Hardness in Drinking-water

Background document for development of WHO Guidelines for Drinking-water Quality

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Preface

One of the primary goals of the World Health Organization (WHO) and its Member States is that "all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water". A major WHO function to achieve such goals is the responsibility "to propose ... regulations, and to make recommendations with respect to international health matters"

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International Standards for Drinking-water*. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO *Guidelines for Drinking-water Quality* (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002. The third edition of the GDWQ was published in 2004, the first addendum to the third edition was published in 2008. The fourth edition will be published in 2011.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared and updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants of potential health concern in drinking-water. In the first and second editions, these constituted Volume 2 of the GDWQ. Since publication of the third edition, they comprise a series of free-standing monographs, including this one.

For each chemical contaminant or substance considered, a lead institution prepared a background document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Japan, the United Kingdom and the United States of America (USA) prepared the documents for the fourth edition.

Under the oversight of a group of coordinators, each of whom was responsible for a group of chemicals considered in the GDWQ, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors. The draft documents were also released to the public domain for comment and submitted for final evaluation by expert meetings.

During the preparation of background documents and at expert meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the Joint FAO/WHO Meetings on Pesticide Residues and the Joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite, in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO Internet site and in the current edition of the GDWQ.

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The first draft of Hardness in Drinking-water, Background document for development of WHO *Guidelines for Drinking-water Quality* (GDWQ), was prepared by Dr Joseph Cotruvo, Washington, DC, USA, to whom special thanks are due. This background document is an update of the background document published in the second edition of the GDWQ.

The work of the following working group coordinators was crucial in the development of this document and others contributing to the fourth edition:

Dr J. Cotruvo, J. Cotruvo Associates, USA (Materials and chemicals)

Mr J.K. Fawell, United Kingdom (Naturally occurring and industrial contaminants and Pesticides)

Ms M. Giddings, Health Canada (Disinfectants and disinfection by-products)

Mr P. Jackson, WRc-NSF, United Kingdom (*Chemicals – practical aspects*)

Professor Y. Magara, Hokkaido University, Japan (Analytical achievability)

Dr Aiwerasia Vera Festo Ngowi, Muhimbili University of Health and Allied Sciences, United Republic of Tanzania (*Pesticides*)

Dr E. Ohanian, Environmental Protection Agency, USA (*Disinfectants and disinfection by-products*)

The draft text was discussed at the Expert Consultation for the fourth edition of the GDWQ, held on 19–23 June 2008. The final version of the document takes into consideration comments from both peer reviewers and the public. The input of those who provided comments and of participants at the meeting is gratefully acknowledged.

The WHO coordinators were Mr R. Bos and Mr B. Gordon, WHO Headquarters. Ms C. Vickers provided a liaison with the International Programme on Chemical Safety, WHO Headquarters. Mr M. Zaim, Public Health and the Environment Programme, WHO Headquarters, provided input on pesticides added to drinking-water for public health purposes.

Ms P. Ward provided invaluable administrative support at the Expert Consultation and throughout the review and publication process. Ms M. Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comments are greatly appreciated.

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Much of this background document was extracted from the book *Calcium and magnesium in drinking-water: public health significance* (WHO, 2009). The interested reader should consult that publication for additional information and for primary references.

1. GENERAL DESCRIPTION

1.1 Identity

Water hardness is the traditional measure of the capacity of water to react with soap, hard water requiring considerably more soap to produce a lather. It is not caused by a single substance but by a variety of dissolved polyvalent metallic ions, predominantly calcium and magnesium cations, although other cations (e.g. barium, iron, manganese, strontium and zinc) also contribute. Hardness is most commonly expressed as milligrams of calcium carbonate equivalent per litre. Water containing calcium carbonate at concentrations below 60 mg/l is generally considered as soft; 60–120 mg/l, moderately hard; 120–180 mg/l, hard; and more than 180 mg/l, very hard (McGowan, 2000). Although hardness is caused by cations, it may also be discussed in terms of carbonate (temporary) and non-carbonate (permanent) hardness.

1.2 Sources

The principal natural sources of hardness in water are dissolved polyvalent metallic ions from sedimentary rocks, seepage and runoff from soils. Calcium and magnesium, the two principal ions, are present in many sedimentary rocks, the most common being limestone and chalk. They are also present in a wide variety of industrial products and are common constituents of food. As mentioned above, a minor contribution to the total hardness of water is also made by other polyvalent ions, such as aluminium, barium, iron, manganese, strontium and zinc.

1.3 Organoleptic properties

The taste threshold for the calcium ion is in the range 100–300 mg/l, depending on the associated anion, but higher concentrations are acceptable to consumers (see also section 4).

2. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

2.1 Water

Calcium concentrations of up to 100 mg/l are common in natural sources of water. Magnesium is less frequently present in natural water sources; when present, it is usually found at lower concentrations than calcium (commonly up to about 10 mg/l). Natural sources rarely contain magnesium at concentrations above 100 mg/l, and it is usually calcium hardness that predominates (National Research Council, 1977).

Estimated daily intakes of magnesium from water of about 2.3 and 52.1 mg in softwater and hard-water areas, respectively, have been reported, based on adults drinking 2 litres of water per day (Neri et al., 1985).

2.2 Food

Food is the principal source of both calcium and magnesium. Dairy products are the richest sources of dietary calcium, contributing over 50% of the total calcium in many diets. Some plant foods, including legumes, green leafy vegetables and broccoli, can also contribute to dietary calcium, but the content is lower than in dairy products, and the bioavailability of calcium in plant foods can be low if the concentration of oxalate or phytate is high. Dietary sources of magnesium are more varied; dairy products, vegetables, grain, fruits and nuts are important contributors.

Typical recommended dietary intakes are about 1000 mg of calcium per day and 200–400 mg of magnesium per day. Moves to reduce the intake of dairy products because of the fat content will lead to a lowering of calcium intake in some groups. Populations that use only a very small amount of dairy products would also have a lower intake of calcium.

2.3 Estimated total exposure and relative contribution of drinking-water

The typical dietary contribution of calcium and magnesium is over 80% of the total daily intake. Of this, approximately 30% of calcium and 35% of magnesium will be absorbed. The bioavailabilities of calcium and magnesium from milk and water are on the order of 50% (Ong, Grandjean & Heaney, 2009). For calcium and magnesium, the typical contribution from water is 5–20% (WHO, 1973; National Research Council, 1977; Neri & Johansen, 1978).

Available evidence suggests that, because of dietary habits, many people in most countries fail to obtain from their diets the recommended intakes of one or both of these nutrients. While the concentrations of calcium and magnesium in drinking-water vary markedly from one supply to another, mineral-rich drinking-waters may provide substantial contributions to total intakes of these nutrients in some populations or population subgroups. Water treatment processes can affect mineral concentrations and, hence, the total intake of calcium and magnesium for some individuals.

3. EFFECTS ON HUMANS

Both calcium and magnesium are essential to human health. Inadequate intake of either nutrient can result in adverse health consequences. Recommended daily intakes of each element have been set at national and international levels. Individuals vary considerably in their needs for and consumption of these elements.

3.1 Calcium

3.1.1 Inadequate intake

Inadequate intakes of calcium have been associated with increased risks of osteoporosis, nephrolithiasis (kidney stones), colorectal cancer, hypertension and stroke, coronary artery disease, insulin resistance and obesity. Most of these disorders have treatments but no cures. Owing to a lack of compelling evidence for the role of calcium as a single contributory element in relation to these diseases, estimates of

calcium requirement have been made on the basis of bone health outcomes, with the goal of optimizing bone mineral density.

Calcium is unique among nutrients, in that the body's reserve is also functional; increasing bone mass is linearly related to reduction in fracture risk. The total body stores are on the order of 1200 g, with about 99% in bones and teeth. A large body of primary evidence from randomized controlled trials shows that increasing calcium intake, especially in those who have had habitually low calcium intakes, increases bone mass during growth and reduces bone loss and fracture risk late in life. Osteoporosis is one of the most prevalent of age-related diseases. Epidemiological evidence is strong that dietary calcium reduces the incidence of kidney stones. In contrast, the results of a large randomized trial suggest an increased risk of kidney stones associated with calcium supplements, possibly because the calcium was not ingested with food or the supplements were taken by those who exceeded the upper level of 2500 mg/day. Although hypertension is multifactorial in origin, adequate calcium intake has been associated with lowered risk of elevated blood pressure in some, but not all, studies. A clear mechanism has not been identified. Dairy products, more than calcium, per se, have been associated with reduced blood pressure in randomized prospective studies and with reduced risk of stroke in prospective studies.

Those individuals who avoid dairy products or lack access to them may be at increased risk of calcium deficiency. Formula-fed infants will not normally be at risk from deficient or excess amounts of calcium, as even extremely low or high calcium concentrations in water would not lead to absorption of unphysiological amounts of calcium from infant formula reconstituted with the water. If, however, other food sources are used that do not provide the calcium content of full-strength formula, then water may represent an important source of the mineral for the infants.

3.1.2 Excess intake

To a great extent, individuals are protected from excess intakes of calcium by a tightly regulated intestinal absorption mechanism through the action of 1,25-dihydroxy-vitamin D, the hormonally active form of vitamin D. When absorbed calcium is in excess of need, the excess is excreted by the kidney in most healthy people. Concern for excess calcium intake is directed primarily to those who are prone to milk alkali syndrome (the simultaneous presence of hypercalcaemia, metabolic alkalosis and renal insufficiency) and hypercalcaemia. Although calcium can interact with iron, zinc, magnesium and phosphorus within the intestine, thereby reducing the absorption of these minerals, available data do not suggest that these minerals are depleted when humans consume diets containing calcium above the recommended levels. For example, even though high intakes of calcium can exert acute effects on iron absorption, there is no evidence of reduced iron status or iron stores with long-term calcium supplementation.

3.2 Magnesium

3.2.1 Inadequate intake

Magnesium is the fourth most abundant cation in the body and the second most abundant cation in intracellular fluid. It is a cofactor for some 350 cellular enzymes,

many of which are involved in energy metabolism. It is also involved in protein and nucleic acid synthesis and is needed for normal vascular tone and insulin sensitivity. Total body stores are on the order of 25 g, with about 60% in bone. Low magnesium levels are associated with endothelial dysfunction, increased vascular reactions, elevated circulating levels of C-reactive protein (a proinflammatory marker that is a risk factor for coronary heart disease) and decreased insulin sensitivity. Low magnesium status has been implicated in hypertension, coronary heart disease, type 2 diabetes mellitus and metabolic syndrome.

Magnesium deficiency has been implicated in the pathogenesis of hypertension, with some epidemiological and experimental studies demonstrating a negative correlation between blood pressure and serum magnesium levels. However, data from clinical studies have been less convincing. Cardiac arrhythmias of ventricular and atrial origin have been reported in patients with hypomagnesaemia. Indeed, a serious cardiac arrhythmia, Torsade de Pointes, is treated with intravenous magnesium therapy.

Pre-eclampsia (defined as hypertension after 20 weeks of gestation) with proteinuria has been treated with magnesium salts for many decades. A recent trial (Altman et al., 2002) using magnesium sulfate showed a 50% decreased risk of eclampsia.

Animal studies have documented an inverse (protective) relationship between magnesium intake and the rate or incidence of atherosclerosis. In humans, there is evidence for an inverse (protective) relationship between magnesium and coronary heart disease mortality. Three cross-sectional studies have now documented an inverse relationship between the concentration of C-reactive protein and magnesium intake or serum magnesium concentration, suggesting that magnesium may have an anti-inflammatory effect.

Several studies have documented the importance of magnesium in type 2 diabetes mellitus. Two recent studies have documented an inverse (protective) relationship between magnesium intake and risk of developing type 2 diabetes mellitus. Oral magnesium supplementation improves insulin sensitivity and metabolic control in type 2 diabetes mellitus.

Alcoholism and intestinal malabsorption are conditions associated with magnesium deficiency. Certain drugs, such as diuretics, some antibiotics and some chemotherapy treatments, increase the loss of magnesium through the kidney.

3.2.2 Excess intake

The major cause of hypermagnesaemia is renal insufficiency associated with a significantly decreased ability to excrete magnesium. Increased intake of magnesium salts may cause a change in bowel habits (diarrhoea), but seldom causes hypermagnesaemia in persons with normal kidney function.

Drinking-water in which both magnesium and sulfate are present in high concentrations (~250 mg/l each) can have a laxative effect, although data suggest that consumers adapt to these levels as exposures continue. Laxative effects have also been associated with excess intake of magnesium taken in the form of supplements, but not with magnesium in diet.

3.3 Epidemiological studies

A large number of studies have investigated the potential health effects of drinkingwater hardness. Most of these have been ecological epidemiological studies and have found an inverse relationship between water hardness and cardiovascular mortality. Inherent weaknesses in the ecological epidemiological study design limit the conclusions that can be drawn from these studies.

Based on identified case—control and cohort studies, the studies do show a negative association (i.e. protective effect) between cardiovascular mortality and drinking-water magnesium. Although this association does not necessarily demonstrate causality, it is consistent with the well-known effects of magnesium on cardiovascular function. There is no evidence of an association between water hardness or calcium and acute myocardial infarction or deaths from cardiovascular disease (acute myocardial infarction, stroke and hypertension). There does not appear to be an association between drinking-water magnesium and acute myocardial infarction.

Case-control and cohort studies are more useful than ecological epidemiological studies for investigating cause-and-effect relationships. Seven case-control studies and two cohort studies of acceptable quality investigating the relationship between calcium or magnesium and cardiovascular disease or mortality were identified in the literature. Of the case-control studies, one addressed the association between calcium and acute myocardial infarction and three the association between calcium and death from cardiovascular disease. None found a positive or inverse correlation between calcium and either morbidity or mortality. Two examined the relationship between magnesium and acute myocardial infarction, finding no association. Five examined the relationship between magnesium and cardiovascular mortality; while some failed to yield statistically significant results, collectively they showed similar trends of reduced cardiovascular mortality as magnesium concentrations in water increased. Statistically significant benefits (where observed) generally occurred at magnesium concentrations of about 10 mg/l and greater. The cohort studies examined the relationship between water hardness (rather than calcium or magnesium content) and cardiovascular disease or mortality and found no association.

3.4 Other health effects

Exposure to hard water has been suggested to be a risk factor that could exacerbate eczema. The environment plays an important part in the etiology of atopic eczema, but specific causes are unknown. A suggested explanation relative to hard water is that increased soap usage in hard water results in deposits that cause skin irritation (Thomas & Sach, 2000). There are reports of a relation between both 1-year period and lifetime prevalence of atopic eczema and water hardness among primary-school children (McNally et al., 1998). Eczema prevalence trends in the secondary-school population were not significant. Eczema prevalence in primary-school children increased in relation to the chlorine content of the water, but the trend across four chlorine content categories was not independently significant after adjustment for confounders. Additional studies are under way.

4. OTHER CONSIDERATIONS

Depending on the interaction with other factors, such as pH and alkalinity, hard water can cause scale deposition in the distribution system, as well as increased soap consumption. In contrast, soft water that is not stabilized has a greater tendency to cause corrosion of pipes, resulting in the presence of certain heavy metals, such as cadmium, copper, lead and zinc, in drinking-water (National Research Council, 1977).

Conditioning of water, including central softening and stabilization, may be necessary to reduce corrosion of piping materials and/or scaling effects in installations and to improve consumer acceptability. Corrosion and scaling can be associated with health risks (from leachates such as lead) and the environment (from leachates such as copper if the water is not conditioned) and reduced lifespan of the distribution network and appliances using water. When conditioning is done, the target is normally to achieve bicarbonate equilibrium and suitable pH and alkalinity. Other ions, such as sulfate, nitrate and chloride, can be implicated in corrosivity.

Modification of calcium and magnesium concentrations in drinking-water for health reasons (e.g. associated with desalinated water; Cotruvo et al., in press) should comply with the technical requirements to provide water suitable for distribution and not compromise disinfection. The choice for the most appropriate conditioning technology will depend on local circumstances (e.g. water quality issues, piping materials, corrosion). Based on local circumstances, water suppliers and public health authorities may wish to further modify drinking-water composition in light of overall mineral nutrition.

Dissolved minerals contribute to the taste of drinking-water to varying degrees. Acceptability of water will usually depend on the individual user's taste and familiarity. Especially high or low mineral content may be considered unpalatable by consumers. Concentrations of calcium and magnesium in water that are detectable by consumers are typically above those that are considered manageable in drinkingwaters.

5. HOUSEHOLD TREATMENT METHODS

Point-of-entry ion exchange (water softener) devices are used in some households to remove hardness (calcium, magnesium) and iron from water. Each divalent ion (e.g. Ca²⁺ or Mg²⁺) in the water is replaced by two sodium ions. Softening will have several aesthetically beneficial effects inside the home, such as reducing scaling in pipes, fixtures and water heaters and improving laundry and washing characteristics, but it also increases the sodium content of the drinking-water. Consumption of calcium and magnesium in drinking-water will, of course, be lower unless the water consumed is not softened or is remineralized.

Point-of-use reverse osmosis and distilling devices remove virtually all the minerals from the input water, functioning as a final barrier against potential trace-level contaminants that may be present, as well as removing nutrients. While this water need not be conditioned if materials not subject to corrosion are used after the treatment, the resultant drinking-water is devoid of minerals. Use of these devices

may result in the reduction of the overall intake of nutrient minerals by the consumers in the households.

Users of these devices should be made aware of the changes in mineral composition that arise and the possible consequences for total nutrient intake and human health. For example, those who sell or install these devices may be encouraged to bring to the attention of the users of these devices the possibility of reduced intake of minerals and various means for their replacement.

One approach is to soften only the hot water line at the entry to the hot water heater, which provides several benefits and also reduces costs. Additionally, the manufacturers of these devices may provide a suitable bypass of a portion of this water to maintain some level of these minerals in the water actually consumed (e.g. to a kitchen tap) or develop and add an appropriate remineralizing unit in the water line prior to the point of consumption.

6. CONCLUSIONS

Hardness is important for drinking-water from the point of view of both aesthetic acceptability and operational considerations. Although there is some evidence from epidemiological studies for a protective effect of magnesium or hardness on cardiovascular mortality, the evidence is being debated and does not prove causality. Further studies are being conducted.

In spite of this, drinking-water may be a source of calcium and magnesium in the diet and could be important for those who are marginal for calcium and magnesium intake. Where drinking-water supplies are supplemented with or replaced by demineralized water that requires conditioning, consideration should be given to adding calcium and magnesium salts to achieve concentrations similar to those that the population received from the original supply.

Consumers should be informed of the mineral composition of their water when it has been altered by piped suppliers or treatment device manufacturers and of means for supplementation, if desired. The contribution of drinking-water minerals to mineral nutrition should be considered where changes in supply are proposed or where novel sources, such as seawater or brackish water, are exploited for drinking-water.

There are insufficient data to suggest either minimum or maximum concentrations of minerals at this time, and so no guideline values are proposed.

7. REFERENCES

Altman D et al. (2002) Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. *Lancet*, 359(9321):1877–1890.

Cotruvo JA et al. (in press) *Desalination technology: health and environmental impacts*. Boca Raton, FL, CRC Press.

McGowan W (2000) Water processing: residential, commercial, light-industrial, 3rd ed. Lisle, IL, Water Quality Association.

McNally NJ et al. (1998) Atopic eczema and domestic water hardness. Lancet, 352(9127):527-531.

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National Research Council (1977) *Drinking water and health*. Washington, DC, National Academy of Sciences.

Neri LC, Johansen HL (1978) Water hardness and cardiovascular mortality. *Annals of the New York Academy of Sciences*, 304:203–221.

Neri LC et al. (1985) Magnesium and certain other elements and cardiovascular disease. *Science of the Total Environment*, 42:49–75.

Ong CN, Grandjean AC, Heaney RP (2009) The mineral composition of water and its contribution to calcium and magnesium intake. In: *Calcium and magnesium in drinking-water: public health significance*. Geneva, World Health Organization.

Thomas KS, Sach TH (2000) A multicentre randomized controlled trial of ion-exchange water softeners for the treatment of eczema in children: protocol for the Softened Water Eczema Trial (SWET) (ISRCTN: 71423189). *British Journal of Dermatology*, 159(3):561–566.

WHO (1973) Trace elements in human nutrition: report of a WHO Expert Committee. Geneva, World Health Organization (WHO Technical Report Series, No. 532).

WHO (2009) Calcium and magnesium in drinking-water: public health significance. Geneva, World Health Organization.