12	x 1.9	x 2.3
St. Yorre	7 ± 1.4	1.09	x 1.8	x 2.3
St. Yorre	10 ± 1.2	1.56	x 2.6	x 3.3
St. Yorre	6.1 ± 1.22	0.95	x 1.6	x 2.0
St. Yorre	7 ± 1.4	1.09	x 1.8	x 2.3
St. Yorre	10 ± 2	1.56	x 2.6	x 3.3
St. Yorre	8 ± 21.6	1.24	x 2.1	x 2.6
Rocwell	5.5 ± 1.1	0.856	x 1.4	x 1.8
Buxton	3.5 ± 0.7	0.544	x 0.91	x 1.1
Buxton	3.8 ± 0.76	0.591	x 0.99	x 1.2
Buxton	3.9 ± 0.78	0.607	x 1.0	x 1.3
Buxton	3.4 ± 0.68	0.529	x 0.89	x 1.1
Buxton	3.4 ± 0.68	0.529	x 0.88	x 1.1
Buxton	3.2 ± 0.64	0.498	x 0.83	x 1.0

\* Uncertainties are quoted at the 95% level and based on propagated counting statistics

29. Of the remaining mineral water samples, the highest level was 2.6 µg/L, representing an intake of 0.404 µg/kg bw/day, which is 67% of the TDI or 84% of the proportion allocated to drinking water. None of the other bottled waters sampled would lead to an exceedance of the TDI.

### ***Other sources of intake***

30. The formula itself may contain trace amounts of uranium. Uranium has not been included in FSA surveys of elements in infant foods. A survey of the scientific literature (MEDLINE and TOXNET) using combinations of the terms “uranium”, “infant”, “feed” and “formula” has not identified any papers which provide information on levels of uranium levels in infant formula.

31. The 2001 Total Diet Study (TDS) included uranium. The highest concentrations of uranium were found in fish and bread. Cereals and bread contributed the greatest to dietary intake. Milk contained very low levels of uranium which were below the limit of quantification. Estimated dietary intakes at the 97.5<sup>th</sup> percentile ranged from 6% of the total TDI in adults to 16% of the total TDI in toddlers aged 1.5-2.5 years. It appears unlikely that infant formula would contribute significantly to total uranium intakes; however, in the absence of data it may be prudent to compare potential intakes from water alone to the 80% of the TDI allocated to drinking water by the WHO, as indicated in column 5 of Table 1.

32. There is currently no regulatory limit for uranium in tap water and therefore no regulatory monitoring. The Drinking Water Inspectorate is conducting research on uranium levels. No information is available at present.

### **Summary**

33. Uranium is ubiquitous in the environment and is found in food and water. Ground waters tend to contain higher levels of uranium than surface

waters, and where uranium is present in water this is usually the major source of intake.

34. A TDI for soluble uranium has been derived by the WHO based on a LOAEL for nephrotoxicity from a 91-day study in rats. The TDI incorporated a 100-fold total uncertainty factor to account for uncertainties in inter-species and inter-individual variability. No specific data have been identified regarding nephrotoxicity in infants. The Committee will wish to consider whether infants may be expected to be any more vulnerable to the effects of uranium.

35. An FSA survey of the radioactivity of bottled waters on sale in the UK was published in 2004, and this included measurements of levels of uranium. All but 6 of 170 samples contained detectable levels of uranium. Intake estimates indicate that for 17 of the bottled waters sampled, representing 5 mineral waters, the TDI would be exceeded.

36. The infant formula may also contain trace amounts of uranium, although no data are available on levels. If 80% of the TDI is allocated to the water, and 20% to other sources, the 80% allocated to drinking water would be exceeded by consuming 23 of the bottled waters sampled, representing 6 mineral waters.

### **Questions on which the views of the Committee are sought**

37. Members are invited to consider the following questions and to raise any other matters that arise.

i). Does the Committee have any comments on the TDI derived by the WHO for uranium?

ii). Is this TDI an appropriate guideline with which to compare intakes by infants, or may infants be expected to be more vulnerable to the effects of uranium? If so is the Committee able to advise on a level of uranium intake that is expected to be without adverse effects in infants?

iii). What does the Committee consider are the health implications to infants of the levels of uranium in natural mineral waters and other bottled waters?

**Secretariat**  
**October 2005**

### **References**

EFSA (2005). Opinion of the AFC Panel related to semicarbazide in food. European Food Safety Authority. Available at:  
[http://www.efsa.eu.int/science/afc/afc\\_opinions/1005\\_en.html](http://www.efsa.eu.int/science/afc/afc_opinions/1005_en.html).

EPA (1989). Integrated Risk Information System (IRIS): Uranium, soluble salts. <http://www.epa.gov/iris/subst/0421.htm>. Last revised 1989.

SCF (2002). Opinion of the Scientific Committee on Food on bisphenol A. Scientific Committee on Food. Available at: [http://europa.eu.int/comm/food/fs/sc/scf/out128\\_en.pdf](http://europa.eu.int/comm/food/fs/sc/scf/out128_en.pdf).

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**Uranium levels in natural mineral water and use to reconstitute infant formula**

Uranium in drinking water: Background document for development of WHO *Guidelines for Drinking-water quality*. WHO, 2004.

[Note: For copyright reasons the document in this Annex will not be included when the paper becomes publicly available. However, the document is available on the internet at [http://www.who.int/water\\_sanitation\\_health/dwq/chemicals/uranium/en/](http://www.who.int/water_sanitation_health/dwq/chemicals/uranium/en/)]

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FSA (2004). Analysis of the natural radioactivity content of bottled waters. Food Survey Information Sheet 67/04, September 2004.

[Note: This document is available on the internet at <http://www.food.gov.uk/multimedia/pdfs/fsis6704.pdf>.]