Opinion On Arsenic, Barium, Fluoride, Boron And Manganese In Natural Mineral Waters (Expressed On 13 December 1996)

Terms of reference

To advise on the acceptability from the public health point of view of the 4 of certain substances in natural mineral waters. The substances the Committee is asked to consider are those natural constituents for which the levels requested by the European industry are above the levels in the drinking water directive or in its proposed amendment.

Background

Directive 80/777/EEC on natural mineral waters defines "natural mineral water" as:

"...microbiologically wholesome water originating in an underground water table or deposit and emerging from a spring tapped at one or more natural or bore exits. Natural mineral water can be distinguished from ordinary drinking water, notably:

by its nature, which is characterised by its mineral content, trace elements and other constituents.

by its original state."

The Directive states that "natural mineral waters are protected from all risk of pollution in order to preserve intact these characteristics", however this Directive of 1980 does not lay down individual limits for the minerals, trace elements or contaminants that may be found in natural mineral waters.

The Committee was informed that a proposal to update Directive 80/777/EEC was in the process of adoption to take into account scientific and technical progress and the mandate from the European Council for rationalising the Directive. Under this new Directive, the SCF must be consulted in questions relating to public health. The European industry1 presented to the Commission a list of proposed limits for these substances which included a number which exceeded the limits in Directive 80/778/EEC2 or in its proposed amendment3 .

Evaluation

Introduction

In preparing this report, the Committee has made use of reviews such as the SCF Report on Nutrient and Energy Intakes for the European Community (SCF, 1993), the WHO guidelines for drinking-water quality, volumes. 1-2 (WHO 1993 + 1994, 1996), IARC and US-NRC, US-ATSDR, ECETOC and RIVM reports and recent papers.

The Committee was provided with information on the consumption of natural mineral waters in the Community. However, this information does not allow estimation of intakes by high level consumers of natural mineral waters. Some natural mineral waters are increasingly consumed as a replacement for tap water. In the absence of other data, the Committee considered that the conventional value of 2 litres per day and per person for the consumption figure, as used by the EU and WHO for risk assessments relating to drinking water, should also be applied to natural mineral waters. The Committee is aware that this is a conservative approach.

In making its risk assessment, the Committee has recognised that drinking water is not the sole dietary source of human

exposure to the substances under consideration. For boron and manganese, the Committee has, in the absence of reliable exposure data, used the WHO default value of 10 % (WHO, 1993a) as the proportion of the TDI (or equivalent value established in this opinion) which can be allocated to natural mineral waters. This approach could not be applied to arsenic which has been classified by the International Agency for Research on Cancer (IARC) as a human carcinogen (IARC 1987). For barium and fluoride the evaluation is based on epidemiological data derived from studies involving consumption of drinking water containing known levels of these elements.

Individual Substances

1. Arsenic (As)

Evaluation

Inorganic arsenic is an established carcinogen able to induce primary skin cancer and has been classified by IARC 1987 (WHO 1987) in Group 1 (carcinogenic to humans). So far it has been found negative in animal carcinogenicity bioassays with one exception, but positive in tumour promotion studies. It has been found essentially non-mutagenic at gene level, but able to induce chromosomal aberrations and micronuclei in a variety of mammalian cells, including human cells. The mechanism of arsenic carcinogenic activity has not yet been clarified. Recent epidemiological studies (Chiou et al., Tsuda et al., 1995; Bates et al., 1995) seem to suggest that the carcinogenicity of arsenic requires the presence of other carcinogenic agents such as cigarette smoke.

All these facts seem to suggest that arsenic is an indirect carcinogen, with promoting and/or co-carcinogenic activity. The lack of knowledge of the precise mechanism of carcinogenic activity and the known problems in applying mathematical models makes the cancer-risk assessment for arsenic very difficult. Based on the increased incidence of skin cancer observed in Taiwan and by using a multistage model, WHO (1993b) has calculated that an excess lifetime skin cancer risk of 10-5 is associated to a concentration of 0.17 mg/ l in drinking water. This value may however overestimate the actual risk due to a number of factors, among which is the possible indirect mechanism of arsenic carcinogenicity. In order to reduce the concentration of arsenic in drinking water, WHO has established a provisional guideline value of 10 µg/l. This value is in line with the proposed amendment of the drinking water Directive3 but it is below the Maximum Admissible Concentration of 50µg/l in the existing Directive2.

Conclusions

In consideration of the fact that inorganic arsenic is an established human carcinogen, exposure should be as low as possible. For the time being an upper level of 10 µg/l in natural mineral waters seems reasonable and is in line with the proposed amendment 3 to the existing drinking water directive.

2. Barium (Ba)

Evaluation

Barium is not considered to be an essential element. Soluble salts of barium are known to be toxic. The acute toxic oral dose of barium chloride for humans is reported to be 0.2-0.5 g and doses above 3 g are lethal.

Sub-chronic studies following oral exposure have been carried out in rats. The most relevant adverse effect reported was a rise in systolic blood pressure when barium was given in the drinking water at 100 mg/l (Perry et al., 1983, 1985). Although even 10 mg/l induced some less marked increase in blood pressure, being only occasionally significant, a no-adverse-effect level of 0.5 mg/kg b.w./day was derived from that concentration, because the increases were deemed small enough not to constitute an adverse effect (WHO, 1996).

In a controlled human study daily doses of barium up to 15 mg did not show effects on blood pressure and on the cardiovascular system (Wones et al., 1990). One retrospective epidemiological study in some Illinois (USA) communities resulted in significantly higher age-adjusted death rates for "all cardiovascular diseases" and "heart

disease" in the areas with high barium levels in the drinking-water (2-10 mg/l) compared to low barium communities (< 0.2 mg/l) (Brenniman et al., 1979). However, this study was difficult to interpret and in a similar, better controlled, study by the same authors it was concluded that levels of barium in drinking-water of 7.3 mg/l do not significantly elevate blood pressure levels in adult males or females (Brenniman and Levy, 1984).

Conclusion

Considering that the concentration of 7.3 mg/l drinking-water does not affect blood pressure and incidence of cardiovascular diseases in humans and applying an uncertainty factor of 10 to account for intra-human variations, an upper level of 1 mg/l in natural mineral waters appears to be acceptable.

3. Fluoride (F)

Evaluation

In 1992 the SCF concluded that there does not appear to be a specific physiological requirement for fluoride and no specific recommendations was made (SCF, 1993). However, it was recognised that the element is beneficial to dental health at low intakes while on the other hand fluoride excess (fluorosis) is endemic in many parts of the world.

Fluoride has been subject to a series of acute, short term, and long term studies, but given the limited character of these animal studies and the large body of data on the toxic effects of fluoride in humans the latter data have priority in the derivation of long-term tolerable intakes for humans.

In humans, acute toxic effects have been reported at doses of 1-10 mg/kg b.w. with values of 14-140 mg/kg b.w. being reported for the acute lethal oral dose of soluble fluorides. The long-term adverse effects starts in its mild form at concentrations within the "beneficial" range with a mild dental fluorosis prevalence of 12-33 % being reported for concentrations in drinking-water of 0.9-1.2 mg/litre. The clinical picture of dental fluorosis in the mild form consists of the presence of opaque white areas on the teeth and is normally considered as a cosmetic effect rather than an adverse effect. Severe forms of this condition occur already at concentrations of 5-7 mg F/litre; in such cases the tooth enamel can become brittle enough to fracture at incisal edges and cusp tips. Climate has been identified as a factor determining the degree to which dental fluorosis will develop. In areas with a temperate climate, manifest dental fluorosis occurs at concentrations above 1.5-2.0 mg/litre whereas in warmer areas, the same effect may be already present at lower concentrations i.e. 0.7 -1.2 mg/litre. This may be attributed to greater water consumption in warmer climates (RIVM, 1989; EUREAU, 1991; WHO, 1992; US-NRC, 1993).

Skeletal fluorosis consists of adverse changes in bone structure due to continuous deposition of fluoride in the bone. The minimum dose required for production of skeletal fluorosis in its various degrees is not known exactly. However various studies of population groups indicate that at levels below 4 mg F/day there is no hazard of a significant degree of accumulation, 6-20 mg/day causes skeletal fluorosis to some degree while the severe form, crippling skeletal fluorosis, requires a daily dose of 20-80 mg. (RIVM, 1989; WHO, 1992; ATSDR, 1993). Fluoride has been used in the past in the treatment of osteoporosis however, clinical trials indicate that the effectiveness of this treatment is questionable. Population studies on bone fracture rate of fluoride in drinking water have also yielded inconclusive results (US-NRC, 1993).

Many mutagenicity studies are available, mostly carried out with NaF (US-NRC, 1993). It has been found negative in bacterial systems; it was positive in cultured mammalian cells (at gene and chromosome level) only at cytotoxic concentrations, probably by an indirect mechanism. So far, no adequate in vivo data are available.

According to IARC (1987) the limited animal data available were evaluated as inadequate. More recent NTP studies performed in rats and mice have shown an increased incidence of osteosarcomas only in male rats. This effect was evaluated by NTP as equivocal evidence (NTP, 1990; US-NRC, 1993).

Numerous epidemiological studies have been carried out to investigate whether there is a relation between the occurrence of cancer and the exposure to fluoride via drinking-water. IARC concluded that the studies provide

inadequate evidence for carcinogenicity in humans (IARC 1982, 1987). More recent studies also have not supplied evidence that there is a relation between fluoride in drinking-water and cancer mortality. (RIVM 1989); ATSDR, 1993).

Conclusion

On the basis of the data reviewed above especially as concerns the occurrence of dental fluorosis at concentrations above 0.7 mg/l (warm climates) and 1.5 mg/l (temperate climates), the Committee has no reason to deviate from the level of 1.5 mg/l, as given in the proposed amendment3 to the existing drinking water Directive, and concludes that this level should also apply to natural mineral waters.

4. Boron (B)

Evaluation

There are conflicting views about the essentiality of boron for man. In its report on nutrient and energy intakes, the SCF concluded that the evidence supporting the essentiality of boron has yet to be substantiated (SCF, 1993).

Boron undergoes little, if any, metabolism in the organism. It is excreted through the kidneys with a half-life of approximately 24 hours or less (Kent and McCance, 1941; Job, 1973, Schou, Jansen and Aggerbeck, 1984) and elimination is similar in rats and in man (Ku et al, 1991). There is no information available on elimination in pregnant women or in people with impaired kidney function.

The most important toxic effects of boron are on the reproductive system. In male laboratory animals testicular lesions have been observed in rats, mice and dogs given boron in the diet or in drinking water (NTP, 1987).

A survey of reproductive performance was carried out in 542 male workers in a borax mine using a questionnaire approach to test any anti-fertility effect of inhalation of borax. The mean exposure over 1 year in the highest exposure group was estimated on the basis of a mean male body weight of 70 kg, to be 0.34 mg of boron/kg b.w./day, and no adverse effect on reproduction was found by this indirect method (Whorton et al. 1994).

Developmental effects have been seen in rats, mice and rabbits. The critical effect was a decreased average fetal weight per litter in the rat. Offspring body weight was decreased at 13.3 mg of boron/kg b.w./day and the NOAEL was 9.6 mg of boron/kg b.w./day (Heindel et al. 1992; Price 1995).

No adequate study on boron is available on the developmental effects in man nor is any human study available of effects of boron during pregnancy nor in persons with decreased function of the major excretory organ for boron, the kidney. The Committee, therefore, found no basis for deviating from the usual safety factor to be applied to the NOAEL in the most sensitive animal species.

The Committee noted that the two recent evaluations of boron (ECETOC, 1994 and European Commission, 1996) had arrived at the same no effect level from the animal studies but had differed in the rationale for the derivation of a safety factor.

Conclusion

A NOAEL of 9.6 mg/kg b.w./day was established on the basis of the rat study (decreased average fetal weight per litter). Application of the usual safety factor of 100 gives a TDI of 0.1 mg boron/kg b.w./day. Consumption of 2 litres of natural mineral water/person/day and an allocation of 10 % of the TDI to this source of exposure would lead to a guideline value of 0.3 mg/l.

5. Manganese (Mn)

Evaluation

Manganese has been shown to be an essential element for animals. Therefore, it is presumed that manganese is also beneficial or essential to humans. On the other hand, higher doses can cause adverse effects, especially on the central nervous system. In humans, neurological effects have been observed in workers following chronic inhalation exposure to manganese dust and fumes. There is, however, only limited evidence that oral exposure might be of concern.

In vitro mutagenicity studies, including tests on bacteria and mammalian cells, have shown that manganese has a genotoxic potential in the absence of metabolic activation. So far, results of in vivo assays have been negative (ATSDR, 1992). Carcinogenicity studies in rats and mice revealed only equivocal evidence of increased tumour incidence (Hejtmancik et al., 1987a and 1987b).

The data on the dose-relationship of changes in the central nervous and reproductive system are insufficient and do not allow no-effect levels to be established. The lowest effective doses were seen in semi-chronic oral studies with MnCl 2, in which the motor activity of male rats was changed significantly at about 10 mg Mn/kg b.w./day (Bonilla, 1984) and testicular changes (Murthy et al., 1980) as well as muscular weakness, rigidity of the lower limbs and marked neuronal degeneration in the region of substantia nigra (Gupta et al., 1980) were noticed in male monkeys at 6.9 mg Mn/kg bw/day.

Conclusion

From the lowest effective doses observed, the semi-chronic oral studies, a no-effect level of 1 mg/kg b.w./day can be estimated. Application of a safety factor of 100 would result in a tolerable daily intake which would be lower than the essential intake from a nutritional point of view. Therefore, an acceptable maximum level for natural mineral waters was based on the safe and adequate range of 1-10 mg/ Mn/day derived by the SCF in setting nutrient intakes (SCF, 1993). Taking the upper value of this range into account and assuming an allocation factor of 10 % for natural mineral waters and a daily consumption of 2 litres, an upper level of 0.5 mg Mn/l in natural mineral waters appears to be acceptable.

Assumptions concerning consumption of natural mineral waters

The Committee stresses that its evaluations have explicitly assumed that the conventional consumption value of 2 l per person per day as used by the EU and WHO for risk assessment of drinking water, also applied to natural mineral waters. The Committee considered this to be a conservative approach but one which allows a certain flexibility for risk management purposes

References

- ATSDR (1992): Toxicological profile for manganese; Agency for Toxic Substances and Disease Registry, Atlanta, GA, US Department of Health and Human Services.
- ATSDR (1993) Toxicological profile for Fluorides, Hydrogen Fluoride, and Fluoride (F). Agency for Toxic Substances and Disease Registry - U.S. Public Health Service, report no. TP-91/19, dated April 1993
- Bates, M.N. et al. (1995) Case-control study of bladder cancer in drinking water. American Journal of Epidemiology, 141: 523-530.
- Bonilla, E. (1984): Chronic manganese intake induces changes in the motor activity of rats; Exp. Neurol. 84, 696-700.
- Brenniman, G.R. et al. (1979): Cardiovascular disease death rates in communities with elevated levels of barium in drinking water; Environ. Res. 20, 318-324.
- Brenniman, G.R. and Levy, P.S. (1984): Epidemiological study of barium in Illinois drinking water supplies. In: Calabrese, E.J. et al. (eds), Advances in modern Environmental Toxicology IX; Princeton Scientific Publications, Princeton New Jersey, 231-240
- Chiou, H.Y.et al. (1995) Incidence of internal cancers and ingested inorganic arsenic: a seven-year follow-up study in Taiwan. Cancer Research, 55: 1296-1300.
- ECETOC (1994): Toxicology and Risk Assessment for Men of the Inorganic Borates. Technical Report 65,

Brussels.
- EUREAU (1991) Drinking-Water Directive 80/778/EC - Proposals for modification: Views of EUREAU. Report dated July 1991
- European Commission, 1996. The Scientific Advisory Committee to Examine the Toxicity and Ecotoxicity on Chemical Compounds Opinion of Scientific Advisory Committee on concerning the toxicologically acceptable parametric values for Boron in drinking waters. 20th February 1996; Document CSTE/96/4/V
- Gupta, S.K. et al. (1980): Neuromelanin in manganese-exposed primates; Toxicology Letters 6, 17-20.
- Heindel, J.J et al (1992): Developmental Toxicity of Boric Acid in Mice and Rats. Fundam. and Applied Toxicology, 18,266-277.
- Hejtmancik, M et al. (1987a): The chronic study of manganese sulfate monohydrate (CAS no. 10034-96-5) in F 344 rats. Report to National Toxicology Program, Research Triangle Park, NC, by Battelle's Columbus Laboratories.
- Hejtmancik, M et al. (1987b): The chronic study of manganese sulfate monohydrate (CAS no. 10034-96-5) in B6C3F 1 mice. Report to National Toxicology Program, Research Triangle Park, NC, by Battelle's Columbus Laboratories.
- IARC (1982) IARC Monographs on the Evaluation of Carcinogenic Risks to Humans - Volume 27; Some Aromatic Amines, Anthraquinones and Nitroso Compounds, and Inorganic Fluorides Used in Drinking-Water and Dental Preparations. IARC-WHO, Lyon, France
- IARC (1987) Monographs on the Evaluation of Carcinogenic Risks to Humans. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. Supplement 7. IARC, Lyon, France
- Job C. (1973): Resorption and excretion of orally administered boron. Z. angew. Bader-Klimaheike. 20, 137-142
- Kent, N. L. & Mc Cance, R. A. (1941): The absorption and excretion of "minor" elements by man. I. silver, gold, lithium, boron and vanadium. Biochem. J. 35, 837-844
- Ku, W. W., Chapin, R. E., Mossmann, R. F., Brink, R. E, Pierce, K. D. & K. Y. Adams (1991) Tissue disposition of boron in Fischer rats & Toxicol. Appl. Pharmacol. III, 145-151
- Ku, W.W., Chapin, R.R., Mossmann, R.F., Brink, R.F., Pierce, K.D. and Adams, K.Y. (1991): Tissue disposition of boron in Fisher rats. Toxicol. Appl. Pharmacol. 111, 145-151.
- Murthy, R.C. et al. (1980): Manganese induced testicular changes in monkeys; Exp. Path. 18, 240-244.
- NTP (1987): Toxicology and Carcinogenicity studies of boric acid in B6C3F1 mice (feed studies). NTP tech. Rep. Ser. No. 324. US DHHS; PHS, HIH, Research Triangle Park, USA
- Perry, H.M. et al. (1983): Cardiovascular effects of chronic barium ingestion. In: Hemphill, D.D. (ed.), Trace Substances in environmental health - XVII; Proceedings of University of Missouri's 17 th annual conference on trace substances in environmental health, University of Missouri Press, Columbia, Mo.
- Perry, H.M. et al. (1985): Barium induced hypertension. In: Calabrese, E., ed. Inorganics in drinking water and cardiovascular disease, Princeton, New Jersey, Princeton Publishing Co., Chapter 20, 221-229.
- Price, C.J., P.L. Strong, M.C. Man, C.B. Meyers and F.J. Murray. (1995): Developmental Toxicity, NOAEL and Postnatal recovery in rats fed boric acid during gestation. Manuscript submitted to IPCS.
- RIVM (1989) Integrated Criteria Document Fluorides: Effects. Appendix to RIVM report no. 75847010, dated September 1989. Authors: P. J. C. M. Janssen, A. G. A. C. Knaap & J. A. Janus. National Institute of Public Health and Environmental Protection (RIVM), Bilthoven, the Netherlands
- Schou, J.S., Jansen, J.A. and and Aggerbeck, B. (1984): Human pharmacokinetics and safety of boric acid. Arch. Toxicol. Suppl 7: 232-235.
- SCF (1993); Reports of the Scientific Committee for Food on Nutrient and Energy Intakes for the European Community, (31 st series), European Commission. [Opinion expressed on the 11th December 1992]
- Tsuda, T. et al. (1995) Ingested arsenic and internal cancer: a historical cohort study followed for 33 years. American Journal of Epidemiology, 141: 198-209.
- US-NRC (1993) Health effects of ingested fluoride. U. S. A. National Research Council - Subcommittee on Health Effects of Ingested Fluoride, Washington, National Academy Press, 1993. ISBN 0-309-04975-X
- WHO (1992) Guidelines for drinking-water quality, Volume 2: Health criteria and other supporting information - Chapter 2: Chemical aspects. PCS/EHC/92.60b.
- WHO (1993a) Guidelines on Drinking Water Quality 2nd Edition; Vol I, Recommendations. WHO, Geneva
- WHO (1993b) Guidelines for drinking water quality. Vol. 1. 2nd edition. International Programme on Chemical Safety, WHO, Geneva.
- WHO (1994): Environmental Health Criteria 170. IPCS. WHO, Geneva

- WHO (1996): Guidelines for Drinking-Water Quality, second edition, Vol. 2: Health Criteria and other supporting information; World Health Organisation Geneva.
- Whorton, M.D., J.L. Haas, L. Trent and O. Wong (1994): Reproductive effects of sodium borate on male employees: Birth rate assessment. Occupational & Environ. Medicine. **51**,761-767
- Wones, R.G. et al. (1990): Lack of effect of drinking water barium on cardiovascular risk factors; Environ. Health Perspectives 85, 355-359.