

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

COT STATEMENT ON URANIUM LEVELS IN WATER USED TO RECONSTITUTE INFANT FORMULA

Background

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 uranium intake. Due to dissolution from mineral deposits, notably granite, ground waters contain higher levels of uranium than surface waters, although the level will vary considerably depending on the local geology.
2. The current advice from the Food Standards Agency is, in general, to avoid using natural mineral water to prepare infant feed as some brands contain high levels of minerals, which may be unsuitable for infants. 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 sold in the UK to make claims for their suitability for infant feeding, provided that they meet specific criteria. It is intended that natural mineral waters that essentially meet the limits required for tap water would be considered acceptable. The legislation will protect consumers by indicating which natural mineral waters are suitable for the preparation of infant feed.
3. In 2005, work conducted by scientists in Germany¹ on the uranium content of various natural mineral waters raised concerns on the acceptability of using natural mineral water and other bottled waters for the preparation of infant feed.
4. The World Health Organization (WHO) established a Tolerable Daily Intake (TDI) of 0.6 µg/kg body weight (bw) per day and a guideline value for uranium in drinking water of 15 µg/L². The Committee was asked to comment on the potential health implications for infants consuming formula milk made up with water containing uranium at this guideline level, to assist the Agency in developing advice on the suitability of using natural mineral water and other bottled waters to reconstitute infant formula.

Absorption, distribution, metabolism and excretion of uranium

5. The average gastrointestinal absorption of soluble uranium has been reported to be 1-2% in humans^{3, 4}. Data from laboratory animals indicate a

comparable range of uranium uptakes. In general, uranium uptake increases with the solubility of the uranium compound and after fasting⁴.

6. Uranium absorption has been reported to be higher in neonatal rats and pigs. For example, when given uranium by gavage two day old rats had uranium uptakes of 1-7%⁵, while 30% of uranium administered on post natal day one was found in the skeleton of pigs, seven days later⁶. There are few data on the extent of uranium uptake in children.

7. Absorbed uranium tends to accumulate in the kidneys and, in particular, in the skeleton where the uranyl ion replaces calcium in hydroxyapatite.

8. Uranium is primarily excreted in the faeces, with approximately 1% excreted via the urine. The overall elimination half-life of uranium in humans has been estimated to be 180-360 days².

Toxicity

9. The critical toxicological effect of uranium is nephrotoxicity, with damage occurring principally to the proximal convoluted tubules². Nephrotoxicity has been observed in acute, sub-acute, sub-chronic and chronic oral studies in rats, mice, rabbits and dogs. Nephritis has been reported to occur in humans following high level exposure to uranium². There is some evidence that uranium inhibits both sodium transport-dependent and sodium transport-independent ATP use and also inhibits mitochondrial oxidative phosphorylation in the renal proximal tubules.

10. Renal toxicity was observed in early studies in rats, dogs and rabbits fed high doses of uranium compounds for periods of 30 days to 2 years discussed by the US Environmental Protection Agency⁷. The lowest dose tested was equivalent to 2.8 mg/kg bw/day uranium in a 30-day study in rabbits, in which "modest" renal damage was noted. In longer term studies in rats and dogs, the renal effects were generally identifiable within 30 days of the start of treatment⁷.

11. More recent studies have been conducted in New Zealand white rabbits and Sprague-Dawley rats treated with uranium for a maximum of 91 days^{8,9,10}.

12. The sub-chronic study in rats⁸ was used as the basis of the WHO TDI. Groups of 15 male and female rats were given drinking water containing 0.96, 4.8, 24, 120 or 600 mg/L uranyl nitrate hexahydrate. The doses received were equivalent to 0.06, 0.31, 1.52, 7.54 and 36.73 mg/kg bw/day uranium in male rats and 0.09, 0.42, 2.01, 9.98 and 53.56 mg/kg bw/day uranium in female rats. There were no treatment related differences in fluid or food consumption. No significant dose-related effects were found in a range of haematological and serum biochemical parameters. Urinalysis was not conducted.

13. Kidney weights were unaffected by uranium treatment. However, treatment related lesions were observed in both sexes at all doses. In males, nuclear vesiculation, cytoplasmic vacuolation and tubular dilation were observed at all dose levels. At doses of 0.31 mg/kg bw/day uranium, glomerular adhesions, apical displacement of the proximal tubular epithelial nuclei and cytoplasmic degranulation were also apparent. The authors considered these effects could result in permanent injury to basement membranes with loss of nephrons and reduced renal function. In females, nuclear vesiculation of the tubular epithelial nuclei, capsular sclerosis of glomeruli and reticulin sclerosis of the interstitial membranes was observed at all doses, and anisokaryosis in all but one of the mid-dose group. The authors considered the capsular sclerosis of the glomeruli and the reticulin sclerosis of the interstitial membranes in the females to be particularly important as although not severe effects, they were non-reversible and thus sustained exposure could lead to more damaged glomeruli and impaired renal function. There was no clear dose-response for the adverse pathological effects observed over a large (600-fold) dose range.

14. In a comparable study in rabbits, dose-dependent histopathological changes in the kidney were reported. The changes observed in the kidneys consisted of foci of cytoplasmic vacuolation in proximal renal tubular epithelium resting on normal basement membrane. This was accompanied by vesiculation and pyknosis of tubular nuclei, where the epithelium was injured prior to any changes in the basement membrane. However, the interpretation of the findings in this study was complicated by the occurrence of *Pasteurella* infection in some of the male rabbits. Urinalysis indicated few significant changes in the treated animals. In a subsequent reversibility study¹⁰ the adverse kidney effects had not completely or consistently recovered after the 91-day recovery period in the top dose animals.

Epidemiology Studies

15. A number of studies of human populations have been conducted in areas of Canada where the drinking water contains naturally high levels of uranium. Although uranium intakes in these populations have not been linked to overt kidney disease, correlations have been shown between uranium exposure and various biomarkers of renal toxicity.

16. Clinical studies discussed by WHO² of 324 persons exposed to concentrations of uranium of up to 700 µg/L in drinking water showed a trend of increasing β-2-microglobulin excretion. This suggested the presence of an early sub-clinical tubular defect with β-2 microglobulin being a useful marker of sub-clinical toxicity.

17. In a preliminary study¹¹, microalbuminuria (a marker for glomerular damage) was assessed in 100 people consuming drinking water containing up to 14.7 µg/L uranium. Linear regression analysis revealed a statistically significant association between 'uranium cumulative index' (based on the level of uranium, the level of consumption of the water and the length of time living at the current residence) and urinary albumin levels. However, most subjects

had levels of urinary albumin within the normal range. The authors concluded that there was a relationship between uranium exposure and microalbuminuria but that it was not clinically significant at the levels of exposure measured in the study.

18. Zamora and colleagues (1998)¹² measured indicators of kidney function in two groups consuming drinking water containing either <1 µg/L or 2-781 µg/L uranium. A correlation was found between uranium intake and urinary levels of glucose, alkaline phosphatase and β-2-microglobulin. The authors concluded that at the levels of intake observed in the study (0.004-9 µg/kg bw) the chronic ingestion of uranium in drinking water affected kidney function at the proximal tubule.

19. A study by Kurttio *et al.*, (2002)¹³ measured a range of serum and urinary parameters (calcium, phosphate, glucose, albumin, creatinine and β-microglobulin) to assess renal function in 325 Finnish subjects exposed to high (>100 µg/L), medium (10-100 µg/L) or low (<10 µg/L) levels of uranium in well water. Urinary uranium levels were associated with increased fractional excretion of calcium, phosphate and glucose. Uranium concentration in drinking water and daily intake of uranium was associated with increased fractional excretion of calcium only. Uranium exposure was not associated with impairment of creatinine clearance or increase in urinary albumin, which are markers of renal injury. The authors concluded that uranium exposure was weakly associated with altered proximal tubule function without a clear threshold, this was taken to suggest that even low uranium levels can cause nephrotoxic effects. However, glomerular function was not affected, even in the high uranium exposure group. The authors considered that the safe concentration of uranium was within the range 2-30 µg/L.

Derivation of the WHO TDI and guideline value for drinking water

20. The WHO considered nephrotoxicity to be the most sensitive adverse effect, and derived a TDI for soluble uranium based on the lowest available lowest observed adverse effect level (LOAEL) of 0.06 mg/kg bw/day uranium from the male rats in the 91-day study⁸. 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. An additional uncertainty factor for extrapolation from a LOAEL to a no observed adverse effect level (NOAEL) was not considered necessary because of the “minimal degree of severity” of the histopathological changes observed. Since the estimated half-life of uranium in the kidney was 15 days and there was no suggestion that the severity of the lesions would be exacerbated following continued exposure, an additional uncertainty factor was not required for extrapolation from sub-chronic to chronic exposure.

21. The WHO then established a provisional “guideline value” for uranium levels in drinking water. Following consideration of uranium levels in food, 80% of the TDI was allocated to intake from drinking water. Based on the

assumption that a 60 kg adult consumes 2 L/day water, this resulted in a provisional guideline of 15 µg/L.

Uranium exposure in infants

22. Recent intake calculations have used a body weight of 4.5 kg and a consumption of 700 mL formula/day to represent the highest ratio between intake and bodyweight in infants^{14, 15} and these values have been used here to estimate potential infant exposures to uranium. Uranium exposure from food has not been taken into account as uranium levels are lower. Data from the 2001 Total Diet Study¹⁶ suggest that at the highest (97.5th) levels of exposure, uranium in food provides 6-16% of the TDI for adults and toddlers respectively.

23. If formula milk was reconstituted with water containing 15 µg/L uranium, consumption of 700 mL/day would represent an intake of 10.5 µg or 2.3 µg/kg bw/day for a 4.5 kg infant compared to the TDI of 0.6 µg/kg bw/day, a 4-fold exceedance. As noted above, this is the highest calculated ratio and would change with body weight and milk consumption. At six months of age, other foods would be introduced to the diet and uranium exposure would be expected to decrease.

Discussion

24. The database for uranium toxicity is limited and further work would be desirable to assist in the risk assessment process. For example, there are few data available on uranium absorption which appears to vary between species. Limited data from laboratory animals suggest that uptake in neonatal animals is higher than in adults. There are no data on uranium uptake in human infants.

25. The study in male rats⁸ used unconventional terminology, which is descriptive of morphology rather than diagnostic. The increase in irreversible capsular sclerosis and reticulin sclerosis in the females can be considered a clear adverse effect but was not dose-related and the severity of the lesions was not clearly graded. The authors did not consider the effects to be severe, suggesting they may be close to the NOAEL. The nuclear effects are of uncertain significance and are not reliable for use in setting the NOAEL. The WHO did not apply an uncertainty factor to extrapolate from a LOAEL to a NOAEL, suggesting that they considered the LOAEL to be a NOAEL.

26. The available data suggest that mild nephrotoxic effects associated with moderate levels of uranium exposure are reversible once exposure has ceased. This was demonstrated in a recovery study in rabbits by Gilman and colleagues¹⁰. As noted previously the half life of uranium is 15 days and the damage is not cumulative.

27. A number of epidemiological studies are available which examine the relationship between kidney function and uranium in drinking water. Some changes in urinary parameters and proximal tubule function are apparent at higher levels of uranium exposure but there is no evidence of effects on renal function. However, the epidemiological studies are of relatively small groups and do not specifically consider infants.

Conclusions

28. There are a number of limitations in the design and interpretation of the study by Gilman *et al* (1998a)⁸ which was used by WHO to establish a TDI. However, despite these limitations, the TDI and accompanying guideline level of 15µg/L for uranium in tap water would be expected to be protective of public health.

29. Reconstituting infant formula with water containing uranium at the WHO guideline value of 15µg/L could lead to uranium intakes by infants up to six months of age exceeding the WHO TDI by about 4-fold.

30. It is possible that uranium absorption is higher in young infants, and the implications of a modest exceedance of the TDI are uncertain.

31. It is noted that the database on uranium toxicity is incomplete, however, on the basis of the available evidence, this potential exposure of formula fed infants does not raise specific concerns for health.

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