

Nutrients in Drinking Water

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PREFACE

The World Health Organization assembled a diverse group of nutrition, medical and scientific experts in Rome in November 2003, at the WHO European Centre for Environment and Health, to address a number of questions relating to the nutrient composition of drinking water and the possibility that drinking water could in some circumstances contribute to total dietary nutrition. The original impetus of the meeting was as a contribution to development of Guidance on health and environmental aspects of desalination that was initiated by the WHO Eastern Mediterranean Regional Office, and intended ultimately to contribute to the development of the 4th edition of the WHO Guidelines for Drinking Water Quality (GDWQ). There were 18 invited experts from Canada, Chile, Czech Republic, Germany, Ireland, Italy, Moldova, Singapore, Sweden, United Kingdom and United States of America. Additional papers were provided by invitees who could not attend. The task was to examine the potential health consequences of long-term consumption of water that had been 'manufactured' or 'modified' to add or delete minerals. In particular, the meeting originated from the question of the consequences of the long-term consumption of waters that had been produced from demineralization processes like desalination of seawater and brackish water as well as possibly some membrane treated fresh waters, and their optimal reconstitution from the health perspective.

The scope of the review included these questions:

- What is the potential contribution of drinking water to human nutrition?
- What is the typical daily consumption of drinking water for individuals, considering climate, exercise, age and other factors?
- Which substances are found in drinking water that can contribute significantly to health and well-being?
 - Under what conditions can drinking water become a significant contribution to the total dietary intake of certain beneficial substances?
- What conclusions can be drawn about the relationship between calcium, magnesium and other trace elements in water and mortality from certain types of cardiovascular disease?
- For which substances, if any, can a case be made from the public health perspective for supplementation of the mineral content of treated drinking water derived from demineralized water?
- What is the role of fluoride in such water with respect to dental benefits, dental fluorosis and skeletal fluorosis?

Drinking water is usually subjected to one or more treatment processes aimed at improving its safety and/or its aesthetic quality. Fresh waters can be treated by one or more processes such as coagulation, sedimentation, granular media filtration, adsorption, ion exchange, membrane filtration, slow sand filtration, and disinfection, and sometimes softening. The conversion of high salinity waters like seawater and brackish waters to potable water by desalination is being increasingly practiced in water-short areas as demand for water increases, and the technology becomes more economically attractive. More than 6 billion gallons of desalinated water are produced daily throughout the world. Remineralization of desalinated water is necessary to control its aggressiveness to piped distribution systems. Since remineralization of desalinated water is required, a logical question is: are there methodologies that could bring with them additional benefits such as by reconstituting certain important minerals?

Natural waters are of widely diverse compositions depending upon their geologic and geographical origin and the treatments that they have undergone. For example, rain waters and some rain water-dominated surface waters have very low salinity and mineralization, whereas some ground waters can become highly, and sometimes excessively mineralized. If

remineralization of processed water is desirable for health reasons, another logical question is whether some natural waters would also be more healthful if they also contained appropriate amounts of beneficial minerals.

The meeting concluded that only a few minerals in natural waters had sufficient concentrations and distribution to expect that their consumption in drinking water might sometimes be a significant supplement to dietary intake in some populations. Magnesium and possibly calcium were the two most likely significant contributors to dietary intake in populations that consumed 'hard' water. Information was provided on about 80 of many epidemiology studies of varying quality over the last 50 years that had addressed the issue of hard water consumption and possibly reduced incidence of ischemic cardiovascular disease in populations. Although the studies were mostly ecological and of varied quality, the meeting concluded that on balance they indicated that the hard water /CVD beneficial hypothesis was probably valid, and that magnesium was the more likely positive contributor to the benefits. This conclusion was supported by several case control studies as well as clinical studies. There were other possible health benefits that had been reported, but there was not sufficient data in hand to address those matters. The meeting also concluded that before making a Guidance determination, WHO should undertake a more detailed assessment of that hypothesis to include an examination of its biological plausibility. A follow-up symposium and meeting is being planned in 2006 to address that recommendation.

In respect to fluoride, the meeting concluded that optimal levels of fluoride intake from water are known to contribute beneficially to dental health. It also noted that higher intake levels can contribute to dental fluorosis, and much higher levels cause skeletal fluorosis. It concluded that a decision to remineralize demineralized water with fluoride would depend upon: the concentration of fluoride in the existing water supply, the volume of water consumed, the prevalence of risk factors for dental caries, oral hygiene practices and the level of public dental health awareness in the community, and the presence of alternative vehicles for dental care and fluoride available to the population.

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WHO especially wishes to acknowledge the organizations that generously sponsored the meeting. These included: the International Life Sciences Institute (ILSI), the U.S. Environmental Protection Agency's Office of Science and Technology (Washington), and Office of Research and Development (Research Triangle Park, North Carolina), the American Water Works Association Research Foundation, the Center for Human Nutrition at the University of Nebraska Medical Center (Omaha), and Health Canada's Water Quality and Health Bureau (Ottawa, Ontario).

1.

NUTRIENTS IN DRINKING WATER

Potential Health Consequences Of Long-Term Consumption Of Demineralized, Remineralized And Altered Mineral Content Drinking Water

Expert Consensus
Meeting Group Report

I. INTRODUCTION

Desalination of sea water and brackish water is widely practiced and it is rapidly growing as the principal source of new fresh water in the world. Water treatment processes including desalination followed by remineralization alter the mineral composition of drinking water compared to water derived from many fresh water sources.

The WHO Guidelines for Drinking-water Quality (GDWQ) provide a point of reference for drinking water quality regulations and standards setting world-wide. The Guidelines are kept up-to-date through a process of 'rolling revision' that includes the development of accompanying documents substantiating the content of the guidelines and providing guidance on experience with good practice in achieving safe drinking-water. This plan of work includes the development of guidance on good practices of desalination as a source of safe drinking water.

In 1999, WHO's Eastern Mediterranean Regional Office initiated a proposal to develop WHO "Guidance for Safe Water: Health and Environmental Aspects of Desalination", because numerous existing facilities had developed on a case-by-case basis with potentially inconsistent consideration of important principles of siting, coastal zone protection, chemicals and contact surfaces used in plant operation, water treatment and plant construction, contaminants, water distribution, microbial control and final product water quality. International guidance would reduce *ad hoc* decision making and facilitate informed decision making, assist the provision of higher quality water, assure consideration of environmental protection factors, reduce costs and allow more rapid project completion. Such guidance would be timely given the rapidly increasing application of desalination world-wide. In 2000, the proposal to proceed was endorsed at a WHO Guidelines for Drinking-water Quality Committee meeting in Berlin, Germany. In May 2001, the proposal was examined at a dedicated expert consultation in Manama, Bahrain and an operating plan and program were proposed. This report and its supporting papers were the product of a meeting conducted in the WHO office for the European Region in Rome, Italy in 2003. That meeting was part of the development plan for the Desalination Guidance describe above.

Health considerations addressed in this report are those potentially arising from long-term consumption of water that has undergone major alteration in its mineral content, such that it must be remineralized to be compatible with piped distribution systems. The report also considers the relationships between calcium and magnesium in drinking water on certain cardiovascular disease risks. In addition there also a brief review of fluoride in remineralized water and dental effects in relation to associated water consumption.

1. Background

Drinking water, regardless of its source, may be subjected to one or more of a variety of treatment processes aimed at improving its safety and/or aesthetic quality. These processes are selected in each case according to the source water and the constituents and contaminants that require removal. Surface fresh waters will often undergo coagulation, sedimentation, rapid sand

filtration and disinfection. Ground waters, which are often naturally filtered, usually undergo less treatment that could be limited to disinfection alone. Other treatment processes may include pH adjustment, softening, corrosion control chemicals addition, alkalinity adjustment, carbon filtration/adsorption, membrane filtration, slow sand filtration and supplemental fluoridation. The disinfectants applied could include chlorine, chlorine dioxide, ozone, or chloramines. Some substances will be added by the chemicals used for treatment, i.e. direct and indirect additives.

For waters with high salinity (e.g. from perhaps 1000 ppm up to about 40,000 ppm) such as brackish waters or sea water, treatment processes must remove most of the dissolved salts in order to make the water potable. The major methods include reverse osmosis, other membrane treatments or several distillation/vapor condensation processes. These processes require extensive pretreatment and water conditioning and subsequent remineralization, so that the finished water that is now significantly different from the source water will not be overly aggressive to the piped distribution systems that it will pass through on the way to consumers.

In the course of treatment of fresh water, contaminants and some potentially beneficial nutrients will be removed and some might be added. Other waters, such as those treated by softening or membrane filtration may also undergo significant changes in their mineral content due to the treatment processes.

Remineralization and increasing alkalinity for the purpose of stabilizing and reducing corrosivity of water from which dissolved solids have been substantially reduced are often accomplished by use of lime or limestone. Sodium hydroxide, sodium bicarbonate, sodium carbonate, phosphates, and silicates are also sometimes used alone or in combination. The mineral composition of limestone is highly variable depending upon the quarry location and it is usually predominantly calcium carbonate, but it sometimes also contains significant amounts of magnesium carbonate along with numerous other minerals. Quality specifications exist in many countries for chemicals and materials including lime used in the treatment of drinking water. These specifications are intended to assure that drinking water treatment grade chemicals will be used and that their addition will not concurrently contribute significant levels of potentially harmful contaminants to the finished drinking water under foreseeable use conditions.

2. Scope of the Review

Several issues were examined relating to the composition of drinking water that has undergone significant treatment relevant to drinking water guidelines aimed at protecting and enhancing public health:

- What is the potential contribution of drinking water to total nutrition?
- What is the typical daily consumption of drinking water for individuals, considering climate, exercise, age etc.?
- Which substances are often found in drinking water that can contribute significantly to health and well-being?
- Under what conditions can drinking water be a significant contribution to the total dietary intake of certain beneficial substances?
- What conclusions can be drawn on the relationship between calcium, magnesium, and other trace elements in water and mortality from certain types of cardiovascular disease?
- For which substances, if any, can a case be made for supplementation of mineral content in treated reduced mineral content drinking water from the public health perspective?
- What is the role of fluoride in remineralized drinking water with respect to dental benefits and dental fluorosis, and skeletal fluorosis?

II. TOPICS EXAMINED IN THE MEETING

1. Drinking Water Consumption

It is important to understand water consumption patterns. The daily water volume ingested will also determine the consumption of any minerals that it contains. An individual's daily aqueous fluid ingestion requirement can be said to roughly equate to the obligatory water losses plus sweat/perspiration losses resulting from increased physical exertion and climate. WHO (2003) and others (ILSI 2004) have reviewed water consumption and hydration needs under a variety of conditions. Table 2.1 provides information on volumes of water required for hydration. An assumed water intake of 2 liters per day for adults is commonly used by WHO and regulators in computing drinking water guidelines and standards. Physical exertion, especially in extreme heat, can significantly increase water requirements. Sweat rates can reach 3 – 4 liters per hour, with variations in rate depending upon work/exercise intensity and duration, age, sex, training/conditioning, heat acclimatization, air temperature, humidity, wind velocity, cloud cover and, clothing. The US Army has estimated hourly water intake in relation to heat categories and has also concluded that liquid intake should not exceed 1.03 liters/hr or 11.35 liters/day. Persons under thermal and physiologic stress need to pay special attention to fluid and total salt (sodium chloride) intake, with salt requirements ranging from 2 to 4 grams per day in cool environments to 6 to 12 grams per day in very hot environments. Hyponatremia can be a fatal consequence of inadequate salt intake under those conditions.

Table 1. Volumes (liters/day) of Water Required for Hydration - Reference value estimates, WHO 2003

	Average Conditions	Manual Labor in High Temperature	Total Needs in Pregnancy/Lactation
Female Adult	2.2	4.5	4.8 (pregnancy) 3.3 (lactation)
Male Adult	2.9	4.5	
Children	1.0	4.5	

Humans ingest water as plain drinking water, water in other beverages, and water in food (inherent, and/or added during preparation) and they also obtain some water from metabolism of food. Approximately one third of the daily average fluid intake is thought to be derived from food. The remaining water requirement must be met from consuming fluids.

Availability, ambient temperature, flavor, flavor variety, beverage temperature, proximity of the beverage to the person, and even beverage container have all been shown to impact total intake. Cultural variations are also known to impact the types of beverages consumed. Obviously, the total daily intake of both potentially harmful contaminants and beneficial elements will be directly associated with the total amount and type of water that is being consumed.

2. Drinking Water as a Source of Essential Minerals

Some 21 mineral elements are known or suspected to be essential for humans. This number includes four that function physiologically as anions or in anionic groupings {chlorine as Cl⁻, phosphorus as PO₄⁻³, molybdenum as MoO₄⁻², fluorine as F⁻}, eight that function in their

simple cationic forms {calcium (Ca^{+2}), magnesium (Mg^{+2}), sodium (Na^{+}), potassium (K^{+}), ferrous iron (Fe^{+2}), copper (Cu^{+2}), zinc (Zn^{+2}), manganese (Mn^{+2})} and which are subject to chelation by either intact proteins or a variety of small, organic molecules; ions of two non-metals {iodine (I) and selenium (Se)} that function as constituents of covalent compounds (e.g., iodothyronine, selenocysteine) that are formed metabolically; and ions from five additional elements: boron (B), chromium (Cr), nickel (Ni), silicon (Si), vanadium (V)} the nutritional significance of which remain to be fully elucidated. Thus, fourteen mineral elements are established as being essential for good health; these elements in combined form affect bone and membrane structure (Ca, P, Mg, F), water and electrolyte balance (Na, K, Cl), metabolic catalysis (Zn, Cu, Se, Mg, Mn, Mo), oxygen binding (Fe), and hormone functions (I, Cr).

Health consequences of micronutrient deficiencies include increased morbidity, mortality due to reduced immune defense systems and impaired physical and mental development. Deficiencies of several mineral elements, particularly iron and iodine, are the basis of health problems in many parts of the world. Nearly 40% of the world's women are estimated to be anemic due, to a great extent, to poorly bioavailable dietary iron. Low intakes of Ca, and perhaps Mg, contribute to rickets in children and osteoporosis in women worldwide. Due to inadequate diets, many children are deficient in Fe, Zn, and Cu and other micronutrients especially in developing countries. One third of the world's children fail to reach their physical and mental potentials and many are made vulnerable to infectious diseases that account for half of all child deaths. Nearly 750 million people have goiter or myxedematous cretinism due to iodine deficiency, and almost 2 billion people have inadequate iodine nutrition. These nutritional deficiencies decrease worker productivity and increase the rates of disease and death in adults. Many result from diets that may also involve insufficient intakes of Cu, Cr and B. In developed countries changing dietary patterns such as reduced milk consumption may predispose to conditions like osteoporosis.

Drinking water supplies may contain some of these essential minerals naturally or through deliberate or incidental addition. Water supplies are highly variable in their mineral contents and, while some contribute appreciable amounts of certain minerals either due to natural conditions (e.g., Ca, Mg, Se, F, Zn), intentional additions (F), or leaching from piping (Cu), most provide lesser amounts of nutritionally - essential minerals. Many persons consume mineral waters because of the perception that they may be more healthful.

The enteric absorption of minerals from drinking water is determined by several factors including the intrinsic properties of particular chemical species that are present, physiological conditions of the gut environment, and exogenous factors related to the meal/diet in which the minerals are ingested. Accordingly, waterborne selenium (selenite, selenate) is passively absorbed at somewhat lower efficiencies (60-80%) than the selenoaminoacids in foods (90-95%) that are actively transported across the gut. The inorganic oxidized iron in water will be absorbed at very low (<5%) efficiencies similar to that of non-heme iron in plant foods. Mineral absorption is also subject to age-related declines in efficiency (Cu, Zn), early post-natal lack of regulation (Fe, Zn, Cr), adaptive increases in efficiency by receptor up-regulation during periods of deficiency (Fe, Zn, Cu, Mn, Cr), dependence on other co-present nutrients for metabolism (Se-I, Cu-Fe), and to anabolic and catabolic effects on tissue sequestration (Zn, Se, Cr).

Minerals in water are subject to most of the same determinants of bioavailability that affect the utilization of those minerals in foods. For example, phytate, phosphorus and triglycerides can each reduce the luminal solubility and, hence, the absorption of calcium. Phytate and other non-fermentable fiber components can bind Fe, Zn, Cu and Mg, and sulfides can bind Cu, reducing the absorption of each. Minerals that share transporters can be mutually inhibitory (SO_3^{2-} vs. SeO_3^{2-} ; Ca^{+2} vs. Zn^{+2} ; Cd^{+2} vs. Zn^{+2} ; Zn^{+2} vs. Cu^{+2}). In contrast, the bioavailability of the divalent cations (Ca^{++} , Fe^{++} , Cu^{++} , Zn^{++}) can be enhanced by certain chelating substances (e.g., unidentified factors in meats, ascorbic acid) that promote their enteric absorption, and by

certain pro-biotic factors (e.g., inulin and other fructo-oligosaccharides) that promote their hind gut absorption. In general, poor bioavailability can be expected of water-borne iron consumed with plant-based diets containing phytates and/or polyphenols and a few promotor substances. Similarly, waterborne calcium will be poorly utilized when consumed with oxalate-containing vegetables (amaranth, spinach, rhubarb, beet greens, chard); and water-born Ca, Fe, Mg, P or Zn will be poorly utilized when consumed with foods/diets high in unrefined, unfermented cereal grains or high phytate soy products. This complexation between calcium and oxalate in the gut could reduce the potential for kidney stone formation. The typical bioavailability and occurrence of these minerals is summarized in Table 2.

The potential contributions of drinking water to nutritional status also depend on water consumption, which is highly variable depending on both behavioral factors and environmental conditions. Individuals with the greatest relative consumption of water include infants, residents in hot climates, and individuals engaged in strenuous physical activity.

Table 2. Typical Bioavailability and Occurrence of Nutritionally Important Minerals in Drinking Water

Bioavailability	Occurrence	
	Moderate Amounts in Some Supplies	Low Amounts in Most Supplies
High	Se* Na Cl F	P K* Mo I* B*
Moderate/Variable	Ca* Mg* Cu* Zn*	Mn
Low	Fe*	Cr

*sub-optimal consumption and/or prevalent deficiency in at least some countries

With all of these considerations in mind, the nutrients sometimes found in drinking water at potentially significant levels of particular interest are:

- Calcium – important in bone health and possibly cardiovascular health
- Magnesium – important in bone and cardiovascular health
- Fluoride – effective in preventing dental caries
- Sodium – an important extracellular electrolyte, lost under conditions of excess sweat
- Copper – important in antioxidant function, iron utilization and cardiovascular health
- Selenium – important in general antioxidant function and in the immune system
- Potassium is important for a variety of biochemical effects but it is usually not found in natural drinking waters at significant levels.

3. Infants and Neonates

The needs of water and essential minerals in infancy and childhood are increased compared to adults in relation to body weight. The highest intake per body weight water volume is needed in the neonate and it decreases with age. Special situations require additional water intake, e.g.

premature or low birth weight infants or diarrhoeal disease. The elderly and infirm often do not consume sufficient water or other fluids and can become dehydrated with significant adverse health consequences (WHO 2003)

The WHO Global Strategy on Infant and Young Child Feeding promotes exclusive breastfeeding in the first six months of life. If this is not feasible, it may be necessary to consider feeding formula. Variable mineral content of drinking water used to reconstitute feeding formula will result in variability in the mineral content of formula milk. Some types of water may not be suitable for use in the reconstitution of infant formula due either to deficiency of appropriate minerals or to the presence of excess salts that may be harmful to infants and young children. Sodium is a good example since the requirement of infants for sodium is low.

Formula-fed infants are also a group at risk for excess intake of potentially toxic elements in drinking water, e.g. excess copper or lead leaching from copper or lead pipes associated with highly corrosive water. In the latter case not using 'first draw' water for formula preparation, by allowing the tap water to run to waste for a short time, would usually significantly reduce the metal content in the water if the lead is derived from lead-containing brass faucet fixtures or from lead soldered pipe joints. Lead services or lead pipe require other actions. Remineralization/stabilization of demineralized water for drinking water supply should take into account the special requirements of infants and children, including calcium, magnesium, and other minerals based upon regional dietary composition.

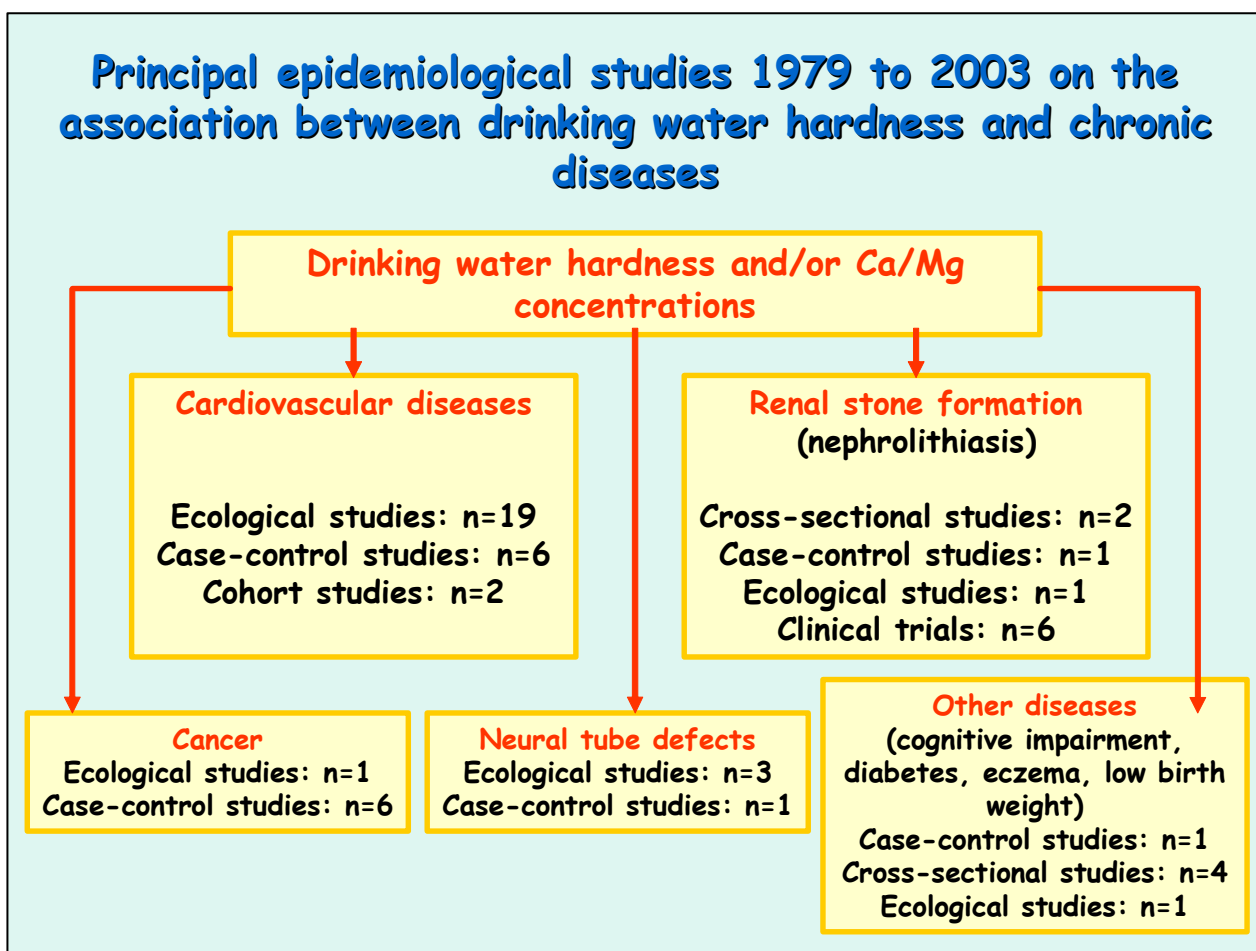
III. DRINKING WATER AND HEALTH RELATIONSHIPS

1. Water Hardness and Cardiovascular Disease: Epidemiological studies of water hardness, Ca and/or Mg, and CVD risks

More than 80 observational epidemiological studies were collected from the worldwide literature published since 1957 which related water hardness and cardiovascular disease risks (see Calderon and Monarca papers and Table 3.1 for partial summaries). These studies were conducted in more than 17 countries, primarily in North America, Europe, and Japan. Most of the studies summarized in this report were published in peer reviewed English-language scientific journals, and some were translated from eastern european literature.

Most, but not all, of the studies found an inverse (protective) association between cardiovascular disease mortality and increased water hardness (measured by calcium carbonate or another hardness parameter and/or the calcium and magnesium content of water). The associations were reported in numerous countries, and by many different investigators, with different study designs. Both population and individual-based studies have observed benefits. The most frequently reported benefit was a reduction in ischemic heart disease mortality. The strongest epidemiologic evidence for beneficial effects was for drinking water magnesium concentrations; there was also evidence - but not as strong - for drinking water calcium concentrations. In addition, there is supporting evidence from experimental and clinical investigations suggesting a plausible mechanism of action for calcium and magnesium. The potential significance of the epidemiological findings is that beneficial health effects may possibly be extended to large population groups on a long-term basis by simple adjustments the water quality.

Figure 1. Principal epidemiological studies 1979-2003



Several intervention and clinical studies (which were not specifically included in this report) for magnesium and also calcium indicate that they may be effective in reducing blood pressure in hypertensive individuals. Magnesium exerts multiple cellular and molecular effects on cardiac and vascular smooth muscle cells, which could be a plausible basis to explain its protective action. Several medical treatment studies involving infusion of magnesium after a cardiac event have had mixed results, but in one example treatment of suspected myocardial infarction cases with intravenous magnesium salts reduced mortality due to arrhythmia and infarction thirty days post therapy. Other controlled human consumption studies have measured physiological differences when comparing persons on low and higher magnesium diets.

2. Studies of other water constituents

Other micronutrients and trace element nutrition studies have not been extensively examined in this review, but nutritional studies suggest that some may have an indirect or direct beneficial role associated with their presence in drinking water. However, a recently published study in Finland suggested that iron and copper in drinking water may be associated with increased risks of heart attack. On the other hand, it has been suggested that the apparent benefits associated with consumption of hard water might also be explainable as an indirect consequence of lower corrosivity compared to soft water, thus reducing human exposures to metals extracted from the pipe and fixtures. More studies are needed to better understand the possible risks and benefits of these essential and other trace elements found in water and the conditions of water exposure.

3. Discussion

Hard water is a dietary source of calcium and sometimes magnesium, although the absolute and relative concentrations will vary greatly by source and the water consumption levels. Consumption of moderately hard water containing typical amounts of calcium and magnesium may provide an important incremental percentage of the daily dietary requirement. Inadequate total dietary intakes of calcium and magnesium are common worldwide, therefore, an incremental contribution from drinking water can be an important supplement to approach more ideal total daily intakes. It has also been suggested that hard water can reduce the losses of calcium, magnesium and other essential minerals from food during cooking. If low mineralized water were used for food and beverage production, reduced levels of Ca, Mg, and other essential elements would also occur in those products. Low intakes would occur not only because of the lower contribution of these minerals from water used in beverages, but also possibly because of higher losses of the minerals from food products (e.g., vegetables, cereals, potatoes or meat) into water during cooking.

Most of the reported epidemiology studies are of the less precise ecological type, but there are also several cohort and case control studies. Based upon the studies that have been reviewed, the meeting concluded that on balance there is sufficient epidemiological and other biological evidence to support the hypothesis of an inverse relationship between magnesium and possibly calcium concentrations in drinking water and (ischemic) cardiovascular disease mortality.

There are no known harmful human health effects in the general public associated with the consumption of calcium and magnesium within a large range, and the nutritional essentiality of calcium and magnesium is well known. In addition, limited but suggestive evidence exists for benefits associated with other diseases (stroke, renal stone formation, cognitive impairment in elderly, very low birth weight, bone fractures among children, pregnancy complications, hypertension, and possibly some cancers). The suggestion is that reintroduction of magnesium and calcium into demineralized water in the remineralization process would likely provide health benefits in consumer populations. Adding calcium and magnesium carbonates (as lime or limestone) to the demineralized water is a common water stabilization practice and is relatively inexpensive. The increased daily intake of those elements from that source does not require individual behavioural change, and it is already done as part of many water treatment processes.

Epidemiological studies in the United Kingdom, United States, Sweden, Russia, and France and research on changes in calcium/phosphorus metabolism and bone decalcification provide information about drinking water levels of calcium and magnesium (and water hardness) that may provide beneficial health effects. Several authors have suggested that reduced cardiovascular mortality and other health benefits would be associated with minimum levels of approximately 20 to 30 mg/l calcium and 10 mg/l magnesium in drinking water. The percentage of the recommended daily allowance of calcium and magnesium provided by drinking water at these minimum levels will vary among and within countries. Thus, lower concentrations in water may be sufficient to provide health benefits in some areas, but higher levels may be beneficial in others. Overall health benefits would be dependent upon total dietary intakes and other factors in addition to water concentrations. Because the exposure-response information is limited, further analyses, and possibly additional studies, are needed to determine the levels of calcium and magnesium that may provide most favorable population benefits in each location.

4. Fluoride in Remineralized Drinking Water

Most drinking waters contain some fluoride. Fluoride is present in seawater at concentrations of about 1.2 to 1.4 mg/l, in groundwater at concentrations from nil to about 67 mg/l, and in surface waters sometimes at concentrations as low as 0.1 mg/litre or less. The

amount of fluoride in treated drinking water is also affected by treatment processes such as anion exchange that will remove it along with the target contaminant (e.g. arsenic). Demineralization and some other treatment processes will also remove fluoride.

Very high levels of excess fluoride intake cause crippling skeletal fluorosis which is almost always associated with high fluoride intake from drinking water. This is a significant irreversible health problem in parts of India, China and Africa, for example. Ingestion of excess fluoride during tooth development, particularly at the maturation stage, may also result in dental fluorosis; these effects may also be mitigated by co-exposure to some minerals such as calcium or magnesium. Mild dental fluorosis presents as barely detectable whitish surface striations in which the enamel is fully functional. As the excess intake of fluoride increases the severity of dental fluorosis also increases. Severely fluorosed enamel is more prone to wear and fracture, and may present as pitted, darkly stained and porous enamel.

Fluoride intake has been known for the past 50 to 60 years to play a beneficial role in dental health; there is some evidence that it may be beneficial for bone formation, but this has not been proven. The optimal drinking water concentration of fluoride for dental health is generally between 0.5 to 1.0 mg/litre and depends upon the volume of drinking water consumed and the uptake and exposure from other sources. These values are based on epidemiological studies conducted over the past 70 years in communities in many countries with natural and added fluoride in their drinking water. In this concentration range the maximum caries preventative effect is achieved while minimizing the levels of dental fluorosis. The WHO drinking-water guideline value for fluoride is 1.5 mg/l. The US Environmental Protection Agency has set a Maximum Contaminant Level of 4.0 mg/l in the U.S. based upon prevention of crippling skeletal fluorosis in its climate, and a guidance level of 2.0 mg/l to avoid moderate to severe dental fluorosis. The prevalence of dental and skeletal fluorosis will also be influenced by inhalation exposure to fluoride from other sources such as burning high fluoride coal (e.g. in parts of China), other dietary sources, and total water consumption. Other water factors, such as lack of calcium and magnesium may possibly also exert some influence.

Dental caries (tooth decay) is the result of an interaction on the tooth surface between certain bacteria in the mouth and simple sugars (e.g. sucrose) in the diet. The level of oral hygiene care and habits of the community, including the use of fluoridated toothpaste, dental treatment such as the topical application of fluoride, and consumption of fluoridated water are major factors contributing to reduction of caries incidence. Dietary sugar intake is a significant contributing tooth decay factor. Communities in which sugar intake is low (less than approximately 15 kg per person/year) will usually have a low risk for dental caries, while communities in which sugar intake is high (greater than approximately 40 kg per person/year) will be at high risk.

Where the risk for skeletal and dental fluorosis is high as a consequence of excess fluoride intake from drinking water, fluoride levels in drinking-water should be reduced to safe levels, or a lower - fluoride source used, especially for young children, and control of significant non-ingestion/inhalation exposures. Where the aggregate risk factors for dental caries are low (and are remaining low) consuming low fluoride water would probably have little or no impact on dental caries, but to guard against possible net loss of fluoride from the skeleton, the meeting participants felt that consideration should be given to maintaining a baseline level of 0.1 to 0.3 mg/l.

Where caries risk is high or increasing authorities may consider addition of fluoride to the demineralized public water supply up to in the range of the WHO GDWQ level of 1.5 mg/l, preferably adjusted to water consumption rates; however, other factors must also be considered. For example, in countries such as those in Scandinavia, where public dental awareness is very high and alternative vehicles for fluoride (e.g. fluoridated toothpaste) are widely available *and*

widely used, a decision to not fluoridate the water, or remove fluoride, or to supply drinking water with suboptimal levels of fluoride would likely be of little consequence. On the other hand in developing and developed countries where public dental health awareness in some population groups (e.g. lower income) might be much lower, water containing either natural or added fluoride at concentrations of 0.5 to 1.0 mg/l would be important for dental health. Some countries use fluoridated table salt as a means of supplementing fluoride in deficient areas. A decision to use demineralized water as a drinking water source without addition of fluoride during remineralization will depend upon: the concentration of fluoride in the existing local supply, the volume of water consumed, the prevalence of risk factors for dental caries (including sugar consumption data), oral hygiene practices and dental care, the level of public dental health awareness, and the presence of alternative vehicles for fluoride intake available to the whole population.

IV. CONCLUSIONS AND RECOMMENDATIONS

The meeting participants concluded that:

- On balance, the hypothesis that consumption of hard water is associated with a somewhat lowered risk of CVD was probably valid, and that magnesium was the more likely contributor of those benefits.
- Stabilization of demineralized and corrosive drinking water should be done where possible with additives that will increase or reestablish calcium and magnesium levels. The general public and health professionals should have access to information on the composition of community supplies and bottled water. Water bottlers may also consider providing some waters with mineral compositions that are beneficial for population segments.
- Unless properly stabilized, demineralized and some natural waters are corrosive to plumbing resulting in damage to the plumbing systems, and also in potentially increased exposure to metals such as copper and lead. Properly stabilized water should be provided by suppliers, and appropriate plumbing materials should be used.
- There is a need for more precise data on the impact of fluid composition and intake, including water and other aqueous beverages, on nutrient intake under a broader range of physiologic and climatic conditions for sensitive population segments in order to more precisely evaluate the importance of minerals in drinking water on mineral nutrition.
- Additional studies should be conducted on potential positive or negative health consequences associated with consumption of both high and low total dissolved solids content waters in addition to consideration of water hardness. Investigators should consider exposures to both calcium and magnesium levels in addition to other minerals and trace elements that may be present in hard and soft waters and in softened waters.
- Information should be provided on methods of application of home water softening devices so that consumers can also have access to mineralized water for drinking and cooking.
- Chemicals such as lime used in the treatment of drinking water should be assured to be of suitable quality for that application so as not to contribute unacceptable amounts of potentially harmful chemicals to the finished water.
- Investigators may take advantage of natural experiments (communities changing water sources and treatment) to conduct population intervention studies to evaluate potential health impacts. For example, studies could compare communities before and after changing source waters, or the introduction of treatment technologies that significantly change water composition.
- Water utilities are encouraged to periodically analyse their waters for calcium, magnesium, and trace elements. This would be helpful in assessing trends and conducting future epidemiologic studies.

- Studies on the mineral nutritional content and adequacy of world diets should be conducted so that adequacies and inadequacies can be documented and possibly mitigated.
- Studies on the mineral nutritional content and adequacy of world diets should be conducted so that adequacies and inadequacies can be documented and possibly mitigated.
- Studies should evaluate a number of potentially relevant health outcomes (e.g., renal stone formation, CVD, hypertension incidence, osteoporosis, stroke, mineral balance, mineral nutritional deficiencies). Exposure assessments should include analyses for calcium, magnesium, and trace elements.
- Studies should evaluate the issue of whether there are adverse health consequences associated with consumption soft corrosive water due to extraction of metals from pipe. There should also be additional studies to determine whether and how softened waters differ in that respect from soft waters.
- Clinical trials of people at high risk of heart attacks and other illnesses such as osteoporosis , should be conducted to assess the potential benefits of mineral supplementation. Results of previous studies have been inconsistent.
- In the revisions of the Guidelines for Drinking-water Quality, WHO should consider the beneficial roles of nutrient minerals including water hardness characteristics.
- This subject is of such potential general public health significance that a detailed state-of-the-art review should be prepared prior to consideration in the next revision of the WHO Guidelines for Drinking Water Quality.

References

1. Calderon, R. and G. Craun, Water Hardness and Cardiovascular Disease: A Review of the Epidemiological Studies 1957-78.
2. Cotruvo, J.A., Desalination Guideline Development for Drinking Water.
3. Craun, G.F., and R. Calderon, How to Interpret Epidemiological Associations.
4. Donohue, J.M., Abernathy, C.O., Lassovszky, P. and G Hallberg. The Contribution of Drinking Water to Total Dietary Intakes of Selected Trace Mineral Nutrients in the USA.
5. Frost, F., Studies of Minerals and Cardiac Health in Selected Populations.
6. Grandjean, A., Water Requirements, Impinging Factors and Recommended Intakes. ILSI North America, Hydration: Fluids for Life, 2004, Monograph Series.
7. Klevay, M. and G.F. Combs Jr., Mineral Elements Related to Cardiovascular Health.
8. Kozisek, F., Health Risks from Drinking Demineralized Water.
9. Lennon, M.A., Whelton, H., O'Mullane, D. and L. Ekstrand, Fluoride.
10. Monarca, S., Zerbini, I. and F. Donato, Drinking Water Hardness and Cardiovascular Diseases: A Review of Epidemiological Studies 1979-2004.
11. Olivares, M. and R. Uauy, Nutrient Minerals in Drinking Water: Overview.
12. Ong, C.N., Minerals from Drinking Water: Bioavailability for Various World Populations and Health Implications.
13. Sievers, E., Nutrient Minerals in Drinking Water: Implications for the Nutrition of Infants and Young Children.
14. WHO 1999, Fluoride in Drinking Water. WHO/WSH/Draft99.4, Geneva 1999.
15. WHO 2003, Howard G. and J. Bartram, Domestic Water Quantity, Service Level and Health, WHO/SDE/WSH/3.02.
16. WHO 2004, Nutrient Minerals in Drinking Water and the Potential Health Consequences of Long-Term Consumption of Demineralized and Remineralized and Altered Mineral Content Drinking Waters, WHO/SDE/WSH/04.01.

2.

DESALINATION GUIDELINES DEVELOPMENT FOR DRINKING WATER: BACKGROUND

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I. INTRODUCTION

Desalination is an important and rapidly growing source of drinking water in the world originating from sea water or brackish water. The mineral composition of the water is significantly altered and then partially reconstituted to achieve a stable product that can be distributed in pipes. This water differs from natural waters in the sense that it's composition is controllable whereas natural waters vary over a very wide range of composition that is a matter of geology and chance. A logical question is whether the ultimate composition of this and other 'manufactured' water may have some positive or negative impact on the health of long-term consumers. The purpose of the World Health Organization Nutrition Meeting described in this volume was to explore those questions ultimately leading to recommendations to WHO as it addresses them in Desalination Guidance and in the Guidelines for Drinking Water Quality. In this introductory chapter background information is provided on water treatment and desalination technology and its context in world water production.

By 1999, more than 11,000 desalination plants were in operation throughout the world producing more than 20 million cubic meters (roughly six billion US gallons) of water per day. About 63% of the capacity exists in West Asia and the Middle East. North America has about 11% and North Africa and Europe account for about 7% each of capacity. Plant sizes and designs range from more than 500,000 m³/day down to 20 to 100 m³/day, and low pressure products can produce as little as a few liters per day for home point-of-use applications. By the end of 2001 a total of 15,233 large desalting units had been installed or contracted providing a total capacity of 32.4 million m³/day.

Most desalination plants use seawater or brackish water as their sources. It appears that comprehensive performance, operating and product quality specifications have evolved virtually on a site-by-site basis relative to source and the specific end product water use. Most drinking water applications outside of North America use World Health Organization Drinking Water Guidelines in some way as quality specifications. WHO Drinking Water Guidelines cover a broad spectrum of contaminants from inorganic and synthetic organic chemicals, disinfection byproducts, microbial indicators and radionuclides. They are aimed at typical drinking water sources and technologies. Because desalination is applied to non-typical source waters, and often uses non-typical technologies, existing WHO Guidelines may not fully cover the unique factors that can be encountered during production and distribution of desalinated water.

II. DRINKING WATER PRODUCTION

Drinking water production processes can be divided into three broad categories each of which will impact the quality of the finished water received by the consumer.

1. Source Water Quality
2. Treatment Technology
3. Distribution

Some of the factors and issues that distinguish desalination processes from most typical drinking water operations are as follows:

1. Source Water Quality (Tables 1, 2)

- Total Dissolved Solids as high as about 40,000 ppm.
- High levels of specific metals and salts including sodium, calcium, magnesium, bromides, iodides, sulfates, chlorides.

Table 1. Major Elements of Seawater

Element	Concentration (mg/L)	Element	Concentration (mg/L)
Oxygen	8.57 x 10 ⁺⁵	Molybdenum	0.01
Hydrogen	1.08 x 10 ⁺⁵	Zinc	0.01
Chlorine	19000	Nickel	0.0054
Sodium	10500	Arsenic	0.003
Magnesium	1350	Copper	0.003
Sulfur	885	Tin	0.003
Calcium	400	Uranium	0.003
Potassium	380	Chromium	0.0003
Bromine	65	Krypton	0.0025
Carbon	28	Manganese	0.002
Strontium	8.1	Vanadium	0.001
Boron	4.6	Titanium	0.001
Silicon	3	Cesium	0.0005
Fluoride	1.3	Cerium	0.0004
Argon	0.6	Antimony	0.00033
Nitrogen	0.5	Silver	0.0003
Lithium	0.18	Yttrium	0.0003
Rubidium	0.12	Cobalt	0.00027
Phosphorus	0.07	Neon	0.00014
Iodine	0.06	Cadmium	0.00011
Barium	0.03	Tungsten	0.0001
Aluminum	0.01	Lead	0.00005
Iron	0.01	Mercury	0.00003
Indium	<0.02	Selenium	0.00002

Table 2. Ionic Composition of Seawater (mg/L)

Constituent	Typical Seawater	Eastern Mediterranean	Arabian Gulf At Kuwait	Red Sea At Jeddah
Chloride (Cl ⁻)	18,980	21,200	23,000	22,219
Sodium (Na ⁺)	10,556	11,800	15,850	14,255
Sulfate (SO ₄ ⁻²)	2,649	2,950	3,200	3,078
Magnesium (Mg ⁺²)	1,262	1,403	1,765	742
Calcium (Ca ⁺²)	400	423	500	225
Potassium (K ⁺)	380	463	460	210
Bicarbonate (HCO ₃ ⁻)	140	~	142	146
Strontium (Sr ⁻²)	13	~	~	~
Bromide (Br ⁻)	65	155	80	72
Boric Acid (H ₃ BO ₃)	26	72	~	~
Fluoride (F ⁻)	1	~	~	~
Silicate (SiO ₃ ⁻²)	1	~	1.5	~
Iodide (I ⁻)	<1	2	~	~
Other	1	~	~	~
Total Dissolved Solids	34,483	38,600	45,000	41,000

~ not reported

2. Total Organic Carbon types:

- Petroleum contamination potential
- Microbial contaminants and other organisms

3. Treatment

- Reverse Osmosis membranes and Distillation
- Leachates from system components
- Pretreatment and antifouling additives
- Disinfection byproducts
- Blending with source waters

4. Distribution

- Corrosion control additives
- Corrosion products
- Bacterial regrowth in distribution networks

Other issues of interest include:

- Whether any risks are imparted from consumption of low TDS water either from general reduced mineralization or reduced dietary consumption of specific minerals.
- Environmental impacts of desalination operations and brine disposal.
- Performance of specific technologies particularly for microbial control
- Bacterial regrowth during distribution especially in warm/hot climates
- Whether microorganisms unique to saline waters may not be adequately controlled by the desalination process or post disinfection.
- Monitoring of source water, process performance, finished water and distributed water to assure consistent quality at the consumer's tap.
- Whether additional water quality guidelines specific to desalination are needed.
- Whether short-term Health Advisory guidelines would be needed to deal with short-term excursions from chronic guidelines caused by system upsets.
- Whether membrane water softening (including home applications) should be included as a subtopic in this WHO assessment.

III. DESALINATION TECHNOLOGIES

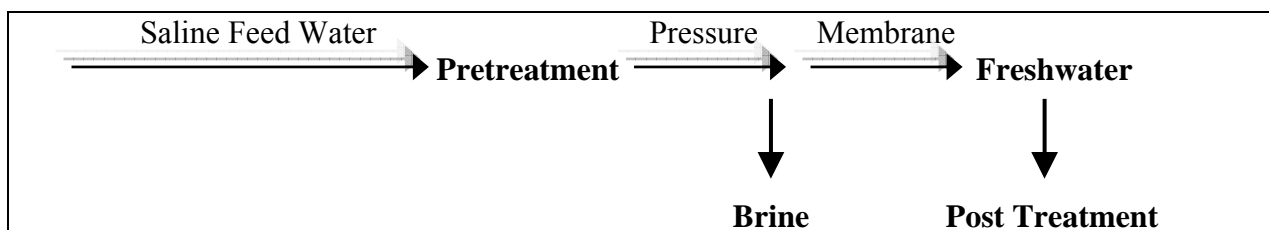
Following is a brief overview of several common desalination technologies. Desalination processes remove dissolved salts and other materials from seawater and brackish water. Related processes are also used for water softening and wastewater reclamation. The principal desalination technologies in use are reverse osmosis (RO), and distillation. Electrodialysis and vacuum freezing also have some applications.

Reverse Osmosis (RO)

Reverse osmosis systems reverse the natural process that is driven by osmotic pressure of solvent transport across a semi-permeable membrane from a region of lower solute concentration into one of higher solute concentration so as to equalize the free energies. In RO external pressure is applied to the high solute (concentrated) water to cause solvent (water) to migrate through the membrane pores leaving the solute (salts and other non permeates) in the more concentrated brine. The membrane provides a form of “hyperfiltration” by restricting passage of many substances. Some membranes will reject 99% of all ionic solids and commonly have molecular weight cut off as low as 50 to 100 Daltons. The mechanisms of salts removal by RO membranes are not fully understood, and some salts (e.g. borate, arsenite) are not removed with high efficiency. Some believe the pure water preferentially passes through the membrane, while others believe that surface charges on the membrane polymer affect the polarity of the water. Increased pressure increases the rate of permeation, however fouling would also increase.

Figure 1 illustrates the basic RO process that includes Pretreatment, Membrane Transport, and Post Treatment prior to distribution. RO processes can produce water in the range of 10 to 500 ppm TDS.

Figure 1.



Pretreatment

Feedwater is treated to protect the membranes and to facilitate membrane operation. Suspended solids are removed by filtration, pH adjustments (lowering) are made to protect the membrane and control precipitation of salts; antiscaling inhibitors are added to control calcium carbonates and sulfates. Iron, manganese (e.g. as hydroxides) and some organics also cause fouling of the membrane. A disinfectant is added to control biofouling of the membrane. Disinfection can involve chlorine species, ozone or UV light and other agents. Marine organisms, algae and bacteria must be eliminated, and when ozone or chlorine are used they should be neutralized prior to contact with the membrane.

IV. MEMBRANES

Common membranes are polymeric materials such as cellulose triacetate or polyamides and polysulfones. Selection factors for membranes include pH stability, working life, mechanical strength, pressurization capacity and selectivity for solutes. Membranes are located in a module and they can be configured as hollow fiber, spiral, plate, and tubular. Each has its own characteristics that affect selection in particular cases. Spiral wound configurations generally have more favorable operating characteristics of performance relative to cost and they are most commonly used. Operating pressures are in the range of 250 – 1000 psi (17 to 68 atm). Membranes are typically layered or thin film composites. The surface contact layer (rejection layer) is adhered to a porous support, which can be produced from the same material as the surface. Thin film membranes can be made by polymerization of the rejection layer to the surface of the porous support. Membrane thicknesses are on the order of 0.05 mm.

Post Treatment

Product water must be treated to stabilize it and make it compatible with the distribution system. Adjustment of pH to approximately 8 is required and addition of corrosion inhibitors like polyphosphates may be necessary. Carbonation or other chemicals may be applied, or blending with source water may be done to increase TDS and stabilize the water. Post disinfection is also necessary to control microorganisms during distribution, as well as to eliminate pathogens from the blending process. Degasification may also be necessary.

V. DISTILLATION TECHNOLOGIES

Principal distillation (vaporization → condensation) systems include Multistage Flash (MSF) distillation, Multiple Effect Distillation (MED) and Vapor Compression Distillation (VCD). Distillation plants can produce water of about 1 to 50 ppm TDS.

In distillation processes source water is heated and vaporized (illustrated in Figure 2) and the condensed vapor has very low TDS, while the concentrated brine is produced as a residual. Low theoretical plate distillation processes can be applicable to desalination because significant amounts of volatile chemicals are usually not present in seawater and brackish waters. Inorganics, salts and high molecular weight natural organics are non volatile and thus easily separated, however there are circumstances where volatile petroleum chemicals are present due to spills and other source water contamination. Even though their vapor pressures can range from low to very high, many of them of higher molecular weight can be steam distilled in a physical process where the vapor pressure of the steam and the vapor pressures of the organic chemicals together contribute to the total vapor pressure of the mixture. In addition, some physical entrainment may also allow low volatility substances to be carried over into the distillate. For water, the boiling point (where the vapor pressure of the liquid is the same as the external pressure) is 100°C

(212°F) at 1 atmosphere (760 mm Hg or 14.7 pounds per square inch). Boiling temperature is a colligative property of solutions; as the concentration of solute increases the boiling point increases and as the pressure is decreased, the boiling temperature decreases.

Figure 2.



The amount of energy required to vaporize a liquid is called the heat of vaporization. For water, this amounts to 2,256 kilojoules per kilogram at 100°C (970 Btu per pound at 212°F). The same amount of heat must be removed from the vapor to condense it back to liquid at the boiling point. In desalination processes, the heat generated from vapor condensation is transferred to feed water to cause its vaporization and thus improve the thermal efficiency of the process and reduce cost and fuel consumption.

Multistage Flash Distillation (MSF)

MSF plants are major contributors to desalting capacity. The principle of MSF distillation is that heated water will boil rapidly (flash) when the pressure of the vapor is rapidly reduced below the vapor pressure of the liquid at that temperature. The vapor that is generated is condensed on to surfaces that are in contact with feed water, thus heating it prior to its introduction into the flash chamber. This will recover most of the heat of vaporization. Approximately 25 to 50% of the flow is recovered as fresh water in multistage plants. Characteristics of MSF plants include high feed water volume and flow, corrosion and scaling in the plant, and high rates of use of treatment chemicals.

Multiple Effect Distillation (MEF)

Several configurations of MEF plants exist including vertical and horizontal tubes. In all cases steam is condensed on one side of a tube causing evaporation of saline water on the other side. Pressure is reduced sequentially in each effect (stage) as the temperature declines, and additional heat is provided in each stage to improve performance. Scale formation and removal seem to be less problematic in vertical tube vs. horizontal tube units.

Vapor Compression Distillation (VCD)

VCD systems do not use steam heat and function by compressing water vapor causing condensation on a heat transfer surface (tube) that allows the heat of condensation to be transported to brine on the other side of the surface resulting in vaporization of water. The principal energy requirement is in the operation of the compressor. The compressor functions to increase the pressure on the vapor side and lower the pressure on the feed water brine side to lower its boiling temperature.

Maintenance

Periodic cleaning is required to remove scale and salts deposits from pipes, tubing and membranes. Alkaline cleaners remove organic fouling and acid cleaners are used to remove scale and salts.

VI. OTHER SYSTEMS

Electrodialysis processes utilize selective membranes that contain cation and anion exchange groups. Under a direct current electric field, cations and anions migrate to the respective electrodes so that ion-rich and ion-depleted streams form in alternate spaces between membranes. Reversal of electric fields reduces scaling and flushes the membranes. Pretreatment is required to

control scale and extend membrane life and to prevent migration of non-ionized substances such as bacteria and organics and silica.

VII. POTENTIAL TECHNICAL ISSUES ASSOCIATED WITH DESALINATION

Health Issues

In general, it is assumed that food is the principal source of nutrients and hazardous substances exposures for humans. Water can also be a source of beneficial dietary substances, as well as harmful contaminants including chemicals and microorganisms that can mitigate dietary components. Presence or absence of beneficial ions can affect public health in the population over the long term, just as the presence or absence of toxicants. Water components can supplement dietary intake of trace micronutrients and macronutrients or contribute undesirable contaminants. As is usual in toxicology and nutrition, the line between health and illness in a population is not a single line but rather a matter of optimal intake, versus adequate intake, versus intake that is inadequate to maintain good health, versus a toxic intake that will lead to frank illness in some segment of the population. Some parts of the population such as young children, pregnant women, the aged and infirm, and the immune compromised can be more sensitive than the typical healthy adult to essential and hazardous dietary components. In many cases the specific requirements for optimal health states and minimal risk are not understood for these high-risk segments of the population, so generalizations must often be the basis for public health decisions.

Some of the chemicals of interest in drinking water include calcium, magnesium, sodium, chloride, lead, selenium, potassium, bromide, iodide, fluoride, chromium, and manganese. Typical fresh waters vary widely in their ionic composition. Seawater is rich in ions such as sodium, chloride, magnesium, calcium, bromide and iodide, but low in some essential ions like zinc, copper, chromium and manganese. Desalination processes significantly reduce virtually all of the ions in drinking water to the point that people who traditionally consume unreconstituted desalinated or distilled water may be consistently receiving smaller amounts of some nutrients compared to people who consume water from some more traditional sources and thus are disadvantaged if their diets do not provide sufficient intake. Since desalinated water is often stabilized by addition of lime and blending, some of these ions will be replenished in that process depending upon the techniques that are utilized.

Calcium/Magnesium/Cardiovascular Disease

Over about 50 years, a body of epidemiology work especially in UK, USA, Canada and Scandanavia has fairly consistently suggested that some types of cardiovascular disease mortality rates in many communities are inversely proportional to the hardness of the water supply. Calcium and magnesium are the principal components of hard water so many researchers have concluded that calcium and particularly magnesium may have a protective effect. There are biochemical arguments that can be raised in support of the hypothesis, however the issue is not resolved with absolute certainty. More recent studies seem to be finding greater positive effects from magnesium rather than calcium intake particularly in regard to reduced risk from stroke or ischemic heart disease.

Some researchers have argued that softening effects also reduce trace nutrients and increase sodium (via ion exchange) in drinking water or that there is a negative health effect from decreased mineralization (total of dissolved salts and electrical conductivity changes). Others argue that demineralized water is more aggressive to piping, and thus increased risks could be caused by exposure to extracted trace elements like lead and cadmium. Some studies have indicated that cooking foods in demineralized water increases the depletion of essential minerals from the foods, thus potentially adversely affecting health.

The health significance of these hypothesized relationships with drinking water in any given population would be highly dependent upon many factors including diet, lifestyle, smoking, population genetics, occupation and other confounders.

Trace Nutrients

In general, drinking water has not been relied upon as a contributor of significant trace nutrients to daily intake, but rather as a serendipitous supplement whenever it occurs. The geographic and geologic distribution of the nutrients in drinking water will be varied and inconsistent so an appropriate diet should be the principal source.

Dietary supplementation is, however, widely practiced for general benefit e.g., Vitamin D in milk, Vitamin C in drinks, iron and B Vitamins and folic acid in bread. The principal therapeutic substance added to drinking water in some areas is fluoride. For fluoride the intent is to strengthen dental enamel and reduce the incidence of tooth decay (dental caries). Water fluoridation is controversial in some quarters, but generally believed by the dental community and many public health officials to be beneficial without demonstrable risk. Fluoridation is a matter of national policy. Seawater contains fluoride and the fluoride is depleted by desalination so desalinated water does not contribute significant fluoride to daily intake unless it is present in blending waters or added in reconstitution. Iodide is added to drinking water in a few locations to supplement inadequate dietary intake that has led to thyroid problems in populations.

Sodium

Sodium is a necessary dietary component. Sodium can be present in desalinated water depending upon the efficiency of salts removal and the post treatment blending or stabilization. Typical daily dietary intake of sodium can be in the range of 2000 to 10,000 mg and more, and is a function of personal taste, dietary and cultural factors. Most experts believe that some segment of the population is salt sensitive (hypertensinogenic) which means that blood pressure elevation and its commensurate adverse effects occur to a greater degree in those individuals associated with their total salt consumption. Estimates of salt sensitivity frequency are in the range of 15% of some populations.

Water is usually not a significant contributor to total daily sodium intake except for persons under physician care who are required to be on highly restricted diets of less than 400 mg sodium per day. Thus, sodium concentrations of 20 mg/l (assuming 2 L per day consumption) would contribute 10% of the total permissible daily intake for those people. It is virtually impossible to limit salt intake from food to less than 360 mg/day.

VIII. PETROLEUM CONTAMINATION

Raw and refined petroleum contains a very large number of toxic substances and also substances that impact undesirable taste to finished water. Crude oil contains aliphatic and aromatic hydrocarbons, and heterocyclic and other components that contain nitrogen and sulfur. Aliphatic hydrocarbons can range from gaseous methane (C₁) and other small molecules, to midrange liquids (C₅ to C₁₆ approximately) like heptane (C₇) and cetane (C₁₃), to high molecular weight solids that are dissolved or suspended in the mixture. Many of these are neurotoxins at higher doses and some like hexane (C₆) are neurotoxins at relatively low doses. Usually these are slightly soluble in water. Aromatic hydrocarbons range from benzene and toluene to polynuclear aromatic naphthalene (2 rings) to benzopyrene (6 rings) and above. Benzene is known to cause leukemia, and benzopyrene causes skin and other cancers.

Numerous sulfur compounds are present both as heterocycles and as thiols and other forms including sulfur, and hydrogen sulfide that is highly toxic and particularly malodorous at very low

concentrations. Refined petrochemicals and gasoline products challenge the treatment processes with high concentrations of mobile, volatile and often more toxic lower and mid-range fractions.

The molecular weight cut off is typically in the range of 100-300 Daltons. Larger molecules are removed by RO membranes, however significant fouling will impede operations. Small molecules pass through the membrane. It is at least theoretically possible that some molecules, although rejected by their size, may, depending on their solubility characteristics and the chemistry of the polymeric membrane, dissolve in the polymer and diffuse through.

Distillation processes can theoretically separate any substance by fractionation based upon boiling point differences, however desalination distillation is not designed to be a fractionating system, thus substances with boiling points lower than water's could easily be carried over in the vapors, and even many higher boiling substances would "steam" distill and be carried into the distillate even though their vapor pressures are very low at the boiling temperature of water.

In general, to avoid contamination of finished water by certain organics in source waters, pretreatments should be applied and these can involve an adsorption process using granular activated carbon or more frequently powdered activated carbon for intermittent contamination. Contaminants in blending waters will be transported to the finished water thus appropriate pretreatment of blending water may also be required.

Waste Management

Wastes from desalination plants include concentrated brines, backwash liquids containing scale and corrosion salts and antifouling chemicals, and pretreatment chemicals in filter waste sludges. Depending upon the location and other circumstances including access to the sea and sensitive aquifers, and concentrations of toxic substances etc., wastes could be discharged directly to the sea, mixed with other waste streams before discharge, discharged to sewers or treated at a sewage treatment plant, placed in lagoons, and dried and disposed in landfills.

Energy Consumption

Desalination plants require significant amounts of electricity and heat depending upon the process, temperature and source water quality. For example, it has been estimated that one plant producing about seven million gallons per day could require about 50 million kWh/yr., which would be similar to the energy demands of an oil refinery or a small steel mill. For this reason, co-generation facilities provide significant opportunities for efficiencies and most new projects consider co-generation.

Environmental Impacts

Installation and operation of a desalination facility will have the potential for adverse impacts on air, water/sea, and ground water and possibly other aspects. These should be considered in environmental impact assessments, and their acceptability and mitigation requirements would usually be matters of national and local regulation and policies. Studies to examine these effects would usually be conducted at each candidate site, and post installation monitoring programs should be instituted. A brief partial listing of issues follows:

- Construction: Coastal zone and sea floor ecology, birds and mammals habitat; erosion, non point source pollution.
- Energy: Fuel source and fuel transportation, cooling water discharges, air emissions from electrical power generation and fuel combustion.
- Air Quality: Energy production related.
- Marine Environment: Constituents in waste discharges, thermal effects, feed water intake process, effects of biocides in discharge water, and toxic metals, oxygen levels, turbidity, salinity, mixing zones, commercial fishing impacts, recreation, and many others.

- Ground Water: Seepage from unlined drying lagoons causing increased salinity and possibly toxic metals deposition.

Disinfection and Microbial Control

Sea and brine waters can contain microorganisms that could be pathogens including bacteria, protozoa and viruses. Disinfection processes can occur at several points during the treatment process. The question is, what is adequate disinfection to protect public health from exposure to pathogenic microbes, and are there any unique risks that may be associated with desalination practices. During pretreatment a disinfectant, often chlorine, will be added to reduce biofouling and protect the membrane from degradation. Membranes also have the capacity to separate microorganisms by preventing their passage through the membranes. So long as the membrane is intact complete removals of microorganisms can occur, however leaks at seals do occur, and some bacteria can grow through the membrane.

Even ultrafiltration membranes that have pores (~0.001 to 0.1 microns) have been demonstrated to achieve significant reductions of viruses and protozoa. Better performance could be expected from RO membranes. Several challenge tests employing giardia lamblia and cryptosporidia cysts and MS2 bacteriophage virus with an ultra-filtration membrane of nominal pore size of 0.035 micron and absolute, 0.1 micron have demonstrated very effective removals.

Guardia cysts can vary from 4 to 14 microns in length and 5 to 10 microns in width; cryptosporidia on cysts range from about 4 to 6 microns. These intact ultrafiltration membranes (0.1 micron nominal) should completely remove the cysts.

MS2 bacteriophage size is approximately 0.027 micron, which is smaller than the pore size of the membrane. However, substantial removal was achieved probably aided by adsorption of the virus on suspended particles, adsorption on the membrane or from the secondary filtration due to fouling of the membrane surface. Indeed there was a tendency for the MS2 removal to improve as membrane fouling increased in the study as indicated by higher transmembrane pressures.

Distillation at high temperatures close to the normal boiling point of water would likely eliminate all pathogens. However, reduced pressures are used in some desalination systems to reduce the boiling point and reduce energy demands. Temperatures as low as 50° to 60°C may be reached. Several pathogenic organisms are denatured or killed in a few seconds to minutes at temperatures in the 60° to 80°C range, but spores and some viruses usually require higher temperatures and longer times.

Disinfection Byproducts

Predisinfection processes certainly produce byproducts, some of which are removed by the desalination process. Since desalinated waters are lower in Total Organic Carbon than most natural waters it would be expected that the disinfectant demand of desalinated water and also disinfectant byproduct formation, would be relatively low, and this has been indicated in some studies of trihalomethane production that have been reported. However, this could be significantly affected by the type of blending water that is used post treatment to stabilize the water. In addition, one of the factors to consider would be the amounts of brominated organic byproducts that could be formed from predisinfection of salt waters containing bromide, and from disinfection of blending waters, if bromide is reintroduced to the finished waters. This is a concern since data is accumulating that some brominated disinfection byproducts may have greater carcinogenic potential than many chlorinated byproducts such as chloroform. Indeed chloroform may not be carcinogenic at all at levels typically found in drinking water. Since the TOC found in seawater could be different than TOC in fresh waters, it is also possible that there could be some differences in the chemistry of the byproduct formation reactions that could lead to different byproducts or different distributions of byproducts.

IX. CONCLUSION

Desalination of seawater and brackish waters offers the opportunity to significantly increase the world's supply of fresh water for drinking and other purposes. These processes remove virtually all of the salts and dissolved organic matter from the water; then due to the aggressiveness of the water substances must be added to the treated water to stabilize it prior to transport to consumers. Because of the non typical (for drinking water) saline source waters and treatment processes involved, certain issues in finished water composition and process arise that are not typically dealt with in usual drinking water supplies. This monograph will address several of those issues in respect to trace mineral composition and contributions to daily diet and health in respect to long-term consumption of water that has been originally drawn from a saline source.

References

1. Wiesman R. IDA Desalination Inventory. *Desalination & Water Reuse Quarterly*, Vol. 12/3, November/December 2003: 10-13.
2. Furukawa D. New Developments in Desalination. In: Cotruvo JA, Craun G, Hearne N, eds. *Providing Safe Drinking Water in Small Systems*. Lewis Publishers, 1999:257-264.
3. Bodzek M. Membrane Techniques in Water Treatment and Renovation. In: Goosen MFA, Shayya WH, eds. *Water Management Purification & Conservation in Arid Climates*, Vol. 2, Technomic Publishing Co., 2000:45-100.
4. Cartwright PS. Membrane Separation Technologies. In: *Proceedings of the International Symposium on Small Drinking Water and Wastewater Systems*, Januar 12-15, 2000.
5. The USAID Desalination Manual, PN-AAJ-122, USAID; 1980.
6. Worldwide Desalination Research and Technology Survey; Ministry of Foreign Affairs, Sultanate of Oman, April 1994.
7. Expert Group Meeting on Health Aspects of the Long-term Use of Desalinated Water, WHO-EM/ES/371. December 1985.
8. Health Effects of the Removal of Substances Occurring Naturally in Drinking Water,
9. Regional Office for Europe, WHO Copenhagen, 1979.
10. Sadhukhan HK, Misra BM, Tewari PK. Desalination and Wastewater Treatment to Augment Water Resources. In: Goosen MFA, Shayya WH, eds. *Water Management Purification & Conservation in Arid Climates*, Vol. 2, Technomic Publishing Co., 2000:1-19.
11. Singh M. Immersed Membrane Technology for Parasite and Microorganism Removal in Surface Water Supplies. In: *Proceedings of the International Symposium on Small Drinking Water and Wastewater Systems*, NSF International, Jan. 12-15, 2000.
12. Seawater Desalination in California; California Coastal Commission, 1999.
13. World Health Organization Guidelines for Drinking Water; World Health Organization, Geneva, 1993.
14. Mayan Kutty PC. Studies in THMs Formation by Various Disinfectants in Seawater Desalination Plants. In: *Proceedings of the International Desalination Association*, Vol. VII, 1995: 367-399.
15. Environmental Sound Management of Seawater Desalination Plants in the Mediterranean Region, United Nations Environment Program, Chapter 4, UNEP(Dec)/Med WG.231/12, 10, April 2003.

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3.

WATER REQUIREMENTS, IMPINGING FACTORS, AND RECOMMENDED INTAKES

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I. INTRODUCTION

Water is an essential nutrient for all known forms of life and the mechanisms by which fluid and electrolyte homeostasis is maintained in humans are well understood. Until recently, our exploration of water requirements has been guided by the need to avoid adverse events such as dehydration. Increasing appreciation for the impinging factors that must be considered when attempting to establish recommendations of water intake presents us with new and challenging questions.

This paper, for the most part, will concentrate on water requirements, adverse consequences of inadequate intakes, and factors that affect fluid requirements. Other pertinent issues will also be mentioned. For example, what are the common sources of dietary water and how do they vary by culture, geography, personal preference, and availability, and is there an optimal fluid intake beyond that needed for water balance?

II. ADVERSE CONSEQUENCES OF INADEQUATE WATER INTAKE, REQUIREMENTS FOR WATER, AND FACTORS THAT AFFECT REQUIREMENTS

1. Adverse Consequences

Dehydration is the adverse consequence of inadequate water intake. The symptoms of acute dehydration vary with the degree of water deficit (1). For example, fluid loss at 1% of body weight impairs thermoregulation and, thirst occurs at this level of dehydration. Thirst increases at 2%, with dry mouth appearing at approximately 3%. Vague discomfort and loss of appetite appear at 2%. The threshold for impaired exercise thermoregulation is 1% dehydration, and at 4% decrements of 20-30% is seen in work capacity. Difficulty concentrating, headache, and sleepiness are observed at 5%. Tingling and numbness of extremities can be seen at 6%, and collapse can occur at around 7% dehydration. A 10% loss of body water through dehydration is life-threatening (2). During the Six-day War of 1967, more than 20,000 Egyptian soldiers died from heat stroke. Egyptian troops were following practices of strict water rationing. During the same time, Israeli troops with abundant field water supplies and command-enforced water policies had minimal heat casualties (3)

While the vague discomfort that accompanies a 2% dehydration may not have a significant impact, the 20 – 30% reduction in work capacity seen at 4% can have a significant negative impact on productivity. Negative health consequences of chronic dehydration are covered later in this paper.

2. Minimum Water Requirements

The minimum requirement for water is the amount that equals losses and prevents adverse effects of insufficient water, such as dehydration. There are numerous limitations associated with the requirement estimates used to make recommendations. A review of the research designed to define fluid requirements of humans increases one's appreciation of the complexity of the issue. A multitude of intra- and inter-individual factors influence water requirements. As stated in the 1989 Recommended Dietary Allowances (4) establishing a recommendation that meets the needs of all is impossible:

- The primary determinant of maintenance water requirement appears to be metabolic, (Holliday and Segar, 1957) but the actual estimation of water requirement is highly variable and quite complex. Because the water requirement is the amount necessary to balance the insensible losses (which can vary markedly) and maintain a tolerable solute load for the kidneys (which may vary with dietary composition and other factors), it is impossible to set a general water requirement.
- The impracticability of establishing a general water requirement was reiterated in the Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate(5):
- Given the extreme variability in water needs which are not solely based on differences in metabolism, but also in environmental conditions and activity, there is not a single level of water intake that would ensure adequate hydration and optimal health for half of all apparently healthy persons in all environmental conditions.

Thus, the Panel determined that an Estimated Average Requirement (EAR), and therefore a Recommended Dietary Allowance (RDA), could not be established. Hence, an Adequate Intake (AI) was established as the reference value for water intake for healthy U.S. and Canadian individuals and populations.

3. Factors That Affect Requirements

For sedentary to moderately active individuals under temperate conditions, water is lost from the body via urine, feces, respiration, and evaporation. During increased physical activity and in conditions other than temperate, sweat loss contributes to body water loss. The minimal amount of fluid loss that can occur is referred to as the obligatory water loss. However, a variety of factors can affect obligatory loss. For example, obligatory urine loss occurs because of the need to remove various solutes from the body. The minimum water required for urine is dependent on the daily solute excretory load, primarily determined by diet, and the maximum urinary concentration achievable (6;7). Urinary concentrating ability varies with age (8;9) and with renal disease. Normally, fecal water loss is small, estimated at about 100 mL/day (4;10).

Water that passes through the skin (transepidermal diffusion) and is then lost by evaporation, and water that is lost from the respiratory tract, is collectively referred to as insensible water loss. Insensible water correlates with metabolic heat dissipation (11;12). The estimate of insensible water loss has been shown to vary more in infants than in adults (13), but Holliday and Segar (14) proposed an average water loss of 50 mL/100 kcal to apply to all ages. Even when caloric expenditure and body surface area are equal, however, insensible water loss through the skin and lungs varies. Environmental temperature and humidity, altitude, volume of air inspired, air currents, clothing, blood circulation through skin, and water content of the body can all affect insensible water loss (15).

A study published in 1930 (16) is the only identified primary reference reporting total water output in a healthy adult under temperate conditions. Five days of total intake and output data were reported on one sedentary 60-kg male subject confined to the laboratory. The average output

was 2675 mL, ranging from 2227 mL to 3205 mL. Insensible loss remained fairly constant (1073–1213 mL), whereas urine water ranged from 1149 to 2132 mL. Some of the commonly referenced average output values are much lower than this 60-kg male's documented output. Nonetheless, the wide range of average daily output reported appears to capture the variability within and among individuals.

Another study assessing the effect of two diets on hydration was conducted on 27 healthy, sedentary, male subjects using a crossover design (17). During the trial that provided water as a portion of the beverage allotment, subjects consumed one-third of their beverages as plain drinking water. In the “without water” trial, no plain drinking water was consumed. Subjects were confined to a metabolic unit during the study and physical activity, sleep/wake cycle, and heat and humidity were controlled. Results showed no difference in the effect on hydration between the two diets, and subjects maintained euhydration on both trials. The mean total water from food and beverages, consumed by subjects in this study, was 1.1 mL/kcal.

Perhaps the most significant conclusions that can be drawn from an examination of water requirements are the limited scientific data, and the magnitude of the variability within and among individuals (16-18). This is important to keep in mind when considering recommendations, because recommendations are not necessarily requirements.

4. Factors that Increase Water Requirements

While young children, pregnant and lactating women, the elderly, and people with certain illnesses may have increased fluid requirements, and/or present additional challenges in meeting their requirements (19), space limitations prevent adequate review of such specific populations. Requirements and recommendations for fluid intake in hot and humid environments will be reviewed here because of the inordinate increase in fluid requirements that can result in such conditions and the large number of people worldwide who perform work in such environments.

5. Thermal and physiological stress

Water lost via sweating is usually low in temperate, sedentary conditions, but profuse sweating can be a major source of water and electrolyte loss for persons exercising or laboring in extreme heat and/or humidity. In physically active individuals, sweating presents the most highly variable water loss. Sweat rates can reach 3 to 4 L/hour, with variation in sweat rate depending upon exercise intensity and duration, age, gender, training, heat acclimatization, air temperature, humidity, wind velocity, cloud cover, clothing, and individual sweat rate (20). Total daily fluid requirements have been shown to range from as little as 2 liters per day to 16 liters per day pending on the work load and the level of heat stress (21).

It has long been known that persons under thermal and physiologic stress need to pay special attention to fluid and salt intake (2,22-24). Military personnel have been studied extensively in this regard. Monographs and scientific publications present some of the extensive research conducted by the United States for purposes of survival and endurance during the Second World War (2,25,26). Scientific findings from the research on military and aerospace personnel continue to provide essential and fundamental information on fluid requirements under conditions of thermal and physiologic stress (27-30). Collectively, research has shown progressive decrements in work performance with increasing levels of dehydration, and inter- and intra-individual variation in sweat rates, water intake, and water requirements.

A study on the effects of heat stress on the health and productivity of forest workers using manual working methods in temperate conditions was conducted in North East Zimbabwe (31,32). The forest workers were given either 0.17 or 0.6 liters of water each half hour. Based on the findings of dehydration and reduced productivity, the researcher concluded that International

Labour Organization recommendations for the consumption of at least 5 liters of fluid per day during heavy forestry work should be extended to work under temperate conditions.

Investigators conducting a field study to assess dehydration in 39 male underground miners concluded that workers who were educated about the need to drink small amounts frequently did not suffer from “voluntary dehydration” (33). The average fluid consumption per shift was 6.48 ± 2.41 L, with a range of 2.40 – 12.50 liters. The mean full shift average consumption rate was 0.8 ± 0.27 , liters per hour, with a range of 0.32 – 1.47. Urinary specific gravity was used to determine hydration status. Start, mid, and end of shift, mean specific gravity were 1.0252, 1.0248 and 1.0254 respectively. However, specific gravity has been shown to be a somewhat unreliable measure of hydration status (34,35).

A study designed to determine if the Zimbabwe National Army rations are adequate for soldiers doing strenuous physical work, or even for those doing normal work in hot dry conditions, compared energy expenditure, and total body water on 12 soldiers (36). Eight soldiers were randomly assigned to the test group (strenuous work), and four were assigned to the control group (normal work). The study period lasted for 12 days. The average daily fluid intake for the test group was 11 liters per day compared to approximately 7 for the control group. The investigators concluded that the standard ration is inadequate.

The United States Army revised their fluid replacement guidelines in 1999. A study to compare the revised guidelines with the previous guidelines was conducted on soldiers engaged in outdoor military combat training in hot weather (37). The revised guidelines effectively reversed the decrease in serum sodium, reduced the increase in body mass, maintained hydration, and minimized overdrinking compared to the previous guidelines.

Table 1 shows the previous guidelines and Table 2 the revised.

Table 1. Previous Army Fluid Replacement Guidelines for Hot Weather Training ^a

Criteria		Controls	
Heat Condition/ Category	WBGT* Index (°F)	Water Intake (qt/h)	Work-Rest Cycle (min)
1	78-81.9	At least 0.5	Continuous
2	82-84.9	At least 0.5	50/10
3	85-87.9	At least 1	45/15
4	88-89.9	At least 1.5	30/30
5	90+	More than 2	20/40

^a: Adapted from: Montain SJ, et al. Fluid Replacement Recommendations for Training in Hot Weather. *Military Medicine*, 164,7:502-508, 1999.

* WBGI = Wet Bulb Globe Temperature

It was determined that the Army’s guidelines may need revision after 190 military personnel were hospitalized for water intoxication (hyposmolality/hyponatremia) between 1989 and 1999 (38). Hyponatremia should be considered a risk when large volumes of plain drinking water are consumed, especially when combined with a diet low in salt (sodium chloride).

Table 2. Revised Fluid Replacement Guidelines for Hot Weather Training (Average Acclimated Soldier Wearing Battle Dress Uniform, Hot Weather) ^a

		Easy Work		Moderate Work		Hard Work	
Heat Category	WBGT* Index (°F)	Work- Rest Cycle (min)	Water Intake (qt/h)	Work- Rest Cycle (min)	Water Intake (qt/h)	Work- Rest Cycle (min)	Water Intake (qt/h)
1	78-81.9	NL**	0.5	NL	0.75	40/20	0.75
2	82-84.9	NL	0.5	50/10	0.75	30/30	1
3	85-87.9	NL	0.75	40/20	0.75	30/30	1
4	88-89.9	NL	0.75	30/30	0.75	20/40	1
5	>90	50/10	1	20/40	1	10/50	1

^aAdapted from: Montain SJ, et al. Fluid Replacement Recommendations for Training in Hot Weather. *Military Medicine*, 164,7:502-508, 1999.

* WBGT = Wet Bulb Globe Temperature

** NL, no limit to work time per hour

6. Recommendations and Estimates of Requirements

The amount of water needed to replace losses is the absolute requirement. Whereas requirements are impossible to predict precisely, except under controlled conditions, recommendations are standards to be used in the assessment and planning of diets for individuals and for groups, and for establishing policy.

The Tropical Agriculture Association has published water requirements for humans, animals and irrigated crops, given as liters per year (<http://www.taa.org.uk>). The minimum water requirement for fluid replacement for a 70kg human in a temperate zone equates to 3L per day, or 42.9mL/kg. Minimum requirements for an individual the same size but in a tropical zone equates to 4.1 to 6L/day, or 58.6 to 85.7mL/kg.

The Recommended Dietary Allowances (RDA), the dietary standards for the United States civilian population, have their roots in national defence. The Food and Nutrition Board (FNB), a part of the National Research Council, was established in 1940 “to advise on nutrition problems in connection with National Defense (39).” The amount of 1 mL water/kcal of energy expenditure has been the recommendation since 1945 (40). In 1989 the FNB added a higher amount, stating, “...there is so seldom a risk of water intoxication that the specified requirement for water is often increased to 1.5 mL/kcal to cover variations in activity level, sweating, and solute load (4).”

Age and gender specific Adequate Intakes (AI) for water were established in 2004 by the Food and Nutrition Board (5). The Dietary Reference Intakes (DRI) for water are shown in Tables 3 and 4.

Table 3. AI for Boys and Girls Birth to Eight Years of Age

0 – 6 months	0.7 L/day of water, assumed to be from human milk.
7 – 12 months	0.8 L/day of water, assumed to be from human milk and complementary foods and beverages
1 – 3 years	1.3L/day
3 – 8 years	1.7 L/day

Table 4. AI for Ages Nine and Older

9 – 13 years	Boys	2.4 L/day
	Girls	2.1 L/day
14 – 18 years	Boys	3.3 L/day
	Girls	2.3 L/day
19 – 70+	Men	3.7 L/day
	Women	2.7 L/day

Athletes, like military personnel, are a population wherein hydration status is critical to performance. Considerable research has been conducted to explore the measurement and the consequences of dehydration during physical performance, as well as strategies and recommendations for fluid intake. Athletes are commonly instructed to replace body water lost (measured by change in body weight) during training and competition with an amount of fluid that is equal to the amount lost, using the guideline that 1 kg equals 1 L. Numerous monographs and papers have been published on fluid needs of physically and environmentally stressed individuals (41-47).

7. Water Intake and Sources

Water intake includes that which is consumed as food and beverage, along with relatively small volumes of water created by oxidation of food (metabolic water) and breakdown of body tissue. Metabolic water is about 350 to 400 mL/d. Determining actual water consumption is difficult for a variety of reasons, one being that many of the published reports are for total water use (drinking water, water used for basic hygiene, etc.). Additionally, some reports on water intake report only tap water, and therefore, water provided as other beverages are not included in the calculations. Williams, et. al. (48) reported that estimates of mean water intake rates reported in the literature range from 1.04 to 1.63 L/person/day.

Humans ingest water as plain drinking water, as beverages, and in food. Water in food can be inherent or added during preparation, and also produced by metabolism. All contribute to the “total water intake.” Unfortunately, there is a paucity of data on total water consumption. The data that do exist show considerable variation in intakes both within and between individuals.

Studies in humans have shown that numerous factors affect fluid intake (49;50). Availability, ambient temperature, flavor, flavor variety, beverage temperature, proximity of the beverage to the person, and even beverage container have all been shown to impact intake. Cultural variations have been reported, although the data is limited (See Table 5).

Table 5. Market Shares (liter per capita) of Beverages in Various Countries ^{a,b}

Beverage	United States of America	Great Britain	Federal Republic of Germany	Italy	Finland
Soft drinks	173	91	78	47	31
Milk	102	126	55	68	104
Beer	89	108	147	2	63
Mineral water	?	2	62	50	8
Fruit juice	28	16	27	4	29
Wine ^c	16	11	23	80	5
Liquors ^d	~	5	19	11	35
Coffee ^d	98	13	96	57	156
Tea ^d	25	40	5	2	3

^a Adapted from Tuorila, H. Individual and cultural factors in the consumption of beverages. In: Ramsay and Booth, eds. *Thirst: physiological and psychological aspects*. London, Springer-Verlag, 1991.

^b The USA consumption from 1985 (Bunch 1987; Putnam 1987), European figures from 1986 (Euromonitor 1988).

^c In the US data includes liquors.

^d Volumes estimated from dry substance with dilution ratios given

Water content of beverages varies. Plain drinking water and diet soft drinks are 100% water, whereas coffee and tea are 99.5%, and sport drinks are 95%. Fruit juices vary from 90 to 94% water. Skim milk, 2% fat milk, and whole milk are 91%, 89%, and 87% respectively. While not consumption data, the market share data in Table 5 reflects consumption patterns. Water intake from these beverages could be estimated with the possible exception of beverages containing alcohol.

Researchers described the diuretic action of alcohol as early as 1932 and subsequent studies substantiated a diuretic effect (51-54). A formula proposed by Stookey (55) applied quantitative estimates of the effects of alcohol to determine the retention of the water consumed. Making numerous assumptions, Stookey estimates water losses of 10 mL/g alcohol. Eggleton, in 1942, found that the diuresis following an alcoholic drink is roughly proportional to the amount of alcohol present and suggested that the ingestion of drinks containing small quantities of alcohol did not impair rehydration in dehydrated individuals (51). A 1995 study supported this notion. Taivainen and colleagues (56) found that while diuresis occurred after healthy adult males consumed a beverage of fruit juice and alcohol (1.2 g alcohol/kg of body weight), there was a subsequent antidiuretic phase that lasted up to 12 hours post alcohol ingestion. The researchers concluded that consuming fluids immediately following alcohol consumption (800 ml over 4 hours) and then 6 hours later (20 ml/kg) will, for the most part, offset the water lost from the alcohol induced diuresis. Thus, assuming adequate fluid intake following acute alcohol ingestion, it appears that alcohol-induced diuresis is transient and will not result in appreciable fluid losses over a 24 hour period.

Shirreffs and Maughan (57) conducted a study designed to determine whether alcohol exerts a diuretic effect when consumed by dehydrated individuals. After an exercised-induced dehydration, the subjects consumed a volume of fluid equal to 150% of the estimated sweat loss. The fluids consumed, in the four different trials, were alcohol-free beer, and alcohol-free beer to which 1, 2, or 4% alcohol was added. The results suggested that the diuretic effect of alcohol is

substantially blunted when consumed by dehydrated individuals. Urine production increased as the quantity of alcohol consumed increased, and there was a significant reduction in the rate of recovery of blood volume when the 4 % alcohol beverage was consumed. It must be noted that in all of the trials in the Shirreffs and Maughan study, the subjects consumed 150% of the estimated sweat loss, leaving to question the results if subjects had consumed only 100%, or less than 100%, of sweat losses, or if the alcohol content of the beverage had been higher.

While research on acute alcohol consumption followed by adequate fluid intake supports a dose-response relationship with moderate intake causing no long-term effects on hydration status, elevated serum osmolality has been observed in chronic alcohol consumers, both at baseline and after ethanol ingestion (58). It is unclear if, and if so to what degree, alcohol induced diuresis, neurohormonal aberrations, perception of thirst, and/or fluid consumption habits, contribute to the dehydration (as determined by serum osmolality) observed in chronic alcohol consumers (58;59)

Further evaluation of alcohol's effect on fluid balance is warranted, especially in view of the numerous cultures that routinely consume alcoholic beverages as part of the daily diet. Chronic consumption, as part of the daily diet, verses acute high volume consumption, and dose response studies would provide useful information for determining how alcohol should be considered when calculating total water intake.

In the United States the majority of individuals' fluid intake is not consumed as plain water, but instead from a variety of foods and beverages as influenced by cultural, economic, social, environmental, and sensory factors (4;60). Ershow, Cantor, et al. (61) analyzed data from the 1977–1978 Nationwide Food Consumption Survey (NFCS). They found that water consumed as plain drinking water averaged 31.4% of total intake. Beverages other than plain water provided 43.6% and food provided 25% of total water intake. The water content of the food portion of the diet can vary widely. For example, whereas the mean intake of water from food for subjects of both sexes, 20 to 64 years of age participating in the 1977–1978 NFCS was 545 gm, the average for the 5th and 99th percentile were 223 and 1254, respectively (61).

Data from the USDA 1994–1996 Continuing Survey of Food Intakes by Individuals (CSFII) showed that approximately one-third of the total fluid intake of persons aged 20 to 64 years of age was consumed as plain water (62). The 1994–1996 CSFII (63) also showed that the average consumption of milk and other beverages totaled 1,115 grams/day for all subjects. Of that, 35% was coffee and tea, 30% was carbonated soft drinks, 17% was milk, 9% was alcohol, and 9% was fruit drinks and ades.

The perception exists that beverages vary in their capacity to maintain hydration status, with caffeine containing beverages purported to have a diuretic effect. This appears to be based on studies showing acute increased urine output after caffeine doses in caffeine naïve individuals (64-70). However, research shows that a tolerance to caffeine develops (71-76). As such, those who are not caffeine naïve do not experience increased urine output or altered indicators of hydration status after consuming caffeinated beverages (18;77).

In addition to unsubstantiated warnings about caffeine, unsubstantiated claims about the essentiality of plain water in meeting fluid requirements are also touted. Public perception in the United States is that plain drinking water is more “hydrating” than other beverages, even though it has long been put forth in medical, military, nutrition, and physiology texts that water from foods and beverages can meet fluid needs (4; 5; 78-82).

8. Is There an Optimal Intake?

While current knowledge allows us to determine insufficient and adequate fluid intake, our scientific knowledge base is inadequate to determine if there is an optimal fluid intake. However, there is a growing body of science indicating that an optimal intake level may indeed exist, and that such an amount is greater than current recommendations.

Research on the relationship of drinking water and the incidence of cancer has been an area of study for some time. For the most part, such studies have been concerned with contaminants in drinking water as a cause of cancer (83-86). More recently, studies have examined the relationship between beverage volume, and in some studies, the specific types of fluids consumed as related to the incidence of various diseases.

Studies examining the fluid-disease relationship have considered various combinations of variables including dehydration, hyperhydration, fluid volume consumed, and types of beverages, as they relate to the absence, presence, or treatment of certain diseases or conditions. For example, dehydration has been linked to increases in risk for urinary tract infections, dental disease, broncho-pulmonary disorders, constipation, kidney stones, and impaired cognitive function (87-92). A relationship between a high fluid intake and decreased risk of a variety of maladies including urinary tract stones, colon and urinary tract cancer, and mitral valve prolapse has been shown (83;87;93-104). Some studies examining the relationship between fluid intake and specific diseases have found no correlation with the types of beverages consumed (83;86;95;101;102), while others have (104-108). For example, one study (108) found an inverse correlation between water intake and risk of fatal coronary heart disease and a positive correlation between intake of other fluids other than water and risk. As the authors noted, however, potential confounding variables need to be considered. Perhaps the water drinkers were more health conscious. Moreover, subjects in the study had an intake of milk higher than the average United States population, and the type of milk consumed was not reported. Perhaps water drinkers consumed less total dietary fat. As with most epidemiology research, known and unknown confounding variables make it impossible to draw definitive cause-effect conclusions.

That fluoridated drinking water protects against dental carries is well documented. Results from a cross-sectional study on 499 Australian Army recruits showed a dose-response relationship, suggesting benefits of lifetime exposure to fluoridated drinking water through young adulthood (109).

Whereas the available information on a fluid-disease relationship is far from conclusive, current data indicates need for further study. Determining the amount of fluid necessary to maintain hydration is one concern when trying to discern recommendations on fluid intake; determining fluid intake necessary to treat or decrease risk of certain diseases or disorders is another.

9. Establishing Recommendations/Guidelines

It is important, for public health purposes, to estimate, as exactly as possible, the water requirements of a population. Doing so is an inordinate task, due to the numerous factors that effect requirements and the variances observed within each of those factors. Acknowledging the caveats, the World Health Organization, in their report, "Domestic Water Quantity, Service Level and Health" (19) estimated requirements. Based on a 70 kg adult male, and a 58 kg adult female, under average conditions, it was estimated that adult females needed 2.2L/day and males 2.5L/day. Manual labour in high temperatures increased requirements to 4.5L for both men and women. Recommendations for children were calculated using 1 liter per day for a 10 kg child and 0.75 liter for a 5 kg child, which resulted in 1.0L/day under average conditions and 4.5L for manual labour in high temperatures.

Table 6 shows the WHO requirements for adults (19) and also estimates from several the studies reviewed in this paper. While studies have shown that a low intake of fluid is associated with some chronic diseases, evidence is insufficient, at this time, to delineate specific amounts needed to prevent various diseases.

Table 6. Volume^a of water recommended and/or found to support hydration under specific conditions.^{bc}

	Sedentary, Temperate Environment		Physically Active and/or Increased Temperature		Optimal (Disease Prevention)
Female Adult	2.2	(19)	4.5	(19)	?
Male Adult	2.9	(19)	4.5	(19)	?
			5.0	(31)	
			0.8/h	(33)	
			11.0	(36)	
Male & Female	2 – 4	(21)	8 – 16	(21)	?
	0.5 qt/h	(37)	¾ - 1 qt/h	(37)	

^a Volume is given as litres per day unless otherwise indicated.

^b When reviewing this table, please keep in mind that data is not comparable in data collection methodology, subjects, environmental conditions, activity intensities (in reports on physically active), length of study/observation period, or purpose of study. Data are presented herein to demonstrate the ranges of recommendations/observations.

^c The number in parentheses after the volume refers to the citation number in the reference list.

An incremental formula by which water requirements could be more precisely estimated for populations, groups of people, and perhaps even individuals would need to consider requirements under sedentary conditions at temperate environment with adjustments for altitude, heat, humidity, activity level, clothing, and other factors. While such a formula does not currently exist, development of such a formula could provide a point from which to more closely estimate requirements.

10. Future Challenges

For six decades, the driving force behind fluid and electrolyte research has been medical care, survival, and optimal physical performance. Empirical and clinical research, and field studies have been conducted on military personnel, athletes, and hospitalized patients. Missing, however, is comprehensive data more pertinent to “average” individuals who comprise the majority of many populations. Additionally, research is surfacing that moves beyond water requirements per se, and examines the relationship between optimal fluid intake and disease prevention, balancing requirements with availability, and exploring nutrients and other compounds (both beneficial and detrimental) that can accompany water. It is appropriate to move beyond the role of fluids in preventing dehydration and decrements in performance, and toward determining the contribution of fluids (and their mineral components) to longer, healthier, and more productive lives.

The current and future challenge is to continue research on topics such as fluid recommendations for various ages, the relationships between disease and the amount and types of fluids consumed, health-promoting properties of nutrients indigenous or endogenous to water, optimal intake levels, and consumption patterns. Additionally, guidelines or formulas that can more precisely determine the amount of water needed by individuals and/or populations would be advantageous.

Reference

1. Greenleaf J, Harrison MH. Water and electrolytes. In: Layman DK, editor. Nutrition and Aerobic Exercise, Washington, DC: American Chemical Society, 1986:107-124.
2. Adolph EF. Heat Exchanges, Sweat Formation, and Water Turnover. In: Adolph EF, editor. Physiology of Man in the Desert, New York: Interscience Publishers, 1947: 33-43.
3. Stewart C. The Spectrum of Heat Illness. In: Stewart C, editor. Environmental Emergencies. Baltimore: Williams & Wilkins, 1990:1-27.
4. Food and Nutrition Board. Recommended Daily Allowances. 10 ed. Washington, DC: National Academy Press, 1989.
5. Food and Nutrition Board. Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate. Washington, DC: The National Academies Press, 2004.
6. Singer G, Brenner B. Fluid and electrolyte disturbances. In: Fauci A, Braunwald E, Isselbacher K, Wilson J, Martin J, Kasper D et al., editors. Harrison's Principles of Internal Medicine. NY, NY: McGraw-Hill, CD-ROM, 1998.
7. Howard L. Enteral and parenteral nutrition therapy. In: Fauci A, Braunwald E, Isselbacher K, Wilson J, Martin J, Kasper D et al., editors. Harrison's Principles of Internal Medicine. NY, NY: McGraw-Hill, CD-ROM, 1998.
8. Bergmann KE, Ziegler EE, Fomon SJ. Water and renal solute load. In: Fomon SJ, editor. Infant Nutrition. Philadelphia: W.B. Saunders, 1974: 245-266.
9. Phillips P, Rolls B, Ledingham D, Forsling M, Morton J, Crowe M, Wollner L. Reduced thirst after water deprivation in healthy elderly men. NEJM 1984; 311:753-759.
10. Alper C. Fluid and Electrolyte Balance. In: Wohl MG, Goodhart RS, editors. Modern Nutrition in Health and Disease, Philadelphia: Lea & Febiger, 1968: 404-424.
11. Benedict FG, Root HF. Insensible perspiration: Its relation to human physiology and pathology. Arch Intern Med 1926; 38(1):1-35.
12. Johnston M, Newburgh L. The determination of the total heat eliminated by the human being. Clinical Invest 1930; viii:147-160.
13. Levine S, Wheatley M. Respiratory metabolism in infancy and in childhood. American Journal of Diseases of Children 1936; 51:1300-1323.
14. Holliday M, Segar W. The maintenance need for water in parenteral fluid therapy. Pediatrics 1957; 823-832.
15. Newburgh L, Johnston M. The insensible loss of water. Physiological Reviews 1942; 22(1):1-18.
16. Newburgh L, Johnston M, Falcon-Lesses M. Measurement of total water exchange. J.Clin Invest 1930; 8:161-196.
17. Grandjean AC, Reimers KJ, Haven MC, Curtis GL. The effect on hydration of two diets, one with and one without plain water. JACN 2003; 22(2):165-173.
18. Grandjean AC, Reimers KJ, Bannick KE, Haven MC. The effect of caffeinated, non-caffeinated, caloric and non-caloric beverages on hydration. JACN 2000; 19(5):591-600.
19. Howard G, Bartram J. Domestic Water Quantity, Service, Level and Health. World Health Organization, 2003. Ref Type: Report

20. Gisolfi C. Water requirements during exercise in the heat. In: Marriott B, editor. *Nutritional Needs in Hot Environments*, Washington, DC: National Academy Press, 1993:87-96.
21. Sawka MN, Montain SJ. Fluid and electrolyte balance: effects on thermoregulation and exercise in the heat. In: Bowman BA, Russell RM, editors. *Present Knowledge in Nutrition*, Washington, DC: ILSI Press, 2001:115-124.
22. Council on Pharmacy and Chemistry. The addition of salt to drinking water. *JAMA* 1945; 129(2):131.
23. Johnson RE. Nutritional standards for men in tropical climates. *Gastroenterology* 1943; 1:832-840.
24. Strydom NB, Van Graan CH, Holdsworth LD. The water requirements of humans. *J. Occup Med* 1965; 7(11):581-587.
25. Adolph EF, Dill DB. Observations on water metabolism in the desert. *Am J Physiol* 1938; 123:369-378.
26. Pitts GC, Johnson RE, Consolazio FC. Work in the heat as affected by intake of water, salt and glucose. *Am J Physiol* 1944; 142:253-259.
27. Greenleaf JE, Harrison MH. Water and electrolytes. In: Layman DK, editor. *Nutrition and Aerobic Exercise*, Washington, D C: American Chemical Society, 1986:107-124.
28. Buskirk ER, Mendez J. Nutrition, environment and work performance with special reference to altitude. *Fed Proc* 1967; 26(6):1760-1767.
29. Mohlman HT, Katchman BJ, Slonim AR. Human water consumption and excretion data for aerospace systems. *Aerosp Med* 1968; 39(4):396-402.
30. Strydom NB, Wyndham CH, Van Graan CH, Holdsworth LD, Morrison JF. The influence of water restriction on the performance of men during a prolonged march. *S. A. Medical Journal* 1966; 539-544.
31. Wasterlund D. Heat stress in forestry work. *Acta Universitatis Agriculturae Suecia*, 2001.
32. Wasterlund D. A review of heat stress research with application to forestry. *Applied Ergonomics* 1998; 29(3):179-183.
33. Brake DJ, Bates GP. Fluid losses and hydration status of industrial workers under thermal stress working extended shifts. *Occup Environ Med* 2003; 60:90-96.
34. Grandjean AC, Reimers KJ. Urine specific gravity is not a reliable indicator of hydration status. *MSSE* 2000; 32[5], S197. Ref Type: Abstract
35. Popowski LA, Oppliger RA, Lambert GP, Johnson AK, Gisolfi CV. Is urine specific gravity a satisfactory measure of hydration status? *MSSE* 1999; 31[5], S323. Ref Type: Abstract
36. Mudambo KSMT, Scrimgeour CM, Rennie MJ. Adequacy of food rations in soldiers during exercise in hot, day-time conditions assessed by doubly labelled water and energy balance methods. *Eur J Apply Physiol* 1997; 76:346-351.
37. Montain SJ, Latzka WA, Sawka MN. Fluid replacement recommendations for training in hot weather. *Mil Med* 1999; 164(7):502-508.
38. Kolka MA, Latzka WA, Montain SJ, Corr WP, O'Brien KK, Sawka MN. Effectiveness of revised fluid replacement guidelines for military training in hot weather. *Aviat Space Environ Med* 2003; 74(3):242-246.

39. Food and Nutrition Board. Recommended Dietary Allowances. Washington, DC: National Academy Press, 1943.
40. Food and Nutrition Board. Recommended Dietary Allowances. National Research Council, 1945.
41. Gisolfi C, Lamb D. Perspectives in exercise science and sports medicine. Vol. 3. Fluid homeostasis during exercise. Carmel (IN): Benchmark Press Inc, 1990.
42. Armstrong LE, Hubbard RW, Szlyk PC, Matthew WT, Sils IV. Voluntary dehydration and electrolyte losses during prolonged exercise in the heat. *Aviat Space Environ Med* 1985; 56:765-770.
43. Casa DJ, Armstrong LE, Hillman SK, Montain SJ, Reiff RV, Rich BSE, Roberts WO, Stone JA. National athletic trainers' association position statement: Fluid replacement for athletes. *Journal of Athletic Training* 2000; 35(2):212-224.
44. Convertino VA, Armstrong LE, Coyle EF, Mack GW, Sawka MN, Senay LC, Sherman WM. American College of Sports Medicine. Position Stand on Exercise and Fluid Replacement. *Med Sci Sports Exerc* 1996; 28(1):i-vii.
45. Epstein Y, Armstrong LE. Fluid-electrolyte balance during labor and exercise: concepts and misconceptions. *Int'l J Sport Nutr* 1999; 9:1-12.
46. Latzka WA, Montain SJ. Water and electrolyte requirements for exercise. *Clinics in Sports Medicine* 1999; 18:513-524.
47. Sawka MN, Francesconi RP, Young J, Pandolf KB. Influence of hydration level and body fluids on exercise performance in the heat. *JAMA* 1984; 252:1165-1169.
48. Williams B, Florez Y, Pettygrove S. Inter- and intra-ethnic variation in water intake, contact, and source estimates among Tucson residents: Implications for exposure analysis. *Journal of Exposure Analysis and Environmental Epidemiology* 2001; 11:510-521.
49. Ramsay DJ, Booth DA. International Life Sciences Institute. Thirst: physiological and psychological aspects. London: Springer-Verlag, 1991.
50. Rozin P, Cines BM. Ethnic differences in coffee use and attitudes to coffee. *Ecology of Food and Nutrition* 1982; 12:79-88.
51. Eggleton MG. The diuretic action of alcohol in man. *J Physiol* 1942; 101:172-191.
52. Murray MM. The diuretic action of alcohol and its relation to pituitrin. *J Physiol (Lond)* 1932; 76:379-386.
53. Roberts KE. Mechanism of dehydration following alcohol ingestion. *Arch Intern Med* 1963; 112:154-157.
54. Rubini ME, Kleeman CR, Lamdin E. Studies on alcohol diuresis. I. The effect of ethyl alcohol ingestion on water, electrolyte and acid-base metabolism. *J Clin Invest* 1955; 34:439-447.
55. Stookey JD. The diuretic effects of alcohol and caffeine and total water intake misclassification. *European Journal of Epidemiology* 1999; 15:181-188.
56. Taivainen H, Laitinen K, Tahtela R, Kilanmaa K, Valimaki MJ. Role of plasma vasopressin in changes of water balance accompanying acute alcohol intoxication. *Alcohol Clin Exp Res* 1995; 19(3):759-762.

57. Shirreffs SM, Maughan RJ. Restoration of fluid balance after exercise-induced dehydration: effects of alcohol consumption. *J Appl Physiol* 1997; 83(4):1152-1158.
58. Collins GB, Bronsnihan KB, Zuti RA, Messina M, Gupta MK. Neuroendocrine, fluid balance, and thirst responses to alcohol in alcoholics. *Alcohol Clin Exp Res* 1992; 16(2):228-233.
59. Oglivie KM, Lee S, Rivier C. Role of arginine vasopressin and corticotropin-releasing factor in mediating alcohol-induced adrenocorticotropin and vasopressin secretion in male rats bearing lesions of the paraventricular nuclei. *Brain Research* 1997; 744:83-95.
60. Rolls B. Homeostatic and non-homeostatic controls of drinking in humans. In: Arnaud MJ, editor. *Hydration throughout life*, London: John Libbey and Company Ltd. 1998:19-28.
61. Ershow AG, Cantor KP, Federation of American Societies for Experimental Biology, Life Sciences Research Office, National Cancer Institute (U.S.), Epidemiology and Biostatistics Program. Total water and tapwater intake in the United States population-based estimates of quantities and sources. Bethesda, MD: Life Sciences Research Office, Federation of American Societies for Experimental Biology, 1989.
62. Heller KE, Sohn W, Burt BA, Eklund SA. Water consumption in the United States in 1994-96 and implications for water fluoridation policy. *J Public Health Dent* 1999; 59(1):3-11.
63. United States Department of Agriculture. 1994-96 Continuing Survey of Food Intake by Individuals. <http://www.barc.usda.gov/bhnrc/foodsurvey/Cd94-96.html>. 1999.
Ref Type: Electronic Citation
64. Bellet S, Roman L, DeCastro O, Kim K, Kershbaum A. Effect of coffee ingestion on catecholamine release. *Metabolism* 1969; 18:288-291.
65. Dorfman LJ, Jarvik ME. Comparative stimulant and diuretic actions of caffeine and theobromine in man. *Clin Pharmacol Ther* 1970; 11(6):869-872.
66. Massey L, Wise K. The effect of dietary caffeine on urinary excretion of calcium, magnesium, sodium and potassium in healthy young females. *Nutr Res* 1984; 4:43-50.
67. Neuhäuser-Berthold M, Beine S, Verwied SC, Luhrmann PM. Coffee consumption and total body water homeostasis as measured by fluid balance and bioelectrical impedance analysis. *Ann Nutr Metab* 1997; 41(1):29-36.
68. Passmore AP, Kondowe GB, Johnston GD. Renal and cardiovascular effects of caffeine: a dose-response study. *Clin Sci (Lond)* 1987; 72(6):749-756.
69. Robertson D, Frölich JC, Carr RK, Watson JT, Hollifield JW, Shand DG, Oates JA. et al. Effects of caffeine on plasma renin activity, catecholamines and blood pressure. *NEJM* 1978; 298:181-186.
70. Wemple R, Lamb D, McKeever K. Caffeine vs caffeine-free sports drinks: effects on urine production at rest and during prolonged exercise. *Int J Sports Med*. 1997; 18:40-46.
71. Colton T, Gosselin R, Smith R. The tolerance of coffee drinkers to caffeine. *Clin Pharmacol Ther* 1968; 9:31-39.
72. Denaro C, Brown C, Jacob PI, Benowitz N. Effects of caffeine with repeated dosing. *Eur J Clin Pharmacol* 1991; 40:273-278.
73. Goldstein A, Kaizer S, Whitby O. Psychotropic effects of caffeine in man. IV. Quantitative and qualitative differences associated with habituation to coffee. *Clin Pharmacol Ther* 1969; 10:489-497.

74. Myers M, Reeves R. The effect of caffeine on daytime ambulatory blood pressure. *Am J Hypertens* 1991; 4:427-431.
75. Robertson D, Wade D, Workman R, Woosley RL, Oates JA. Tolerance to the humoral and hemodynamic effects of caffeine in man. *J Clin Invest* 1981; 67(4):1111-1117.
76. Eddy NB, Downs AW. Tolerance and cross-tolerance in the human subject to the diuretic effect of caffeine, theobromine and theophylline. *J Pharmacol Exp Ther* 1928; 33:167-174.
77. Armstrong LE. Caffeine, body fluid-electrolyte balance, and exercise performance. *Int J Sport Nutr and Exer Metab* 2002; 12:189-206.
78. Alper C. Fluid and Electrolyte Balance. In: Wohl MG, Goodhart RS, editors. *Modern Nutrition in Health and Disease*. 1968:404-424.
79. Bland JH. Basic physiologic considerations of body water and electrolyte. *Clinical Metabolism of Body Water and Electrolytes*. Philadelphia: Saunders, 1963: 10-53.
80. Food and Nutrition Board. *Water*. 7 ed. Washington, DC: National Academy Press, 1968.
81. Food and Nutrition Board. *Water*. 8 ed. Washington, DC: National Academy Press, 1974.
82. Food and Nutrition Board. *Water and Electrolytes*. 9 ed. Washington, DC: National Academy Press, 1980.
83. Wilkens LR, Kadir MM, Kolonel LN, Nomura AM, Hankin JH. Risk factors for lower urinary tract cancer: the role of total fluid consumption, nitrites and nitrosamines, and selected foods. *Cancer Epidemiol Biomarkers Prev* 1996; 5(3):161-166.
84. Mirvish SS, Grandjean AC, Moller H, Fike S, Maynard T, Jones L, Rosinsky S, Nie G. N-nitrosoproline excretion by rural Nebraskans drinking water of varied nitrate content. *Cancer Epidemiol Biomarkers Prev* 1992; 1(6):455-461.
85. Vena JE, Graham S, Freudenheim J, Marshall J, Zielezny M, Swanson M, Sufrin G. Drinking water, fluid intake, and bladder cancer in western New York. *Arch Environ Health* 1993; 48(3):191-198.
86. Bruemmer B, White E, Vaughan TL, Cheney CL. Fluid intake and the incidence of bladder cancer among middle-aged men and women in a three-county area of western Washington. *Nutr Cancer* 1997; 29(2):163-168.
87. Borghi L, Meschi T, Amato F, Briganti A, Novarini A, Giannini A. Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: a 5-year randomized prospect study. *J Urol* 1996; 155(3):839-843.
88. Embon OM, Rose GA, Rosenbaum T. Chronic dehydration stone disease. *Br J Urol* 1990; 66(4):357-362.
89. Inouye SK. Prevention of delirium in hospitalized older patients: risk factors and targeted intervention strategies. *Ann Med* 2000; 32:257-263.
90. Lawlor PG, Gagnon B, Mancini IL, Pereira JL, Hanson J, Suarez-Almazor ME, Bruera ED. Occurrence, causes, and outcome of delirium in patients with advanced cancer. A prospective study. *Arch Intern Med* 2000; 160:786-794.
91. Read NW, Celik AF, Katsinelos P. Constipation and incontinence in the elderly. *J Clin Gastroenterol* 1995; 20(1):61-70.

92. Ship JA, Fischer DJ. The relationship between dehydration and parotid salivary gland function in young and older healthy adults. *J Gerontology: Medical Sciences* 1997; 52A(5):M310-M319.
93. Curhan GC, Willett WC, Knight EL, Stampfer MJ. Dietary factors and the risk of incident kidney stones in younger women. *Nurses' Health Study II* 2004; 64:885-891.
94. Rodgers AL. Effect of mineral water containing calcium and magnesium on calcium oxalate urolithiasis risk factors. *Urol Int* 1997; 58(2):93-99.
95. Bitterman WA, Farhadian H, Abu SC, Lerner D, Amoun H, Krapf D, Makov UE. Environmental and nutritional factors significantly associated with cancer of the urinary tract among different ethnic groups. *Urol Clin North Am* 1991; 18(3):501-508.
96. Braver DJ, Modan M, Chetrit A, Lusky A, Braf Z. Drinking, micturition habits, and urine concentration as potential risk factors in urinary bladder cancer. *J Nat'l Cancer Ins* 1987; 78(3):437-440.
97. Hosking DH, Erickson SB, Van den Berg CJ, Wilson DM, Smith LH. The stone clinic effect in patients with idiopathic calcium urolithiasis. *J Urol* 1983; 130(6):1115-1118.
98. Hughes J, Norman RW. Diet and calcium stones. *CMAJ* 1992; 146(2):137-143.
99. Iguchi M, Umekawa T, Ishikawa Y, Katayama Y, Kodama M, Takada M, Katoh Y, Kataoka K, Kohri K, Kurita T. Clinical effects of prophylactic dietary treatment on renal stones. *J Urol* 1990; 144(2 Pt 1):229-232.
100. Lax D, Eicher M, Goldberg SJ. Mild dehydration induces echocardiographic signs of mitral valve prolapse in healthy females with prior normal cardiac findings. *Am Heart J* 1992; 124(6):1533-1540.
101. Lubin F, Rozen P, Arieli B, Farbstein M, Knaani Y, Bat L, Farbstein H. Nutritional and lifestyle habits and water-fiber interaction in colorectal adenoma etiology. *Cancer Epidemiol Biomarkers Prev* 1997; 6(2):79-85.
102. Michaud DS, Spiegelman D, Clinton SK, Rimm EB, Curhan GC, Willett WC, Giovannucci EL. Fluid intake and the risk of bladder cancer in men. *NEJM* 1999; 340(18):1390-1397.
103. Pohlabein H, Jockel KH, Bolm-Audorff U. Non-occupational risk factors for cancer of the lower urinary tract in Germany. *Eur J Epidemiol* 1999; 15(5):411-419.
104. Slattery ML, Caan BJ, Anderson KE, Potter JD. Intake of fluids and methylxanthine-containing beverages: association with colon cancer. *Int J Cancer* 1999; 81(2):199-204.
105. Shannon J, White E, Shattuck AL, Potter JD. Relationship of food groups and water intake to colon cancer risk. *Cancer Epidemiol Biomarkers Prev* 1996; 5(7):495-502.
106. Geoffroy-Perez B, Cordier S. Fluid consumption and the risk of bladder cancer: results of a multicenter case-control study. *Int J Cancer* 2001; 93(6):880-887.
107. Slattery ML, West DW, Robison LM. Fluid intake and bladder cancer in Utah. *Int J Cancer* 1988; 42:17-22.
108. Chan J, Knutsen SF, Blix GG, Lee JW, Fraser GE. Water, other fluids, and fatal coronary heart disease: the Adventist Health Study. *Am J Epidemiol* 2002; 155(9):827-833.
109. Hopcraft MS, Morgan VM. Exposure to fluoridated drinking water and dental caries experience in Australian army recruits, 1996. *Community Dent Oral Epidemiol* 2003; 31:68-74.

4.

ESSENTIAL NUTRIENTS IN DRINKING WATER

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I. INTRODUCTION

Most of the inorganic chemicals in drinking water are naturally occurring. They are acquired by the contact of water with rocks and soil and the effects of the geological setting, including climate (1-4). However, the chemical composition of drinking water also depends on the contaminating effects of industry, human settlements, agricultural activities and water treatment and distribution (1-4). Depending on water quality at the source, filtration, coagulation, and addition of chemicals to adjust pH and/or control corrosion treatments are employed (1-5). In addition, chlorination or iodination may be used for disinfection and fluoridation for the prevention of dental caries (6-8). Leaching of minerals from metal components used in water treatment plants and plumbing materials occurs when pH and hardness of water are not adjusted. Some of the main sources of dissolved metals include: for Cu- copper or brass plumbing system; Fe- cast iron, steel, and galvanised plumbing system; Zn- zinc galvanised pipes; Ni- chromium-nickel stainless plumbing system; Pb- derived from tin-lead or lead solder; and for Cd- as an impurity in zinc galvanised pipes or cadmium containing solders (1-4,9). Recently, fortification of drinking water has been used in the prevention of iron deficiency in children (10) and to provide iodine in select populations (11).

II. DEFINITION OF NUTRITIONAL REQUIREMENTS AND RECOMMENDATIONS

Experts from many countries and international organisations have defined nutritional needs and recommendations. The requirement of a nutrient, as defined by the World Health Organization, Food and Agriculture Organization of the United Nations and the International Atomic Energy Agency (WHO/FAO/IAEA) Expert Consultation on Trace Elements in Human Nutrition and Health, is “the lowest continuing level of nutrient intake that, at a specified efficiency of utilisation, will maintain the defined level of nutriture in the individual” (12). Basal requirement is the “intake needed to prevent pathologically relevant and clinically detectable signs of impaired function attributable to inadequacy of the nutrient”. However, the basal requirement does not account for the needs to maintain nutrient reserves in the body or consider the amount sufficient to ensure that absorption and retention were not operating at maximum capacity. Therefore, the value needed to fulfill the basal requirement plus these additional needs to maintain a level of tissue storage or other reserves constitutes the normative requirement (12).

However, how important reserves are is an open question. The criterion utilised to define nutrient inadequacy may differ for individuals at different life stage. On the other hand, the knowledge of the criteria used to define nutrient inadequacy is important to integrate and/or compare requirements obtained from different sources of evidence.

Several methods have been utilised to estimate requirements and each has particular strengths and weaknesses. Nutrient requirements can be calculated by using metabolic balance studies at different levels of intake, factorial modelling, in which the amount of the nutrient needed to replace utilisation and losses is calculated, depletion/repletion studies, and/or epidemiological evidence (12-17). Balance studies and factorial analysis calculations can be biased since individuals can adapt to the level of nutrient intake by modifying absorption and/or losses. As previously mentioned, micromineral requirements can be studied by experimental diets with different micromineral intakes, thus determining the minimal nutrient intake that prevents the development of biochemical abnormalities or functions. However, these experimental diets may also have modifications in other nutrients that could affect absorption of the studied nutrient or influence the biochemical or physiological parameters employed in the assessment of its status. In addition, the biochemical parameters may not be sufficiently sensitive and/or specific in detecting marginal nutrient status. Another method is to calculate the requirements based on epidemiological studies of nutrient status carried out in healthy populations with different nutrient intake profiles (12-15,17).

Dietary reference intakes are provided to promote optimal health by avoiding consequences of nutrient deficiency and excess. However, for some nutrients there is limited information to scientifically support the nutritional needs across age ranges, gender and physiological states.

The Institute of Medicine of the US National Academy of Sciences (IOM) has developed dietary reference intakes (DRI) that include the Estimated Average Requirement (EAR), Recommended Dietary Allowance (RDA), Adequate Intake (AI) and Tolerable Upper Intake Level (UL) (13). The EAR, RDA, and AI values represent the amount of the nutrient to be supplied by foods from a diet similar to those consumed in Canada and the United States. EAR is the daily intake of a nutrient that is estimated to meet the requirement of 50% of apparently healthy individuals of a given sex and age. The RDA is the average daily intake level that is sufficient to meet the nutrient requirement of 97.5% of the population of apparently healthy persons of a given sex and age. This value is intended to be used as a goal for daily intake by all individuals to be reached as an average over a given time; usually weeks or months. When there is insufficient information available to calculate an EAR, an AI value based on experimentally derived intake levels or approximations of customary mean nutrient intakes by group or groups of healthy subjects, is used instead of the traditional RDA. The UL is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effect for almost all individuals in a specified sex and age group. The development of a UL for a nutrient requires: 1. Hazard identification (identification of all known adverse effects associated with the nutrient). 2. Analysis of dose response studies to identify the lowest no observed adverse effect level (NOAEL) based on all identified hazards, and 3. Application of an uncertainty factor, that compensates for extrapolation from the observed to the general population (13,18).

WHO/FAO/IAEA has established safe levels of population mean intakes that would suffice to ensure a low prevalence of individuals at risk of either inadequate or excessive intakes (12). The lower limit of the population mean intake is “the lowest mean intake at which the population risks of depletion remain acceptable when judged by normative criteria”, while the upper limit is “the maximum population mean intake at which the risks of toxicity remain tolerable”. Between these limits the risk of inadequacy or excess is acceptably low. In addition, the lower limit of the population mean intake was established based on the basal requirement criteria. Below this limit there is a gradual increase on the prevalence of individuals expected to show demonstrable signs

of functional impairment. Recently FAO/WHO defined recommended nutrient intake (RNI) as “the daily intake, which meets the nutrient requirements of almost all (97.5 percent) apparently healthy individuals in an age and sex-specific population group” (19). This definition is equivalent to that of RDA. RNI considers the nutrient intake from food including water.

In 1993 the Scientific Committee for Food of the European Commission (15) defined the Lowest Threshold Intake (LTI) as “the intake below which nearly all individuals will be unable to maintain metabolic integrity according to the criterion chosen for each nutrient”. The Average Requirement (AR) is the intake that covers 50% of requirements for the group according to criteria chosen. The Population Reference Intake (PRI) is “the intake that will meet the needs of nearly all healthy people in a group” (97.5%).

An interesting modification in the approach to define the regulatory framework for assessing risks for essential trace elements is the concept of including the risk of both deficiency and excess in the model. In 2001 the International Programme on Chemical Safety (IPCS) proposed a methodology to establish a homeostatic model for determining the Adequate Range of Oral Intake (AROI) of essential trace elements (20). This model includes weighing the evidence of hazards linked to deficit with that related to excess and selecting relevant endpoints of deficiency and toxicity at different ages, gender and conditions. In addition, the probability of risk and the severity of various effects are quantified and those that are critical to determine cut-off points for deficiency and toxicity are selected. The AROI is established by balancing endpoints of comparable health significance on the deficiency and excessive intake sides.

III. WHAT ARE THE IMPORTANT DIETARY MINERALS AND ELECTROLYTES IN THE DIET AND POTENTIALLY IN WATER THAT ARE ESSENTIAL FOR NUTRITION AND WELLBEING?

Calcium, Na, K, Cl, Mg, Fe, Zn, Cu, Cr, I, Co, Mo and Se are unequivocally essential for human health; although not commonly realised drinking water provides some of these elements. A second group of elements that have some beneficial health effects, include F in the prevention of dental caries and B, Mn, Ni, Si and Va, that may be considered essential for humans based on emerging information. The third group is composed of the potentially toxic elements Pb, Cd, Hg, As, Al, Li and Sn (1,3,12,21).

The relative contribution of water to total dietary intake of selected trace elements and electrolytes is between 1 and 20%. The micronutrients with the largest proportion of intake from drinking water relative to that provided by food are calcium and magnesium. For these elements water may provide up to 20% of the required total daily intake. For the majority of other elements drinking water provides less than 5 % of total intake (1,3,12,21). An exception may be the high contribution of fluoride and arsenic in certain geographic regions (eg. deep-water wells, water passing through volcanic run-offs, desert sources) (1,3,12,21).

It is customarily assumed that the intake of essential elements is primarily covered by foods, thus minimum desirable levels in drinking water are not considered necessary. Yet for populations that have low consumption of animal flesh foods the intake of Fe, Zn and Cu may in fact be marginal or lower than needed, in which case sufficiency may depend on the metal contamination of foods and water. Some epidemiological evidence suggests that water hardness is associated with beneficial effects for human health. The ample epidemiological evidence, which is supported by case control studies, demonstrates an inverse relationship between drinking water hardness and cardiovascular or cerebrovascular diseases (3). However, available information is insufficient to conclude that the relationship is causal.

IV. WHAT ARE THE RDAS FOR MINERALS AND ELECTROLYTES AND HOW ARE THEY DETERMINED?

We will review and analyse how RDAs for iron, zinc, copper, iodine, calcium, phosphorus, magnesium, fluoride, sodium, potassium and chloride were established. AIs are provided instead of RDAs when there is insufficient scientific information to estimate requirements. The nutrient intake of breast-fed infants is frequently utilised to set AIs for infants from 0 to 6 months of age; for infants 7 to 12 months of age the average intake from human milk plus the additional intake provided by complementary foods is utilised (12,14,15). Determining values for requirements during pregnancy usually includes an estimate of the quantity of the element required by the foetus and other products of pregnancy, and required for body changes that occur during this stage of the life cycle (i.e. expansion of blood volume) (12,14,15,19). Requirements for lactation include the need to replace the amount of the nutrient lost daily in human milk (12,14,15,19). The dietary reference intakes and WHO standard for drinking water for iron, zinc, copper, iodine, calcium, phosphorus, magnesium, fluoride, sodium, potassium and chloride are summarised in tables 1 to 9.

1. Iron

Iron participates in numerous processes necessary for normal body functions: oxygen transport, oxidative phosphorylation, metabolism of neurotransmitters, and DNA synthesis require iron (22). While the main effect of iron deficiency is anaemia, other manifestations of iron deficiency include impaired mental and motor development and altered behaviour. Other symptoms that may be observed with iron deficiency are delayed nerve conduction affecting the auditory and visual systems, decreased capacity for physical work, increased spontaneous motor activity, impaired cell-mediated immunity and bactericidal capacity of neutrophils, impaired thermoregulation, functional and histologic abnormalities of the gastrointestinal tract, defective mobilisation of liver vitamin A, increased risk of premature birth, low birth-weight and growth retardation, increased perinatal morbidity and reduced iron transfer to the foetus (23-26). Iron deficiency is the single most common nutritional disorder worldwide and the main cause of anaemia in infancy, childhood and pregnancy (27). It is prevalent in most of the developing world and it is probably the only significant nutritional deficiency found in industrialised countries. The main cause of iron deficit is a diet low in bioavailable iron (27).

Requirements of absorbed iron are calculated by factorial modelling. The estimate is derived from the sum of basal iron losses, menstrual losses in women of fertile age, body iron accretion for growth and iron needed by foetus, placenta and expansion of the red cell mass in pregnancy, iron losses by milk in nursing women, and needs to maintain minimal iron stores to ensure normal function (14,15,19,28). Basal losses include obligatory losses of iron in the faeces, physiological blood loss and enterocyte desquamation, urine, sweat, and exfoliation of skin cells. Body iron stores, composition of the diet and rate of erythropoiesis influences the proportion of absorbed iron (22). The balance of dietary components that inhibit or enhance iron absorption have a crucial role in determining non-haeme iron absorption (22). However, because haeme-iron is absorbed intact into the enterocyte its absorption is practically not affected by the diet or diet related factors. The IOM calculated average dietary iron requirements assuming an average iron absorption that varies among the different age, gender and physiological groups (10% for infants 7 to 12 months, upper limit of 18% for children and adolescents, adults and lactating women, and an upper limit of 25% for pregnant women) (14). The FAO/WHO Expert Consultation estimated dietary iron requirements for subjects consuming diets of low (5%), intermediate (10%) and high iron bioavailability (15%) (28). The recent FAO/WHO expert committee on vitamin and minerals provided recommended intakes considering diets of 5, 10, 12 and 15% of iron bioavailability (19).

The Scientific Committee for Food of the European Commission utilised a value of 15% for iron bioavailability (15).

2. Zinc

Zinc is an essential trace element that is a catalytic component of over 300 enzymes, which also has a role in the structural integrity of proteins and membranes, in the union of hormones to its receptors, and in gene expression (29). Zinc is required for growth, normal development, DNA synthesis, immunity, and sensory functions. Manifestations of zinc deficiency include growth retardation, delayed sexual and skeletal maturation, alteration in cell-mediated immunity, impaired resistance to infections, anorexia, impaired taste, delayed wound healing, behavioural effects, skin lesions and alopecia (29-32). The true prevalence of zinc deficiency at a global level is not known because of the lack of sensitive indicators of zinc status (33). It has been estimated using information on the inadequacy of daily zinc intake in developing and industrialised countries. Recently, an UNICEF expert consultation group concluded that zinc deficiency is a prevalent problem in developing countries and that its magnitude should be very similar to that of iron deficiency (34).

Zinc requirements have been determined using factorial analysis. The value is based on the minimal amount of absorbed zinc necessary to replace daily excretion of endogenous zinc and tissue growth, zinc accretion during pregnancy and zinc losses by milk in the case of nursing women (12,14,15,19). Excretion of endogenous zinc by the intestine is the main component of zinc losses, while losses in urine, menses, semen and integument exfoliation contribute to a lesser extent (35). This serves to estimate the required amount of absorbed zinc to compensate for losses. Zinc absorption is inversely related to dietary intake and efficiency of absorption is influenced by the physical and chemical properties of zinc in foods and the interaction of zinc with absorption inhibitors and enhancers (36). Diets have been characterised as of low, intermediate and high zinc bioavailability, based on the composition of the diet (12). FAO/WHO/IAEA and FAO/WHO have provided recommendations for age and sex groups consuming diets with high, moderate and low availability (12,19), while IOM recommendations are based on studies in which zinc bioavailability was likely to be representative of typical diets in North America (14). For some life stage groupings requirements were corroborated by secondary indicators of zinc depletion and results of the effect of supplementation on biochemical and other laboratory parameters of zinc status, zinc intake and linear growth (12,14).

3. Copper

Copper is responsible for structural and catalytic properties of multiple enzymes necessary for normal body functions (37). This metal is required for infant growth, host defence mechanisms, bone strength, red and white cell maturation, iron transport and brain development (38). Anaemia, neutropenia, and bone abnormalities (osteoporosis, fractures, etc.) are the main manifestations of copper deficiency. Other effects described include hypopigmentation of the hair and skin, hypotonia, impaired growth, increased incidence of infections and altered immunity (37-39). In Menkes disease, a genetic form of copper deficiency, symptoms include abnormal spiral twisting of the hair, lax skin and articulations, tortuosity and dilatation of major arteries, varicosities of veins, retinal dystrophy, profound central nervous system damage, and death (38). Some epidemiological studies have shown an association between cardiovascular mortality with low copper intake and/or low serum copper levels (40-43). Acquired deficiency occurs mainly in young infants; however, it has also been diagnosed in children and in adults (38). Most cases have been described in malnourished children (37-40). The true global prevalence of copper deficiency is unknown, but it is associated with common conditions such as low birth weight and child malnutrition.

Copper requirements have been estimated from controlled studies in which the effects of copper intake on copper status were measured. Copper nutrition in infants and in adults has been evaluated using a combination of laboratory indicators (12,14,15). Requirements of children and adolescents were interpolated from the infant and adult data on requirements.

4. Iodine

Iodine is a critical component of thyroid hormones (44). Approximately 60% of the total body iodine is stored in the thyroid gland. Thyroid hormones are necessary for cell growth and differentiation, the maintenance of metabolic rate and overall cellular metabolism (45). Iodine deficiency is frequently observed in populations living in environments where the soil is devoid of iodine due to leaching by the action of glaciation, rain or floods. Twenty-nine percent of the world's population lives in areas at risk of iodine deficiency (46). Iodine deficiency induces enhanced iodine uptake by thyroid cells and an increase size of the thyroid gland (goitre). If these compensatory mechanisms are not enough to produce normal serum levels of thyroid hormones, symptoms and signs of hypothyroidism develop including impaired growth, mental retardation, and reproductive failure (47). Iodine deficiency is recognised as the most important preventable cause of mental retardation in the world today. The iodination of table salt has been introduced worldwide as a public health measure to eradicate iodine deficiency (47). The prevalence of this disorder has progressively declined in populations with access to this fortified product, however, there are large segments of the world's population that are not yet covered by these programs.

Requirements have been estimated from balance studies, thyroidal radiiodine accumulation and turnover, and iodine intake necessary to maintain a normal thyroid size and to provide thyroid iodine stores sufficient for a normal thyroid hormone synthesis (14,15,19). Additional iodine needs during pregnancy were estimated based on the thyroid iodine content of new-born infants, iodine balance studies, and the effect of iodine supplementation on maternal thyroid volume and/or thyroid function (14,19).

5. Calcium

Calcium is the most abundant mineral in the body (1.5 – 2.0% of the total body weight). The total body content of an adult is approximately 1.2 Kg, 99% of which is stored in the skeleton and 1% in extra- and intracellular fluids and cellular membranes (13,15,48-50). In addition to its major function as a primary structural constituent of the skeleton, calcium is also important for the regulation of multiple enzymes and hormonal responses, blood clotting, nerve transmission, muscle contraction/relaxation (including normal heart rhythm), vascular contraction and vasodilation, and glandular secretion (13,48-51). Calcium deficiency leads to decrease in bone mineral content and mass that results in a weaker bone structure, leading to increased risk for bone fractures (13,48-51).

According to the IOM insufficient information is available to establish precise requirements, thus an AI is provided for each of the life stage groups. The AIs were derived from balance studies, factorial modelling using calcium accretion based on bone mineral accretion and clinical trials which evaluated the response/change in bone mineral content/density or fracture rate to varying calcium intakes (50). The Scientific Committee for Food of the European Commission utilised factorial analysis to estimate requirements for calcium (15). The recent FAO/WHO expert committee on vitamin and minerals provided recommended intakes considering the effect of protein and salt intake, thus calcium recommendations are substantially lower for populations in developing countries with lower salt and protein intakes (19). This is relevant since most populations in developing countries not consuming dairy products have difficulty meeting the traditional calcium recommendations based on data obtained in industrialised countries.

6. Phosphorus

Phosphorus as calcium phosphate (calcium hydroxyapatite) is a structural component of bones it is found in a 1:2 mass ratio relative to calcium (13,15, 48-50). Eighty-five percent of total body phosphorus is found in the skeleton. This element plays an important role as a structural component of cell membrane phospholipids; it is essential for energy production and storage, phosphorylation of numerous enzymes, hormones and cell signalling molecules, and to maintain a normal acid-base equilibrium (51,52). Phosphorus deficiency is rare at the population level, although it has been described in small premature infants exclusively receiving human milk, and in patients receiving aluminium hydroxide containing antacids over extended periods of time (13). Deficiency results in bone mass loss, muscle weakness, malaise, and pain (13).

Requirements of children and adolescents are calculated using a factorial approach based on body accretion in bone and soft tissues, efficiency of absorption and urinary excretion (50). Adult requirements are based on the relationship between serum inorganic phosphorus and dietary intake (50). The Scientific Committee for Food of the European Commission proposed the use of phosphorus intakes that correspond on a molar basis with that for calcium for estimating phosphorus requirements (15).

7. Magnesium

This element is the second most abundant intracellular cation. Adult body content is 20-28 g, 60-65% of which is found in the skeleton and 1% in extracellular fluid (15,53). Magnesium is a cofactor in over 300 enzymatic reactions (15,53). Magnesium is involved in the function of enzymes of carbohydrate, lipid, protein, and nucleic acid metabolisms (15,53). It is essential for the mineralisation and development of the skeleton, and also plays a role in cellular permeability and neuromuscular excitability (15,53).

Magnesium deficiency induces increased neuromuscular excitability, and it enhances potassium renal excretion (15,53). Deficiency of this element has been implicated in hypertension and type II diabetes (15,53). Low magnesium intake has been associated with an increased risk of cardiovascular disease (15,53).

Balance studies provided the basis for the estimation of magnesium requirement (50). Other criteria utilised to provide Mg recommendation are based on the relationship between magnesium intake and magnesium serum levels or magnesium and potassium content of the muscle, and on studies performed in young children recovering from malnutrition with diets containing different concentrations of this mineral (19). The Scientific Committee for Food of the European Commission provided a recommended intake based on observed acceptable range of intakes (15). In the FAO/WHO report 2002 (19) (Table 8), the upper limits of 65 mg for children ages 1-3 years, 110 mg for 4-10 years, and 350 mg for adolescents and adults are suggested as tolerable limits for the content of soluble magnesium in foods and drinking water based on the IOM report published in 1997 (50). However, according to IOM these upper limits are for non-food source, because magnesium has not been shown to produce any toxic effects when ingested as a naturally occurring substance in foods (50).

8. Fluoride

The essentiality of fluoride for humans has not been proven unequivocally (8,12,50). However, this element has beneficial effects on the prevention of dental caries due to the formation of crystalline hydroxyfluorapatite leading to a more acid resistant enamel form (8,12,50). Because there is no sufficient available data to calculate requirements, an AI is provided based on the fluoride intake that reduce the occurrence of dental caries maximally,

without causing untoward effects linked to excess exposure, such as fluorosis (stained enamel) (50).

9. Sodium, Potassium, and Chloride

Sodium is the principal cation in the extracellular fluid, while potassium is predominantly an intracellular cation, and chloride is the main extracellular anion (54,55). These electrolytes have important physiological roles in the maintenance of extracellular fluid volume, extra- and intracellular osmolarity, regulation of acid – base balance, generation of trans-membrane electrochemical gradients, transmission of nerve impulses, and muscle contractions (54,55). In addition to its functions as an electrolyte, chloride is indispensable for gastric hydrochloric acid production (54,55).

Hyponatremia is the most common electrolyte disorder (55). This deficiency usually is the consequence of excessive losses from the body, commonly occurring during prolonged and/or severe diarrhoea or vomiting, or in hot, humid conditions in which a large amount of sodium is lost in sweat (55). Manifestations of hyponatremia, cerebral oedema and neuromuscular hyperexcitability, are the consequences of changes in extracellular fluid volume (55). Symptoms of CNS dysfunction are the most common. Dehydration or metabolic acidosis usually accompanies sodium deficit and these are commonly responsible in part for the clinical findings (55). Signs of sodium deficiency include cramps, weakness, fatigue, nausea, mental apathy, low blood pressure, confusion and seizures (55).

Hypokalemia, low serum potassium, usually occurs as a consequence of increased gastrointestinal losses due to diarrhoea or vomiting (55). Muscle weakness, muscle cramping, paralytic ileus, and cardiac arrhythmia characterise this condition (55).

Deficiency of chloride is rare and results from excessive gastrointestinal loss of chloride-rich fluids (e.g. prolonged episodes of vomiting, diarrhoea) and is associated with a metabolic alkalosis (55).

Balance studies, factorial analysis, daily intakes and biochemical indicators provided the basis for the estimation of sodium and potassium minimum requirements of healthy subjects proposed by the US National Research Council (13) as well as for the acceptable range of intakes for sodium and chloride or population reference intakes for potassium proposed by the Scientific Committee for Food of the European Commission (15). Because both the intakes and losses of chloride normally matched those of sodium, the minimum requirements and acceptable range of intakes of chloride should match those for sodium.

References

1. National Academy of Sciences (NAS). Drinking water and health. Volume I. Washington,DC: National Academy Press, 1977.
2. WHO, International Programme of Chemical Safety. (1993) Guidelines for drinking-water quality. Recommendations. 2nd ed. Vol. 1, Geneva: World Health Organization, 1993.
3. WHO, International Programme of Chemical Safety. Guidelines for drinking-water quality. Health criteria and other supporting information. 2nd ed. Vol. 2, Geneva: World Health Organization, 1996.
4. WHO, International Programme of Chemical Safety. Guidelines for drinking-water quality. Addendum to volume 2 health criteria and other supporting information. Geneva: World Health Organization, 1998.
5. Letterman RD, American Water Work Association, Mays LW. Water quality & treatment handbook. New York, NY: McGraw Hill Book Company, 1999.
6. White GC. Handbook of chlorination and alternative disinfectants. 4th Edition. New York, NY: Wiley-Interscience, 1999.
7. Backer H, Hollowell J. Use of iodine for water disinfection: iodine toxicity and maximum recommended dose. *Environ Health Perspect* 2000;108:679-684.
8. International Programme on Chemical Safety (IPCS). Fluorides. Environmental Health Criteria No 227. Geneva:World Health Organization, 2002.
9. Alam IA, Sadiq M. Metal contamination of drinking water from corrosion of distribution pipes. *Environ Pollut* 1989;57:167-178.
10. Dutra de Oliveira JE, Nogueira de Almeida CA. Domestic drinking water – an effective way to prevent anemia among low socioeconomic families in Brazil. *Food Nutr Bull* 2002;23 (suppl.):213-216.
11. Elnagar B, Eltom, M, Karisson FA, et al. Control of iodine deficiency using iodination of water in a goitre endemic area. *Int J Food Sci Nutr* 1997;48:119-127.
12. WHO/FAO/IAEA. Trace elements in human nutrition and health. Geneva: World Health Organization, 1996.
13. National Research Council (NRC). Food and Nutrition Board. Recommended dietary allowances, 10th ed. Washington, DC: National Academy Press, 1989.
14. Institute of Medicine (IOM), Food and Nutrition Board. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington, DC: National Academy Press, 2002.
15. Scientific Committee for Food (SCF). Nutrient and energy intakes for the European Community. Reports of the Scientific Committee for Food, Thirty-first Series. Luxembourg: European Commission, 1993.
16. Lukaski HC, Penland JG. Functional changes appropriate for determining mineral element requirements. *J Nutr* 1996;126:2354S-2364S.
17. Beaton GH. Statistical approaches to establish mineral element recommendations. *J Nutr* 1996;126:2320S-2328S.
18. Institute of Medicine, Food and Nutrition Board. Dietary reference intakes: a risk assessment model for establishing upper intake levels for nutrients. Washington, DC: National Academy Press, 1998.

19. FAO/WHO. Human vitamin and mineral requirements. Report of a Joint FAO/WHO Expert Consultation, Bangkok, Thailand. Rome: World Health Organization and Food and Nutrition Organization of the United Nations, 2002
20. International Programme on Chemical Safety (IPCS). Principles and methods for the assessment of risk from essential trace elements. Environmental Health Criteria No 228. Geneva: World Health Organization, 2002.
21. National Academy of Sciences (NAS). Drinking water and health. Vol. 3. Washington, DC: National Academy Press, 1980.
22. Bothwell TH, Charlton RW, Cook, JD, Finch CA. Iron metabolism in man. Oxford: Blackwell Scientific, 1979.
23. Lozoff B, Wachs TD. Functional correlates of nutritional anemias in infancy and early childhood -child development and behavior. In: Ramakrishnan U, ed. Nutritional anemias. Boca Raton, FL: CRC Press 2001:70-88.
24. Beard JL. Functional consequences of nutritional anemia in adults. In: Ramakrishnan U, ed. Nutritional anemias. Boca Raton, FL: CRC Press 2001:111-128.
25. Walter T, Olivares M, Pizarro F, Muñoz C. Iron, anemia, and infection. *Nutr Rev* 1997;55:111-124.
26. Ramakrishnan U. Functional consequences of nutritional anemia during pregnancy and early childhood. In: Ramakrishnan U, ed. Nutritional anemias. Boca Raton, FL: CRC Press 2001:44-68.
27. Allen L, Casterline-Sabel J. Prevalence and causes of nutritional anemias. In: Ramakrishnan U, ed. Nutritional anemias. Boca Raton, FL: CRC Press 2001:7-21.
28. FAO/WHO. Requirements of vitamin A, iron, folate and vitamin B12. Report of a Joint FAO/WHO Expert Consultation. Food and Nutrition Series No. 23. Rome: FAO/WHO, 1988:1-107.
29. Hambidge H. Human zinc deficiency. *J Nutr* 2000;130:1344S-1349S.
30. Black RE. (2003) Zinc deficiency, infectious disease and mortality in the developing world. *J Nutr* 2003;133:1485S–1489S.
31. Ibs K-H, Rink L. Zinc-altered immune function. *J Nutr* 2003;133:1452S-1456S.
32. Castillo-Durán C, Weisstaub G. Zinc supplementation and growth of the fetus and low birth weight infant. *J. Nutr.* 2003;133:1494S-1497S.
33. Gibson RS, Ferguson EL. Assessment of dietary zinc in a population. *Am J Clin Nutr* 1998;68:430S– 434S.
34. United Nations Administrative Committee on Coordination. Subcommittee on Nutrition (UN ACC-SCN). *SCN News* 1995:8-9.
35. Krebs NE, Hambidge KM. Zinc metabolism and homeostasis: application of tracer techniques to human zinc physiology. *Biometals* 2001;14:397-412.
36. Lönnerdal B. Dietary factors influencing zinc absorption. *J Nutr* 2000;130:1378S-1383S.
37. Uauy R, Olivares M, González M. Essentiality of copper in humans. *Am J Clin Nutr* 1998;67:952S-959S.
38. Olivares M, Araya M, Uauy R. Copper homeostasis in infant nutrition: deficit and excess. *J Pediatr Gastroenterol Nutr* 2000;31:102-111.

39. Cordano A. Clinical manifestations of nutritional copper deficiency in infants and children. *Am J Clin Nutr* 1998;67:1012S-1016S.
40. Olivares M, Uauy R. Copper as an essential nutrient. *Am. J. Clin. Nutr.* 1996;63:791S-796S.
41. Kok FJ, Duijn C.M.V, Hofman A, et al. Serum copper and zinc and the risk of death from cancer and cardiovascular disease. *Am J Epidemiol* 1988;128:352– 359.
42. Ford ES. Serum copper concentration and coronary heart disease among US adults. *Am J Epidemiol* 2000;151:1182-1188.
43. Klevay LM. Cardiovascular disease from copper deficiency – a history. *J Nutr* 2000;130:489S-492S.
44. Taurog, A. Hormone synthesis: thyroid iodine metabolism. In: Braverman LE, Utiger RD, eds. *The thyroid. A fundamental and clinical text*. Philadelphia: Lippincott JB Publ, 1991:51-97.
45. Davis PF. Cellular actions of thyroid hormones. In: Braverman LE, Utiger RD, eds. *The thyroid. A fundamental and clinical text*. Philadelphia: Lippincott JB Publ, 1991:190-203.
46. WHO/UNICEF/International Council for the Control of Iodine Deficiency Disorders. *Global prevalence of iodine deficiency disorders*, MDIS Working Paper No. 1, World Geneva: Health Organization, 1993.
47. Hetzel BS, Dunn JT. The iodine deficiency disorders: their nature and prevention. *Annu Rev Nutr* 1989;9:21-38.
48. Arnaud CD, Sanchez SD. Calcium and phosphorus. In: Brown ML, ed. *Present knowledge in nutrition*. Washington, DC: International Life Science Institute – Nutrition Foundation, 1990:212-223.
49. Brown EM. The extracellular Ca²⁺ -Sensing receptor: central mediator of systemic calcium homeostasis. *Annu Rev Nutr* 2000;20:507-533.
50. Institute of Medicine (IOM), Food and Nutrition Board. *Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D and fluoride*. Washington, DC: National Academy Press, 1997.
51. Wood, R.J. Calcium and phosphorus. In: Stipanuck MH, ed. *Biochemical and physiological aspects of human nutrition*. Philadelphia: WB Saunders Company, 2000:643-670.
52. Guyton AC, Hall JE. *Medical physiology*. Tenth edition. Philadelphia: WB Saunders Company, 2000.
53. Saris N-EL, Mervaala E, Karppanen H, et al. Magnesium: an update on physiological, clinical and analytical aspects. *Clinical Chimica Acta* 2000;294:1–26.
54. Sheng, H-P. Sodium, chloride and potassium. In: Stipanuck MH, ed. *Biochemical and physiological aspects of human nutrition*. Philadelphia: WB Saunders Company, 2000:686-710.
55. Rose BD, Post,D, Rose B, Narins R. *Clinical physiology of acid-base and electrolyte disorders*. New York, NY: McGraw-Hill Companies, 2000.
56. WHO, International Programme of Chemical Safety. *Guidelines for drinking-water quality*. Third edition. Geneva: World Health Organization, 2003.
http://who.int/water_sanitation_health/dwq/guidelines3rd/en/

Table 1. Recommended daily intakes (iron, zinc and copper) for infants and children.

Group	Years	Fe (mg)						Zn (mg)						Cu (mg)		
		I ^{a,c}		II ^d		III ^e		I ^{b,c}		II ^d		III ^e		IV ^f	II ^d	III ^e
Infants	0-0.25			0.27 ^g				1.1 2.8 6.6		2				0.33-0.55	0.2 ^g	
	0.25-0.5			0.27 ^g				1.1 2.8 6.6		2 ^g				0.37-0.62	0.2 ^g	
	0.5-1	6.2	7.7	9.3	18.6	11	6	2.5	4.1	8.4	3 ^g	4		0.6	0.22 ^g	0.3
Children	1-2	3.9	4.8	5.8	11.6	7	4	2.4	4.1	8.3	3	4		0.56	0.34	0.4
	3	3.9	4.8	5.8	11.6	7	4	2.4	4.1	8.3	3	4		0.56	0.34	0.4
	4-5	4.2	5.3	6.3	12.6	10	4	2.9	4.8	9.6	5	6		0.57	0.44	0.6
	6	4.2	5.3	6.3	12.6	10	4	2.9	4.8	9.6	5	6		0.57	0.44	0.6
	7-8	5.9	7.4	8.9	17.8	10	6	3.3	5.6	11.2	5	7		0.75	0.44	0.7
	9-10	5.9	7.4	8.9	17.8	8	6	3.3	5.6	11.2	8	7		0.75	0.70	0.7

I (19), II (14), III (15), IV (12)

^a Diet of 5%, 10%, 12% and 15% bioavailability.

^b Diet of high, moderate and- low bioavailability.

^c Recommended nutrient intake.

^d Recommended dietary allowances.

^e Population reference intakes.

^f Lowest limit of the population mean intake to meet normative needs.

^g Adequate intake.

Table 2. Recommended daily intakes (iodine, calcium, phosphorus, magnesium and fluoride) for infants and children.

Group	Years	I (ug)			Ca (mg)		P (mg)		Mg (mg)	F (mg)
		I ^a	II ^b	III ^c	V	III ^c	V ^b	III ^c	V ^b	V
Infants	0-0.5	90	110 ^d		210 ^d		100 ^d		30 ^d	0.01 ^d
	0.5-1	90	130 ^d	50	270 ^d	400	275 ^d	300	75 ^d	0.5 ^d
Children	1-3	90	90	70	500 ^d	400	460	300	80	0.7 ^d
	4-6	90	90	90	800 ^d	450	500	350	130	1.0 ^d
	7-8	120	90	100	800 ^d	550	500	450	130	1.0 ^d
	9-10	120	120	100	1300 ^d	550	1250	450	240	2.0 ^d

I (19), II (14), III (15), V (50)

^a Recommended nutrient intake.

^b Recommended dietary allowances.

^c Population reference intakes.

^d Adequate intake.

Table 3. Recommended daily dietary intakes (sodium, potassium and chloride) for the different life stage groups.

Group (years)	Na (mg)		K (mg)		Cl (mg)
	VI ^b	III ^c	VI ^b	III ^d	VI ^b
0-0.5 ^a	120		500		180
0.5-1 ^a	200		700	800	300
1 ^a	225		1000	800	350
2-3 ^a	300		1400	800	500
4-5 ^a	300		1400	1100	500
6 ^a	400		1600	1100	600
7-9 ^a	400		1600	2000	600
10 [*]	500		2000	2000	750
11-17 ^a	500		2000	3100	750
≥18 ^a	500	575-3500	2000	3100	750
Pregnancy	500			3100	
Lactation	500			3100	

III (15), VI (13)

^a Males and females.

^b Minimum requirements.

^c Acceptable range of intakes.

^d Population reference intakes.

Table 4. Recommended daily intakes (iron, zinc and copper) for males.

Group (years)	Fe (mg)						Zn (mg)					Cu (mg)		
	I ^{a,c}		II ^d		III ^e		I ^{b,c}		II ^d		III ^e	IV ^f	II ^d	III ^e
11-12	9.7	12.2	14.6	29.2	8	10	5.1	8.6	17.1	8	9.0	0.73	0.70	0.8
13	9.7	12.2	14.6	29.2	8	10	5.1	8.6	17.1	8	9.0	1.00	0.70	0.8
14	9.7	12.2	14.6	29.2	11	10	5.1	8.6	17.1	11	9.0	1.00	0.89	0.8
15	12.5	15.7	18.8	37.6	11	13	5.1	8.6	17.1	11	9.0	1.00	0.89	1.0
16	12.5	15.7	18.8	37.6	11	13	5.1	8.6	17.1	11	9.0	1.33	0.89	1.0
17	12.5	15.7	18.8	37.6	11	13	5.1	8.6	17.1	11	9.0	1.33	0.89	1.0
18	9.1	11.4	13.7	27.4	11	9	5.1	8.6	17.1	11	9.0	1.33	0.89	1.1
≥19	9.1	11.4	13.7	27.4	8	9	4.2	7.0	14.0	11	9.5	1.35	0.90	1.1

I (19), II (14), III (15), IV (12)

^a Diet of 5%, 10%, 12% and 15% bioavailability.

^b Diet of high, moderate and- low bioavailability.

^c Recommended nutrient intake.

^d Recommended dietary allowances.

^e Population reference intakes.

^f Lowest limit of the population mean intake to meet normative needs.

Table 5. Recommended daily intakes (iron, zinc and copper) for females.

Group (years)	Fe (mg)						Zn (mg)					
	I ^{a,c}				II ^d	III ^e	I ^{b,c}				II ^d	III ^e
11-12	9.3	11.7	14.0	28.0	8	22	4.3	7.2	14.4	8	9	
13	9.3	11.7	14.0	28.0	8	22	4.3	7.2	14.4	8	9	
14	9.3	11.7	14.0	28.0	15	22	4.3	7.2	14.4	9	9	
15	20.7	25.8	31.0	62.0	15	21	4.3	7.2	14.4	9	7	
16-17	20.7	25.8	31.0	62.0	15	21	4.3	7.2	14.4	9	7	
18	19.6	24.5	29.4	58.8	15	20	4.3	7.2	14.4	9	7	
≥19	19.6	24.5	29.4	58.8	18	20	3.0	4.9	9.8	8	7	
Post-menopausal	7.5	9.4	11.3	22.6	8	8	3.0	4.9	9.8			
Pregnancy												
1 st trimester					27		3.4	5.5	11.0	11 (13) ^g	7	
2 nd trimester					27		4.2	7.0	14.0	11 (13) ^g	7	
3 rd trimester					27		6.0	10.0	20.0	11 (13) ^g	7	
Lactation												
0-3 mo	10.0	12.5	15.0	30.0						12 (14) ^g	12	
3-6 mo	10.0	12.5	15.0	30.0						12 (14) ^g	12	
6-12 mo	10.0	12.5	15.0	30.0						12 (14) ^g	12	
Copper												
Group (years)	Cu (mg)											
	IV ^f	II ^d	III ^e									
11-12	0.77	0.70	0.8									
13	1.00	0.70	0.8									
14	1.00	0.89	0.8									
15	1.00	0.89	1.0									
16-17	1.15	0.89	1.0									
18	1.15	0.89	1.1									
≥19	1.15	0.90	1.1									
Pregnancy	1.15	1.00	1.1									
Lactation	1.25	1.30	1.4									

I (19), II (14), III (15), IV (12)

^a Diet of 5%, 10%, 12% and 15% bioavailability.

^b Diet of high - moderate - low bioavailability.

^c Recommended nutrient intake.

^d Recommended dietary allowances.

^e Population reference intakes.

^f Lowest limit of the population mean intake to meet normative needs.

^g in parenthesis are values for pregnant women ≤18 years old.

Table 6. Recommended daily intakes (iodine, calcium, phosphorus, magnesium and fluoride) for males.

Group (years)	I (ug)			Ca (mg)		P (mg)		Mg (mg)	F (mg)
	I ^a	II ^b	III ^c	V	III ^c	V ^b	III ^c	V ^b	V
11-12	120	120	120	1300 ^d	1000	1250	775	240	2.0 ^d
13	150	120	120	1300 ^d	1000	1250	775	240	2.0 ^d
14	150	150	120	1300 ^d	1000	1250	775	410	3.0 ^d
15-17	150	150	130	1300 ^d	1000	1250	775	410	3.0 ^d
18	150	150	130	1300 ^d	700	1250	550	410	3.0 ^d
≥19	150	150	130	1300 ^d	700	700	550	400	4.0 ^d
≥31								420	
≥51				1200 ^d					

I (19), II (14), III (15), V IOM (50)

^a Recommended nutrient intake.

^b Recommended dietary allowances.

^c Population reference intakes.

^d Adequate intake.

Table 7. Recommended daily intakes (iodine, calcium, phosphorus, magnesium and fluoride) for females.

Group (years)	I (ug)			Ca (mg)		P (mg)		Mg (mg)	F (mg)
	I ^a	II ^b	III ^c	V	III ^c	V ^b	III ^c	V ^b	V
11-12	120	120	120	1300 ^d	800	1250	625	240	2.0 ^d
13	150	120	120	1300 ^d	800	1250	625	240	2.0 ^d
14	150	150	120	1300 ^d	800	1250	625	360	3.0 ^d
15-17	150	150	130	1300 ^d	800	1250	625	360	3.0 ^d
18	150	150	130	1300 ^d	800	1250	550	360	3.0 ^d
≥19	150	150	130	1000 ^d	700	700	550	310	
≥31									
≥51				1200 ^d				320	
Pregnancy									
≤18	200	220	130	1300 ^d	700	1250	550	400	3.0 ^d
19-30	200	220	130	1000 ^d	700	700	550	350	3.0 ^d
31-50	200	220	130	1000 ^d	700	700	550	360	3.0 ^d
Lactation									
≤18	200	290	160	1300 ^d	1200	700	950	360	3.0 ^d
19-30	200	290	160	1000 ^d	1200	700	950	310	3.0 ^d
31-50	200	290	160	1000 ^d	1200	700	950	320	3.0 ^d

I (19), II (14), III (15), V IOM (50).

^a Recommended nutrient intake.

^b Recommended dietary allowances.

^c Population reference intakes.

^d Adequate intake

Table 8. Upper limit of daily dietary intakes (iron, zinc, copper, iodine, calcium, phosphorus, magnesium and fluoride) for the different life stage groups.

Group (years)	Fe (mg)		Zn (mg)			Cu (mg)			I(ug)		Ca(g)		P(g)		Mg(mg)	F(mg)
	II ^c	II ^c	III ^e	IV ^d	IV ^f	II ^c	III ^e	I ^d	II ^c	III ^e	V ^c	V ^c	I ^d	III ^e	V ^c	
0-0.5	40	4	7		150 ^b			150 ^b								0.7
0.6-12	40	5	7	13	150 ^b			140 ^b								0.9
1-2	40	7	10	23	1.5	1	1	50 ^b	200	200	2.5	3	65			1.3
3	40	7	10	23	1.5	1	1	50 ^b	200	200	2.5	3	65			1.3
4-6	40	12	10	23	1.5	3	2	50 ^b	300	250	2.5	3	110	250		2.2
7-8	40	12	13	28	3	3	4	50 ^b	300	300	2.5	3	110	250		2.2
9-10	40	23	13	28	3	5	4	50 ^b	600	300	2.5	4	350	250		10.0
11-12	40	23	18	32	36 ^a 6	5	4	50 ^b	600	450	2.5	4	350	250		10.0
13	40	23	18	36	40 ^a 8	5	4	30 ^b	600	450	2.5	4	350	250		10.0
14	45	34	18	36	40 ^a 8	8	4	30 ^b	900	450	2.5	4	350	250		10.0
15	45	34	22	36	40 ^a 8	8	4	30 ^b	900	500	2.5	4	350	250		10.0
16-17	45	34	22	38	48 ^a 10	8	4	30 ^b	900	500	2.5	4	350	250		10.0
18	45	34	25	38	48 ^a 10	8	5	30 ^b	900	600	2.5	4	350	250		10.0
≥ 19	45	40	25	35	45 ^a 10	10	5	30 ^b	1100	600	2.5	4	350	250		10.0

I (19), II (14), III (15), IV (12), V (50).

^a females & males, respectively.

^b ug/kg/d.

^c Tolerable upper intake level.

^d Upper tolerable nutrient intake level.

^e Tolerable upper intake levels.

^f Upper limit of the safe range of population mean intakes.

Table 9. WHO Guidelines for drinking water (2-4,56).

	WHO Guideline (mg/L)
Iron	0.3 ^a
Zinc	3.0 ^a
Copper	2.0 ^b
Iodine	N/A
Calcium	N/A
Phosphorus	N/A
Magnesium	N/A
Fluoride	1.5 ^b
Sodium	200 ^a
Potassium	N/A
Chloride	250 ^a

^a Levels likely to give rise to consumer complaints.

^b Guideline Value.

N/A = non available.

5. MINERALS FROM DRINKING WATER: BIOAVAILABILITY FOR VARIOUS WORLD POPULATIONS AND HEALTH IMPLICATIONS

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I. INTRODUCTION

Low mineral intakes from foods and water are common in many parts of the world. Today, sub-clinical deficiencies of iron, zinc and calcium prevail in the developed and developing world. Although dozens of geographical studies have been conducted on minerals in drinking water and their relationships to various diseases, the daily intake and the status of deficiency as well as their health consequence are still largely unknown. Furthermore, mineral bioavailability may change due to different stage of growth and ageing. In this chapter the health implication of low mineral content in drinking water in different age groups and gender from various parts of the world is assessed. Studies from Asia, North America, Europe, Africa and Australia were reviewed with regard to minerals in drinking water and the health effects reported.

II. STUDIES IN ASIA

Soft water is commonly consumed in most parts of Asia. The levels of calcium, magnesium and zinc in drinking water are usually low. Several epidemiological investigations on the possible associations between the risk of esophageal, gastric, rectal and colon cancers and minerals in drinking water, in particular hardness have been reported in Taiwan. These case-control studies showed excess risk of several types of cancers in relation to the use of soft water. In one of their studies, Yang and his colleagues reported a 42% excess risk of mortality from esophageal cancer in relation to the use of soft water (1). For rectal cancer the odds ratio were 1.24 and 1.38 respectively, for exposure to moderately hard water and soft water compared with the use of hard water (2). The same group of researchers also showed that there was a significant negative relationship between drinking water hardness and colon cancer mortality, with odds ratio of 1.22 and 1.46, respectively, for exposure to moderately hard water and soft water compared with the use of hard water (3). Their earlier study also showed a significant negative relationship between drinking water hardness and gastric cancer mortality. The odds ratios were 1.16 and 1.65 respectively, for exposure to moderately hard water and soft water compared with the use of hard water (4).

In view of the limited data available from the Asian region on the daily intake of nutritionally essential trace elements, a recent study was undertaken to estimate the daily dietary intake and organ content of some selected trace elements. Nine Asian countries - Bangladesh, China, India, Indonesia, Japan, South Korea, Pakistan, Philippines, and Vietnam--which represented more than 50% of the world's population, participated in this study. Analysis of about 700 diet samples was carried out for four common (calcium, potassium, magnesium, and sodium) and eight trace (chromium, cobalt, copper, iron, iodine, manganese, selenium, and zinc) elements. These samples consisted of total cooked foods, market basket and 225 staple foods. The

maximum inter-country variation was observed for iodine intake (factor of more than 45), being highest for Japan and lowest for Pakistan. For iron, an important trace element, the variation between the intakes was a factor of four being lowest for Vietnam and highest for Pakistan (5). Overall data suggest that the intake of minerals from diet varied tremendously and residents in many of the studied countries have low intakes of various essential minerals.

A number of studies carried out in several Asian countries have shown negative correlations between coronary mortality and the presence of trace elements in water supplies. A cross-sectional survey was conducted in 20 randomly selected streets in North India to determine the association of magnesium with risk of coronary artery disease (CAD). The results suggest that magnesium intake and serum magnesium were inversely correlated with CAD. The odds ratio for dietary magnesium intake indicates a higher prevalence of CAD at lower intakes of magnesium in both rural (0.67) and urban (0.72) subjects. Multivariate regression analysis showed that serum and dietary magnesium, but not hypertension, were significantly associated with CAD (6,7). Data on water hardness throughout Taiwan have been collected to examine the ecological correlation between deaths from coronary disease (1981-1990) and total hardness in drinking water. Analysis demonstrates a significant negative association between drinking water hardness and coronary mortality. After adjustment for the urbanization index, coronary mortality in municipalities with soft water was estimated to be 9.6% higher than that in municipalities with hard water. The weighted multivariate-adjusted regression coefficient indicated a decrease of 0.053 in standardized mortality ratios (SMRs) for every 100 mg/L increase in total hardness in drinking water after allowing for the urbanization condition (8). The same group of researchers further examined specifically whether calcium and magnesium in drinking water are protective against cerebrovascular disease and the general finding suggests that there was a significant protective effect of magnesium intake from drinking water on the risk of cerebrovascular disease (9).

1. Hypertension

Hypertension is a complex, heterogeneous disorder whose exact etiology is unknown. The difficulty in ascribing an independent role to a single dietary constituent in blood pressure regulation may be due to interactions among nutrients that influence blood pressure. Several clinical, experimental and epidemiologic studies have supported the role of magnesium in hypertension, whereas a few studies negate this role. Magnesium deficiency can predispose to increased contractility of the arteries and its excess can modulate smooth muscle contractility caused by bradykinin, angiotensin II, serotonin, prostaglandins and catecholamines. The possible association of magnesium and hypertension was examined in a cross-sectional survey in two randomly selected villages in North India; the overall findings suggest that intake of magnesium, and also serum magnesium levels were inversely associated with the risk of hypertension (7).

2. Cognitive Function

The relation between trace element levels in drinking water and cognitive function was investigated in a population-based study of elderly residents ($n = 1,016$) in rural China. There was a significant quadratic effect for calcium and a significant zinc-cadmium interaction. Cognitive function increased with calcium level up to a certain point and then decreased as calcium in water continued to increase. In contrast, zinc showed a positive relation with cognitive function at low cadmium levels but a negative relation at high levels (10).

3. Fluoride

A large scale epidemiological study was conducted among 45,725 children in India exposed to high intake of endemic fluoride in the drinking water since their birth. Children with adequate (dietary calcium > 800 mg/d) and inadequate (dietary calcium < 300 mg/d) calcium nutrition and

with comparable intakes of fluoride (mean 9.5 +/- 1.9 mg/d) were compared. The toxic-effects of fluoride were severe and more complex and the incidence of metabolic bone disease (rickets, osteoporosis, and PTH bone disease) and bony leg deformities (genu valgum, genu varum, bowing, rotational and wind-swept) was greater (>90%) in children with calcium deficiency as compared to <25% in children with adequate calcium who largely had the osteosclerotic form of skeletal fluorosis with minimal secondary hyperparathyroidism. The findings suggest that children with calcium deficiency rickets reported in the literature should be re-investigated for possible fluoride interactions. Drinking water supply with fluoride <0.5 ppm and improvement of calcium nutrition provide protection against the toxic effects of fluoride and are recommended as the cost effective and practical public health measures for the prevention and control of endemic fluorosis (11).

4. Low Birth Weight

Magnesium is required in higher quantities, during the phase of rapid growth in children. Its level in the ground water in Kerala, India is low and is believed to cause magnesium deficiency, especially in children from the lower socio-economic groups who also suffer from nutritional insufficiency. Nair and colleagues (12) compared the serum and erythrocyte magnesium levels of school children from high and low socio-economic classes. The results showed that serum and erythrocyte magnesium levels were significantly lower in both boys and girls from low socio-economic groups who also consumed ground water and had lower body mass indices.

A few previous studies have looked at the relationship between pregnancy outcome and magnesium nutritional intake and found that magnesium supplementation could have beneficial effects on prenatal outcome. One study (13) examined the relationship between the levels of magnesium in drinking water and the risk of delivering a child of very low birth weight (birth weight less than 1500 g; VLBW). The study population comprised 1,781 women residing in 252 municipalities in Taiwan who had a first parity singleton birth during a five-year period, for whom complete information on maternal age, education, gestational age, birth weight, and sex of the baby were available. The results showed that there was a significant trend toward a decreased risk of having a child of VLBW with increasing magnesium levels in drinking water (14). It was hypothesized that calcium supplementation can reduce smooth muscle contractibility and tone and that this effect can be clinically manifested by a reduction in blood pressure and a reduction in the incidence of premature delivery. A study similar to that on magnesium was also conducted on the relationship between the levels of calcium in drinking water and the risk of delivering a child of very low birth weight (VLBW) in Taiwan. The study population comprised 1781 women residing in 252 municipalities in Taiwan who had a first-parity singlet birth between January 1, 1993 and December 31, 1997 and for whom complete information on maternal age, education, gestational age, birth weight, and sex of the baby were available. The results suggest a significant protective effect of calcium intake from drinking water on the risk of delivering a VLBW baby (14).

III. STUDIES IN PAN-AMERICA

Iron deficiency and related anemia are common in the developing world. Dutra-de-Oliveira and deAlmeida (15) evaluated the feasibility of iron fortification of domestic drinking water to prevent and control iron deficiency and iron-deficiency anemia. Twenty-one families representing 88 persons, including children, were selected to participate in this study. Iron-fortified drinking water increased hemoglobin. No significant changes in hemoglobin and ferritin were found in the placebo group after 4 months.

IV. STUDIES IN AFRICA

Similar to Latin America, relatively few studies have been conducted in Africa on minerals and water consumption. The mortality rates for acute myocardial infarction and ischemic heart disease (IHD) of white males and females in South Africa were noted to be much higher than those in the USA, Australia, England and Wales when individuals in the 15- to 64-year age group are considered. Magnesium levels in the drinking water of 12 South African districts and deaths due to IHD were assessed in white residents in the South Africa and a significant negative correlation was found between these two variables (16). An increased incidence of sudden death associated with ischemic heart disease has been found in some areas in South Africa which soil and drinking water lack magnesium. It was demonstrated experimentally that reduction of the plasma magnesium level is associated with arterial spasm (17).

V. STUDIES IN NORTH AMERICA

The US diet is low in magnesium, and with modern water systems, very little is ingested in the drinking water (18). Of major concern of this low intake of magnesium is the association between cardiovascular problems, such as myocardial infarction, hypertension, congestive heart failure, and hypomagnesaemia. In addition, evidence is mounting regarding the relationship between both types I and type II Diabetes Mellitus, and magnesium deficit.

Turner et al (19) determined the nutrient intake from food across trimesters for middle-to upper-income pregnant women compared with estimated average requirements (EAR) to determine whether food intake exceeded the tolerable upper intake level (UL) for any nutrient. The findings suggest probabilities of usual nutrient intake from food being less than the EAR were highest for iron (0.91), magnesium (0.53), zinc (0.31), vitamin B6 (0.21), selenium (0.20), and vitamin C (0.12). In contrast, women were not at risk of exceeding the UL from food intake for any nutrient studied. These data provide evidence that the study participants did not consume adequate amounts of iron from food to meet the needs of pregnancy, and therefore the authors recommended iron supplementation for this population.

Annual mortality rates for 1968 of six types of cardiovascular diseases among persons over 45 years of age in 24 Texas communities were compared with respective community drinking water and urine metal levels of calcium, magnesium, potassium, lithium, strontium, and silicon. Numerous inverse correlations were found between mortality rates and the levels of various metals in both drinking water and urine. Positive correlations were also observed between several of the mortality rates and the ratio of the concentration of sodium to that of the other metals in both water and urine. Mean community urinary levels of lithium, magnesium, strontium, and silicon showed a direct correlation to the levels of exposure via the drinking water. The results of this study suggest that calcium, magnesium, lithium strontium, and silicon may protect against cardiovascular mortality; possibly, by competing with sodium and potassium for transport in the intestinal lumen, increasing excretion of sodium, or other mechanism (20). Another investigation was conducted in 1980 to evaluate the association of cardiovascular diseases and drinking water constituents. A sample of 4200 adults was randomly selected from 35 geographic areas to represent the civilian noninstitutionalized population of the contiguous United States. Each participant was interviewed and given a thorough physical examination and a tap water grab sample was collected from each participant's residence and analyzed for 80 inorganic chemical constituents. Hardness and calcium appeared to follow the normal trend of negative associations with the mortality rates for most groups of cardiovascular diseases, whereas the area means for copper and lead were positively associated. Zinc and cadmium associations were examined, but

the range of constituent levels in the sampled drinking waters was too small for meaningful interpretation of the results (21).

Bloom and Peric-Golia (22) searched for evidence of myocyte calcification in hearts of patients found to have AMI at autopsy in Salt Lake City, a region with a low myocardial infection death rate, and Washington, DC, a region with a high myocardial infection death rate. The basis of this difference in myocyte calcification is unknown, but it may be related to the fact that the Salt Lake City drinking water contains a higher level of magnesium, which is known to protect against soft tissue calcification, than does that of Washington, DC. This finding is consistent with the apparent protection that dietary magnesium exerts against myocardial infarction death.

In both humans and experimental animals, dietary induced magnesium deficiency is correlated with insulin resistance. A study was performed to determine whether dietary magnesium intake is associated with insulin sensitivity or blood pressure in a sample of nondiabetic, young adult black Americans. The authors (23) examined dietary calcium, potassium, and sodium intake of young adults and who had been followed longitudinally. Nutrient intake was assessed by obtaining a 24-hour recall interview of dietary intake. There was a significant negative correlation of total dietary magnesium intake with the sum of insulin levels measured during an oral glucose tolerance test. The results suggest a possible role for dietary magnesium in insulin resistance. Lower levels of dietary and serum magnesium have been associated with an increased prevalence of hypertension, insulin resistance, and diabetes. Studies suggest a greater prevalence of occult magnesium deficiency among African-Americans compared to other populations. This increased prevalence of hypomagnesaemia may contribute to increased insulin resistance leading to accelerated atherosclerosis and premature death (24).

Schwartz and colleagues (25) conducted a study to assess the impact of water hardness on urinary stone formation. Patients who form calcium stones ($n = 4833$) were identified geographically by their zip codes. Water hardness information from distinct geographic public water supplies was obtained, and 24-hour urine chemistries were evaluated. The calcium and magnesium levels in the drinking water were analyzed as independent variables. The results indicated that the number of total lifetime stone episodes was similar between patients residing in areas with soft public water and hard public water. Patients consuming the softest water decile formed 3.4 lifetime stones and those who consumed the hardest water developed 3.0 lifetime stones ($P=0.0017$). The 24-hour urine calcium, magnesium, and citrate levels increased directly with drinking water hardness, and no significant change was found in urinary oxalate, uric acid, pH, or volume. The impact of water hardness on urinary stone formation remains unclear, despite a weak correlation between water hardness and urinary calcium, magnesium, and citrate excretion. Tap water, however, can affect urinary electrolytes in patients who form calcium stones (25).

VI. STUDIES IN EUROPE

The role of water hardness as a risk factor for cardiovascular disease has been widely investigated and evaluated with regard to regional differences in Europe. Water constituents like magnesium, calcium, etc. were found to be usually negatively associated with cardiovascular diseases in a study of more than 600 water supply areas in the Federal Republic of Germany (26). To study the influence of drinking water composition on the risk of myocardial infarction a study was conducted in 1983 on men 30-64 years of age who had been discharged with a first acute myocardial infarction (AMI) in a hospital in Finland. Results were consistent with the hypothesis that both low fluoride and a low Mg intake are conducive to atherosclerosis leading to AMI (27).

Ischemic heart disease (IHD) is a major public health problem in most industrialized countries. In the death rates from IHD, marked differences exist between various countries and also between different areas of individual countries. Unfavorable dietary factors appear to play an important role in the etiology of IHD, and thus differences in dietary habits and the quality of food may be mainly responsible for the geographic differences in the prevalence of IHD. Reduced intakes of potassium and magnesium may increase the death rate from IHD by predisposing the heart to fatal arrhythmias, and also by other mechanisms. The likelihood of magnesium deficiency also appears to be influenced by the area of residence. Karppanen (28) claimed that the higher-than-average death rates from IHD in the North Karala area in eastern Finland and in some other areas with exceptionally high death rates from this disease may be at least partly due to the very low levels of magnesium in the soil and drinking water. He concluded that electrolyte disturbances have important implications in the etiology and pathogenesis of IHD. Leoni et al (29) studied the pattern of mortality resulting from cardiovascular diseases, ischemic heart diseases, and cerebrovascular diseases in the region of Abruzzo, Italy, which has a population of 594,323. These variables were then correlated with mortality rate and water hardness. An inverse correlation was observed between drinking water hardness and mortality due to cardiovascular disease, for individuals aged 45-64 yr. The incidence of sudden cardiac death among the population of the Media Valle del Serchio area in Italy, which made up of 35,000 residents, was found to be twice that of the European average (9 per 10,000 in the examined year). The high incidence of sudden cardiac death among the residents correlated with water that was of very low total hardness (30).

The relation between death from acute myocardial infarction and the level of magnesium in drinking water was examined using mortality registers and a case-control design. The study area comprised 17 municipalities in the southern part of Sweden that have different magnesium levels in the drinking water. The odds ratios for death from acute myocardial infarction in the groups were inversely related to the amount of magnesium in drinking water. For the group with the highest levels of magnesium in drinking water, the odds ratio adjusted for age and calcium level was 0.65. There was no such relation for calcium. For the magnesium/calcium quotient, the odds ratio was lower only for the group with the highest quotient. Magnesium in drinking water correlated as an important protective factor for death from acute myocardial infarction among males (31).

To examine whether higher concentrations of magnesium in drinking water supplies are associated with lower mortality from acute myocardial infarction a geographical study using 13,794 census enumeration districts was studied. Water constituent concentrations (magnesium, calcium, fluoride, lead) were measured according to water supply zones in North England. The relative risk of mortality from acute myocardial infarction for a quadrupling of magnesium concentrations in drinking water (for example, 20 mg/l vs 5 mg/l) was 1.01. There was no evidence of a protective effect for acute myocardial infarction even among age, sex, and deprivation groups that were likely to be relatively magnesium deficient. For ischemic heart disease mortality, however, there was an apparent protective effect of magnesium and calcium (with calcium predominating in the joint model), but these were no longer significant when the geographical trends were incorporated. The authors suggested that there was no evidence of an association between magnesium concentrations in drinking water supplies and mortality from acute myocardial infarction. The main finding of this study does not support the hypothesis that magnesium is the key water factor in relation to mortality from heart disease (32). In another case-control study, Rubenowitz and his colleagues investigated the levels of magnesium and calcium in drinking water and death from acute myocardial infarction among women. The study population encompassed 16 municipalities in southern Sweden. Cases were women who had died from acute myocardial infarction between the ages of 50 and 69 years during 1982-1993 (N = 378), and

controls were women who had died from cancer (N = 1,368). The results suggest that magnesium and calcium in drinking water are important protective factors for death from acute myocardial infarction among women (33). Rubenowitz *et al* (34) further investigated the importance of magnesium and calcium in drinking water in relation to morbidity and mortality from acute myocardial infarction. Cases were men and women 50-74 years of age living in 18 Swedish municipalities who had suffered an acute myocardial infarction some time between October 1, 1994, and June 30, 1996. They classified subjects by quartile of water magnesium or calcium levels. The risk of death was 7.6% lower in the quartile with high magnesium levels (≥ 8.3 mg/liter). The odds ratio for death from acute myocardial infarction in relation to water magnesium was 0.64 for the highest quartile relative to the three lower ones. Multivariate analyses showed that other risk factors were not important confounders. These data suggested that magnesium in drinking water is associated with lower mortality from acute myocardial infarction (34).

Drinking water could be an important source of calcium in the elderly particularly because of increased needs and decreased consumption of dairy products. Information about all deaths (14,311) occurring in 69 parishes of the South-West of France for a seven-year study period from 1990 to 1996) were investigated. A significant relationship was observed between calcium and cardiovascular mortality with a relative risk, RR: 0.90 for non-cerebrovascular causes and RR: 0.86 for cerebrovascular. There was a protective correlational effect of magnesium concentrations between 4 and 11 mg/l with a RR: 0.92 for non-cerebrovascular and RR: 0.7 for cerebrovascular mortality, as compared to concentrations lower than 4 mg/l. These findings suggest a potential protective dose-effect relation between calcium in drinking water and some CVD. However, for magnesium, a U-shape effect is possible, especially for cerebrovascular mortality (35).

A study was performed to evaluate the relation between calcium and magnesium in drinking water and diet and risk factors for cardiovascular disease in individuals living in hard and soft water areas with considerable differences in cardiovascular mortality in Sweden. Intake of magnesium and calcium was calculated from the diet questionnaire with special consideration to the use of local water. Household water samples were analyzed for magnesium and calcium. No correlation was seen with magnesium content in household water to any of the risk factors. Magnesium in diet was positively correlated to diastolic blood pressure (DBP). This study of individuals living in soft and hard water areas showed significant correlations between the content of calcium in water and major cardiovascular risk factors. Regression analyses indicated that calcium content in water could be a factor in the complexity of relationships and importance of cardiovascular risk factors. However, based on these results the authors were unable to conclude any definite causal relation and suggest that further research is needed (36).

Calcium and magnesium deficiencies in particular have been considered as risk factors for elderly people and have been implicated in the aging process. Their deficiencies in the elderly can occur due to inadequate nutrient intakes from food and water, multiple drug use, or altered gastrointestinal function. It is not known to what extent suboptimal intakes of trace elements such as calcium and magnesium may affect the aging process; however, magnesium-deficient conditions have been associated with neuromuscular and cardiovascular disorders, endocrine disturbances and insulin resistance. Data presented in a review by Costello and Moser-Veillon suggest that there was a decreased availability of magnesium in the food supply, lower intakes of magnesium by elderly people, and widespread supplementation practices (37).

Gullestad *et al* (38) studied magnesium status among healthy elderly subjects. A study was thus carried out on 36 healthy elderly subjects and their magnesium status was assessed by serum Mg, basal urinary Mg output, and with a Mg loading test, and compared with 53 healthy younger subjects. Their dietary intake was assessed by a quantified food frequency questionnaire. Basal

urinary Mg excretion was 3.3 \pm 1.1 mmol/day and 24-hour Mg retention after a Mg load was 28 \pm 16% compared to 6 \pm 11% in younger controls, suggesting Mg deficiency in the elderly. Their study also found a significant sub-clinical Mg deficit, not detected by serum Mg, in many healthy elderly subjects. The data further indicated that Mg supplementation improved Mg status and renal function.

A study aimed to examine the relationship between nitrate, zinc and magnesium in drinking water and the risk of childhood-onset Type 1 diabetes mellitus was conducted by Zhao *et al.* (39) in the far south-west of England. Five hundred and seventeen children, aged 0-15 years, diagnosed with Type 1 diabetes mellitus between 1975 and 1996, were identified for inclusion in the study. Poisson regression analyses showed that only zinc and magnesium were significant factors. The data suggest that the incidence rate of childhood diabetes is significantly lower when the concentrations of zinc and magnesium in the domestic drinking water are in the range 22.27-27.00 microgram/l, 0.76) and greater than 2.61 mg/l, 0.72; respectively. Their findings suggest evidence of a possible association between zinc and magnesium in the domestic drinking water and childhood diabetes. However, these possible protective effects of zinc and magnesium in domestic drinking water warrant further confirmation (39).

The role of calcium in the formation of kidney stones is controversial. Both amount and timing of dietary calcium intake influence the recurrence of renal calcium stones. Bellizzi *et al* (40) evaluated whether the hardness of drinking water modified the risk for calcium stones. The urinary levels of calcium, oxalate and citrate, i.e., the main urinary risk factors for calcium stones, were measured in 18 patients with idiopathic nephrolithiasis, in a double-blind randomized, crossover fashion. As compared with both tap and soft water, hard water was associated with a significant (50%) increase of the urinary calcium concentration in the absence of changes of oxalate excretion; the calcium-citrate index revealed a significant three fold increase during ingestion of hard water as compared with respect to soft water. This study suggests that, in the preventive approach to calcium nephrolithiasis, the intake of soft water is may be preferable to hard water, since it was associated with a lower risk for recurrence of calcium stones (40).

VII. STUDIES IN THE WESTERN PACIFIC REGION

An attempt was made to determine whether an association existed between hardness of water and certain cardiovascular diseases in primitive population groups who drink untreated water collected directly from rivers. Blood pressure was measured in persons living in villages along the banks of the Wogupmeri River in New Guinea. The water was analyzed for calcium content. Trace element concentrations were also determined in toenails from the same subjects to see whether a correlation existed (41). Calcium content of the river water decreased as the river flows downstream, while blood pressure of the villagers living along this river increased. The trace element analysis of toenails revealed strong correlations between aluminum and vanadium. The concentrations of these two elements decrease with age. This association was present in both sexes, in adults and in children. A similarly strong correlation also existed between these two elements in staple food. This investigation tended to confirm the findings of earlier studies indicating an apparently beneficial effect of relatively hard water on cardiovascular parameters.

VIII. CONCLUSION

This chapter has highlighted some recent studies on minerals in drinking water and their relationship with various diseases. Most of these studies were conducted in Europe, Asia and the US and the common minerals studied were calcium and/or magnesium. Among various diseases studied, the cardiovascular system attracted the most attention. The relationship between the

cardiovascular mortality and the mineral content of drinking water was first described by Kobayashi (42) in Japan and Schoeder (43) in the US. Since then many studies have shown an inverse relationship between cardiovascular disease (CVD) and the water hardness, especially the magnesium content of the drinking water. Most of the investigations before 1980 were with ecological design and geographical areas defined. Often, the mineral content of drinking water was determined at the time of study after the time of the CVD events and thus the results could not reflect the exact quality of water the persons have ingested before their death or were exposed to. Furthermore, in most of these earlier studies the relationship between CVD mortality and drinking water hardness was tested by simple regression analysis, without considering potential confounding factors.

Based on epidemiological and clinical observations Marier and Neri (44) carried out a study in 1985 to quantify the effect of waterborne magnesium on human mortality/morbidity in several regions of the world. A consistent pattern emerged, indicating a global phenomenon that waterborne magnesium could play an important role in protecting against cardiovascular trauma and other ailments. The finding also attests to the inadequate magnesium status, especially of those who reside in ultra-soft-water areas. A more recent comprehensive review was conducted by Sauvant and Pepin (45) and arrived with a similar conclusion. The authors however cautioned that although there is a relationship between drinking water and CVD mortality, based on over 30 ecological and geographical investigations, its causality is still not proven, but there are many supporting arguments. Although there appears to be a close association of magnesium and cardiovascular disease, it seems unlikely that this relationship can only be attributed to a deficiency of calcium and magnesium in drinking water, because only 10-20% of the total daily intake of calcium and magnesium is derived from drinking water, unless that marginal contribution were significant to deficient diets. In some geographical areas, the magnesium content of drinking water may provide 20-40% of a person's daily requirement. For example, a liter of water with 100 mg/liter of magnesium could make up 25% or more of the daily magnesium requirement of 300 – 400 mg per day. A liter of water that is low in magnesium (<10 mg /liter) provides less than 3% of the daily requirement. It is true that the contribution of magnesium in water to the total intake may be small, compared to the amount ingested in food. On the other hand, the speciation of magnesium could explain its high bioavailability from water, rather than from food (46). Because of this the magnesium supplementation of drinking water has been suggested to reduce the incidence of some types of cardiovascular disease (47).

Calcium is found predominantly in milk, milk products and in hard water. The bioavailability of this mineral in water is believed to be at least as high as that of milk and milk products (48). Finnish women, with the highest daily consumption of calcium (1,300 mg/day) had the lowest frequency of fractures. In comparison, Japanese women, with the lowest calcium intake (400 mg/day) had the greatest frequency of fractures (49). Significant subgroups in most European populations have intake below the RDAs – below 10 to 40% of the RDA in zinc, iron, calcium and magnesium (50). The intake of calcium either from diet or water among Asians are known to be low because of soft water supply, dietary habits and cost. Recent studies have shown that the intakes of calcium, zinc, magnesium, potassium and other essential minerals were insufficient, and are a traditional problem in the Chinese diet (51).

A study conducted by Haring *et al* (52) investigated changes in the mineral composition of food when cooked in waters of different hardness. The most significant differences were found for calcium; the concentration of this element in potatoes and vegetables usually increased when cooked in hard-water, while a decrease was noted when soft water was used. This finding suggests that water used for cooking could indirectly affect the dietary intake of various trace elements (52).

Several studies have been conducted in Asia focusing on use of soft water and cancers, in particular in southern Taiwan. This region is supplied by both soft and hard water. The authors reported excess risks of several types of gastrointestinal cancers including esophageal, gastric, pancreatic colon and rectum (1-4). Based on empirical material from the Polish Cancer Registry a recent study in Poland also suggested the hypothesis that there is a possible association between drinking water composition and an increase of liver cancer (53), although the status of hepatitis and exposure to hepatotoxicants have not been investigated. Consumption of soft waters, especially those low in calcium and magnesium, has also been associated with very low birth weight, suggesting that the use of water with low mineral content may affect fetal growth (13,14). However, no other similar studies have been conducted in other parts of the world.

References

1. Yang CY, Chiu HF, Cheng MF, Tsai SS, Hung CF, Lin MC. Esophageal cancer mortality and total hardness levels in Taiwan's drinking water. *Environ Res* 1999; 81:302-8.
2. Yang CY, Tsai SS, Lai TC, Hung CF, Chiu HF. Rectal cancer mortality and total hardness levels in Taiwan's drinking water. *Environ Res* 1999; 80:311-6.
3. Yang CY, Hung CF. Colon cancer mortality and total hardness levels in Taiwan's drinking water. *Arch Environ Contam Toxicol* 1998 ; 35:148-51.
4. Yang CY, Chiu HF, Chiu JF, Cheng MF, Kao WY. Gastric cancer mortality and drinking water qualities in Taiwan. *Arch Environ Contam Toxicol* 1997; 33:336-40.
5. Iyengar GV, Kawamura H, Parr RM, Miah FK, Wang JX, Dang HS, Djojosebroto H, Cho SY, Akher P, Natera ES, Nguy MS. Dietary intake of essential minor and trace elements. *Asian Diets Food Nutr Bull* 2002; 23:124-8.
6. Singh RB, Niaz MA, Ghosh S, Rastogi V, Raghuvanshi RS, Moshiri M. Epidemiological study of magnesium status and risk of coronary artery disease in elderly rural and urban populations of north India. *Magnes Res* 1996; 9:165-72.
7. Singh RB, Rastogi V, Niaz MA, Sharma JP, Raghuvanshi R, Moshira M. Epidemiological study of magnesium status and risk of hypertension in a rural population of north India. *Magnes Res* 1996; 9:173-81.
8. Yang CY, Chiu JF, Chiu HF, Wang TN, Lee CH, Ko YC. Relationship between water hardness and coronary mortality in Taiwan. *J Toxicol Environ Health* 1996; 49:1-9.
9. Yang CY. Calcium and magnesium in drinking water and risk of death from cerebrovascular disease. *Stroke* 1998; 29:411-4.
10. Emsley CL, Gao S, Li Y, Liang C, Ji R, Hall KS, Cao J, Ma F, Wu Y, Ying P, Zhang Y, Sun S, Unverzagt FW, Slemenda CW, Hendrie HC. Trace element levels in drinking water and cognitive function among elderly Chinese. *Am J Epidemiol* 2000; 151:913-20.
11. Teotia M, Teotia SP, Singh KP. Endemic chronic fluoride toxicity and dietary calcium deficiency interaction syndromes of metabolic bone disease and deformities in India: year 2000. *Indian J Pediatr* 1998; 65:371-81.
12. Nair RR, Eapen JT, Radhakumary C, Rajasree S. Magnesium levels in serum and erythrocytes of children from Kerala. *Natl Med J India* 1995; 8:118-20.
13. Yang CY, Chiu HF, Tsai SS, Chang CC, Sung FC. Magnesium in drinking water and the risk of delivering a child of very low birth Weight. *Magnes Res* 2002; 15 :207-13
14. Yang CY, Chiu HF, Chang CC, Wu TN, Sung FC. Association of very low birth weight with calcium levels in drinking water. *Environ Res* 2002 ;89:189-94.
15. Dutra-de-Oliveira JE, de Almeida CA. Domestic drinking water--an effective way to prevent anemia among low socioeconomic families in Brazil. *Food Nutr Bull* 2002; :213-6.
16. Leary WP. Content of magnesium in drinking water and deaths from ischaemic heart disease in white South Africans. *Magnesium* 1986; 5:150-3.
17. Leary WP, Reyes AJ. Magnesium and sudden death. *S Afr Med J.* ; 1983; 64:697-8. 18.

18. Innerarity S. Hypomagnesemia in acute and chronic illness. *Crit Care Nurs Q* 2000; 23:1-19.
19. Turner RE, Langkamp-Henken B, Littell RC, Lukowski MJ, Suarez MF. Comparing nutrient intake from food to the estimated average requirements shows middle- to upper-income pregnant women lack iron and possibly magnesium. *J Am Diet Assoc* 2003; 103:461-6.
20. Dawson EB, Frey MJ, Moore TD, McGanity WJ. Relationship of metal metabolism to vascular disease mortality rates in Texas. *Am J Clin Nutr* 1978; 31:1188-97.
21. Greathouse DG, Osborne RH. Preliminary report on nationwide study of drinking water and cardiovascular diseases. *J Environ Pathol Toxicol* 1980; 4:65-76.
22. Bloom S, Peric-Golia L. Geographic variation in the incidence of myocardial calcification associated with acute myocardial infarction. *Hum Pathol* 1989; 20:726-31.
23. Humphries S, Kushner H, Falkner B. Low dietary magnesium is associated with insulin resistance in a sample of young, nondiabetic Black Americans. *Am J Hypertens* 1999; 12:747-56.
24. Fox CH, Mahoney MC, Ramsoomair D, Carter CA. Magnesium deficiency in African-Americans: does it contribute to increased cardiovascular risk factors? *J Natl Med Assoc* 2003; 95:257-62.
25. Schwartz BF, Schenkman NS, Bruce JE, Leslie SW, Stoller ML. Calcium nephrolithiasis: effect of water hardness on urinary electrolytes. *Urology* 2002; 60:23-7.
26. Sonneborn M, Mandelkow J. German studies on health effects of inorganic drinking water constituents. *Sci Total Environ* 1981; 18:47-60.
27. Luoma H, Aromaa A, Helminen S, Murtomaa H, Kiviluoto L, Punsar, S, Knekt P. Risk of myocardial infarction in Finnish men in relation to fluoride, magnesium and calcium concentration in drinking water. *Acta Med Scand* 1983; 213:171-6.
28. Karppanen H. Ischaemic heart disease. An epidemiological perspective with special reference to electrolytes. *Drugs* 1984; 28, Suppl 1:17-27.
29. Leoni V, Fabiani L, Ticchiarelli L. Water hardness and cardiovascular mortality rate in Abruzzo, Italy. *Arch Environ Health* 1985; 40:274-8.
30. Bernardi D, Dini FL, Azzarelli A, Giaconi A, Volterrani C, Lunardi M. Sudden cardiac death rate in an area characterized by high incidence of coronary artery disease and low hardness of drinking water. *Angiology* 1995; 46:145-9.
31. Rubenowitz E, Axelsson G, Rylander R. Magnesium in drinking water and death from acute myocardial infarction. *Am J Epidemiol* 1996; 143:456-62.
32. Maheswaran R, Morris S, Falconer S, Grossinho A, Perry I, Wakefield J, Elliott P. Magnesium in drinking water supplies and mortality from acute myocardial infarction in north west England. *Heart* 1999; 82:455-60.
33. Rubenowitz E, Axelsson G, Rylander R. Magnesium and calcium in drinking water and death from acute myocardial infarction in women. *Epidemiology* 1999; 10:31-6.
34. Rubenowitz E, Molin I, Axelsson G, Rylander R. Magnesium in drinking water in relation to morbidity and mortality from acute myocardial infarction. *Epidemiology* 2000; 11:416-21.

35. Marque S, Jacqmin-Gadda H, Dartigues JF, Commenges D. Cardiovascular mortality and calcium and magnesium in drinking water: an ecological study in elderly people. *Eur J Epidemiol* 2003; 18:305-9.
36. Nerbrand C, Agreus L, Lenner RA, Nyberg P, Svardsudd K. The influence of calcium and magnesium in drinking water and diet on cardiovascular risk factors in individuals living in hard and soft water areas with differences in cardiovascular mortality. *BMC Public Health* 2003; 18: 3-21.
37. Costello RB, Moser-Veillon PB. A review of magnesium intake in the elderly. A cause for concern? *Magnes Res* 1992; 5:61-7.
38. Gullestad L, Nes M, Ronneberg R, Midtvedt K, Falch D, Kjekshus J. Magnesium status in healthy free-living elderly Norwegians. *J Am Coll Nutr* 1994 13:45-50.
39. Zhao HX, Mold MD, Stenhouse EA, Bird SC, Wright DE, Demaine AG, Millward BA. Drinking water composition and childhood-onset Type 1 diabetes mellitus in Devon and Cornwall, England. *Diabet Med* 2001;18:709-17.
40. Bellizzi V, De Nicola L, Minutolo R, Russo D, Cianciaruso B, Andreucci M, Conte G, Andreucci VE. Effects of water hardness on urinary risk factors for kidney stones in patients with idiopathic nephrolithiasis. *Nephron* 1999; 81 Suppl 1:66-70.
41. Masironi R, Koirtiyohann SR, Pierce JO, Schamschula RG. Calcium content of river water, trace element concentrations in toenails, and blood pressure in village populations in New Guinea. *Sci Total Environ* ; 1976; 6:41-53.
42. Kobayashi Y. Geographical relationship between the chemical nature of river water and death rate from apoplexy. *Okayama University* 1957; 11: 12-21.
43. Schoeder HA. Relation between mortality from cardiovascular disease and treated water supplies. *J. Am. Med. Assoc.* 1960; 172: 98-10454. Tukiendorf, A., Krasowski, G., Rybak, Z Thyroid cancer morbidity in Opole province, Poland, after Czernobyl disaster. *Eur J Public Health* .2003; 11:98-101.
44. Marier JR, Neri LC. Quantifying the role of magnesium in the interrelationship between human mortality. *Magnesium* 1985; 4:53-9.
45. Sauvant MP, Pepin D. Drinking water and cardiovascular disease. *Food Chem Toxicol* 2002; 40:1311-25.
46. Durlach J, Bara M, Guet-Bara A.. Magnesium level in drinking water and cardiovascular risk factor: a hypothesis. *Magnesium* 1985; 4:5-15.
47. Eisenberg MJ. Magnesium deficiency and sudden death. *Am Heart J* 1992; 124:544-9.
48. Heaney RP. Quantifying human calcium absorption using pharmacokinetic methods. *J Nutr* 2003; 133:1224-6.
49. Heaney RP, Dowell MS. Absorbability of the calcium in a high-calcium mineral water. *Osteoporos Int* 1994;. 4:323-4.
50. Flynn A, Moreiras O, Stehle P, Fletcher RJ, Muller DJ, Rolland V. Vitamins and minerals: A model for safe addition to foods. *Eur J Nutr* 2003; 42:118-30.
51. Chen J, Gao J. The Chinese total diet study in 1990. Part II. Nutrients. *JAOAC Int* 1993; 76:1206-13.

52. Haring BS, Van Delft W. Changes in the mineral composition of food as a result of cooking in "hard" and "soft" waters. *Arch Environ Health* 1981; 36:33-5.
53. Tukiendorf A, Krasowski G, Rybak Z. Thyroid cancer morbidity in Opole province, Poland, after the Chernobyl disaster. *Eur J Public Health* 2003; 11:98-101.

6.

THE CONTRIBUTION OF DRINKING WATER TO TOTAL DAILY DIETARY INTAKES OF SELECTED TRACE MINERAL NUTRIENTS IN THE UNITED STATES

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I. INTRODUCTION

Although foods are the major source of mineral nutrients in the diet, drinking water can contribute variable fractions of the total intake. The magnitude of the drinking water contribution, however, has not been characterized because little work has been done to quantify its contribution. The major reason is that drinking water intake is not included in most dietary surveys, and programs that measure the concentrations of nutrients in the diet by analysis include only the water used to prepare the food items analyzed. These factors make it difficult to assess the contributions of drinking water to total nutrient exposure.

Inorganic minerals generally gain access to surface water and groundwater as a result of their presence in the earth's crust and their aqueous solubility. Accordingly, they may be widely distributed throughout the aquatic environment. Minerals are not uniformly distributed in earth materials, however, and the amount in water can vary significantly with local geologic and hydrologic conditions. Additional amounts of some nutrients can gain access to ambient water from anthropogenic activities, including industrial discharges, runoff from land, and waste disposal practices.

Some mineral nutrients are present in drinking water because of treatment processes. For example, fluoride is added directly to water to obtain final concentrations between 0.7 and 1.2 mg/L in drinking water systems that elect to fluoridate as a means of preventing dental decay. Calcium, zinc, manganese, phosphate, and sodium compounds may be added directly to water as a result of treatment processes such as pH adjustment or corrosion control. Other mineral nutrients such as copper and zinc can leach from plumbing materials; chromium and selenium can be present as impurities in paints, sands, and other water contact materials.

As part of its 2003 review of its drinking water regulations, the U.S. Environmental Protection Agency (EPA) has recently analyzed the concentrations of a large number of contaminants found in public water systems (PWSs). Several mineral nutrients (chromium, fluoride, and selenium) were assessed as part of this process. Data on others, such as manganese and sodium, were collected and evaluated during regulatory determination for the Contaminant Candidate List (CCL). These data can be used to provide information on the prevalence and magnitude of mineral nutrient exposures through drinking water in the United States.

As freshwater resources become scarce, the world will become increasingly reliant on desalination or demineralization to provide potable water. The process of desalination, either by flash evaporation or reverse osmosis, depletes the source water of its mineral contents. This has increased the interest in the role that drinking water minerals play in human nutrition.

It has been suggested that there may be adverse outcomes from reliance on desalinated or demineralized water as a result of the loss of mineral nutrients. Some individuals have proposed post treatment replenishment of the mineral nutrients that were removed. However, to determine whether the loss of mineral nutrients from water constitutes a nutritional problem, it must first be determined whether drinking water plays a significant role in the total dietary intake of trace minerals.

This report utilizes data on the dietary intake of selected mineral nutrients in the United States as well as data on the concentrations in drinking water to determine the relative contribution of food items and drinking water to total exposure. This review considers chromium, copper, fluoride, iron, manganese, selenium, sodium, and zinc.

II. SOURCES OF INFORMATION

The primary sources of the dietary information included in this report are the National Academy of Sciences Institute of Medicine (IOM) Dietary Reference Intake volumes that cover the mineral nutrients (1,2,3). These documents provide data on the Adequate Intakes (AIs), Estimated Average Requirements, Recommended Daily Allowances (RDAs), and Tolerable Upper Intake Levels (ULs) for each nutrient. Also included in the appropriate reference volume is information on population nutrient intake that was compiled from the National Health and Nutrition Survey III (NHANES III) for the years 1988 through 1994, the Continuing Survey of Food Intake by Individuals (CSFII) for 1991 through 1994, and the Total Diet Study (TDS) for 1991 to 1997.

The NHANES is a national U.S. population survey conducted periodically by the National Center for Health Statistics of the Centers for Disease Control and Prevention. In the NHANES, dietary data are gathered through a 24-hour recall interview conducted by a trained professional. In the 24-hour recall interview, the subject is asked to provide information on all food items consumed over the previous 24-hour period (food items and quantities). The interview is structured, and various props are used to help quantify portion sizes.

The CSFII is conducted by the U.S. Department of Agriculture on a periodic basis. One purpose of this survey is to provide information on the kinds and amounts of food eaten by the U.S. population. Each survey covers 3 years. In each of the survey years, a nationally representative sample of the population is interviewed to provide information on 2 nonconsecutive days of food intake using the 24-hour recall interview approach.

Additional data on dietary intake are provided by the U.S. Food and Drug Administration TDS. This survey differs from the NHANES III and CSFII approaches in that it relies on chemical analysis of a typical diet using foods purchased from four geographic regions of the country (northeast, south, north-central, and west). The composition of the typical diet for a number of age/sex groupings is derived from the CSFII data. The foods are prepared as they would be served and analyzed to measure the analytes of interest.

Data on the concentration of mineral nutrients in drinking water were provided primarily from two U.S. EPA reports. They are the Analysis of National Occurrence of the 1998 Contaminant Candidate List (CCL) Regulatory Determination Priority Contaminants in Public

Water Systems (4) and Occurrence Estimation Methodology and Occurrence Findings Report for the Six-Year Review of Existing National Primary Drinking Water Regulations (5).

The data for copper, iron, manganese, sodium, and zinc primarily come from the National Inorganic and Radionuclide Survey (NIRS) conducted from 1984 through 1986 (4). The data represent only PWSs that rely on groundwater as their drinking water source. Each system tested was randomly selected to be statistically representative of groundwater systems in 49 States and Puerto Rico. When there were PWS data from surface water systems on these same nutrients, they were also evaluated (4).

The NIRS study provided data on many cationic inorganic ions in water including calcium and magnesium. Neither of these minerals is included in this report. However, they were found in 99.7% of systems for calcium and 98.7% of systems for magnesium. Mean concentrations (49 mg/L for calcium and 16 mg/L for magnesium) were low compared to their dietary requirements. The 90th percentile values (97 mg/L for calcium and 36 mg/L for magnesium) would make more substantial contributions to dietary intake,

The data for chromium, fluoride, and selenium come from the monitoring data collected by 16 States as part of their compliance with the National Potable Drinking Water Regulations (5). The 16 States represent a cross-section of PWSs across the United States that submitted their data to the U.S. EPA in a format that could be utilized in the analysis and met selected quality control criteria.

Copper, iron, and zinc are included in this report even though they were not covered in the U.S. EPA reports identified above. They are important mineral nutrients and are frequently present in water because of geology, industrial discharge, leaching from pipes or conveyance materials, and/or addition as treatment chemicals. Alternate sources of information were used for this group of nutrients and include:

- Unpublished NIRS data (4)
- Data submitted to the U.S. EPA under the requirements of the Lead and Copper Rule
- Information from Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profiles
- U.S. EPA Secondary Drinking Water Standards
- National Science Foundation (NSF) International/American National Standards Institute (ANSI) standards for drinking water treatment chemicals

III. DATA AND ANALYSIS

To determine whether drinking water provides a significant portion of the total dietary intake for each of the selected nutrients, data on dietary exposures and intake recommendations were compiled from the IOM (1,2,3). The 5th, 50th, and 95th percentile dietary intakes for all ages from the NHANES III, CSFII, and TDS—as compiled by the IOM—were abstracted, where available, and are summarized in Table 1.

Table 1. Dietary Intake (All Individuals)

Mineral	Percentile			Source
	5th	50th	95th	
Chromium	NA	NA	NA	ND
Copper (mg/day)	0.72	1.24	2.09	NHANES III
Copper (mg/day)	0.58	1.1	2.01	CSFII
Copper (mg/day)	0.22	0.57	1.39	TDS
Fluoride (mg/day)	NA	NA	NA	ND
Iron (mg/day)	7.7	14.1	25.8	NHANES III
Iron (mg/day)	7.4	14.3	26.7	CSFII
Iron (mg/day)	3.83	9.74	24.26	TDS
Manganese (mg/day)	0.49	1.71	4.79	TDS
Selenium (µg/day)	57	106	193	NHANES III
Sodium (mg/day)	NA	3000	NA	TDS
Zinc (mg/day)	6.1	10.7	18.4	NHANES III
Zinc (mg/day)	5.5	10.4	18.8	CSFII
Zinc (mg/day)	2.84	7.36	18.63	TDS

NA = not analyzed; ND = no data. Note: Adapted from IOM (2,3) and Pennington and Schoen (6)

The RDA and/or AI values plus the UL recommendations for adults also were extracted from the IOM reports and are compiled in Table 2. The RDA values represent target nutrient intakes for specific age/sex groupings and are considered to be adequate to cover the nutritional needs of about 97% of the population. In cases where the data are not adequate to establish an RDA for a nutrient, the IOM sets an AI value that appears to provide an adequate nutrient intake for at least 50% of the target population. The UL value, on the other hand, is a recommended upper bound on nutrient intake that should not be exceeded on a daily basis. Intakes at or below the UL are not anticipated to cause any adverse effects.

Table 2. Adult Dietary Reference Intakes

Mineral	RDA or AI (female/male) (mg/day)	UL(mg/day)
Chromium	0.024/0.035 ^a	NE
Copper	0.9	10
Fluoride	3/4 ^a	10
Iron	18/8	45
Manganese	1.6/2.2	11
Selenium	0.055	0.4
Sodium	2500	NE
Zinc	8/11	40

^aAI value NE = none established. Note: Adapted from IOM (1,2,3)

The data on mineral intakes from drinking water vary according to the information source and are summarized in Table 3. Information from U.S. EPA reports (4,5) provided data on the percentage of the population exposed below the Minimum Reporting Level (MRL) for each mineral. The MRL is the mean of the minimum reporting levels reported by the States. Information was also available on the percentage of the population exposed at concentrations above the regulatory Maximum Contaminant Level (MCL) or the Health Reference Level (HRL). The HRL is the health-based benchmark that was used in examining occurrence during the CCL regulatory determination process. The HRL was derived using the methodology that the U.S. EPA Office of Water uses for calculating a Lifetime Health Advisory.

Table 3. Population Exposure to Mineral Nutrients Through Drinking Water

Mineral	Minimum Reporting Level (mg/L)	Population Exposed (%)	MCL or HRL (mg/L)	Population Exposed (%)
Chromium	0.01	29	0.1	1
Copper	1.3	NA	1.3	NA
Fluoride	0.1	97	4	5
Manganese	0.001	55	0.3 ^a	3
Selenium	0.005	23	0.05	0.3
Sodium	0.91	100	120 ^a	8.3

^aHRL value NA = not available. Note: Adapted from U.S. EPA (4,5)

A single exceedance of the MCL does not constitute a violation of the National Primary Drinking Water Regulations since violations are based on the average of four quarterly readings. However, when the HRL is the benchmark for comparison (manganese, sodium), the occurrence data come from unregulated contaminant monitoring, and the values are based on a single exceedance of the HRL rather than on an average of quarterly readings. Information on the median concentration of the detections and the 99th percentile concentration of the detections, when available, was used in the analysis.

In the analysis of the data described above, the percentage of the population exposed below the MRL was compared with the 5th and 50th percentile dietary intakes to examine the contribution of drinking water to dietary intake for this segment of the population. In most cases, population estimates were rounded to the nearest whole percent. An average drinking water intake from all sources of 1.2 L/day, as determined by the U.S. EPA (7), was used for this analysis rather than the 84th percentile 2 L/day value. The percentage of the population exposed to concentrations between the MRL and the MCL/HRL also was compared with the 5th and 50th percentile dietary intakes. The portions of the population exposed to levels greater than the MCL or HRL were compared with the 95th percentile dietary intakes to determine whether there might be a toxicity concern. For this analysis, the 2 L/day drinking water intake value (7) was used in determining the drinking water exposure.

There are several limitations in the present analysis. In three cases (chromium, fluoride, and sodium), complete dietary intake data were not available. For these three chemicals, the drinking water exposure was compared with the AI level (chromium, fluoride) or the average dietary intake (sodium) rather than with population percentile data. In addition, the drinking water measurements often covered a wide range of concentrations because they were analyzed by the U.S. EPA for different purposes. The concentration interval range limits the precision of the

drinking water contribution assessment. Also, some of the drinking water data provided estimates of the exposed populations, whereas in other cases, the data apply to PWSs or homes. The data limitations are mentioned in the relevant discussions that follow.

IV. RESULTS

The results of the analyses described above are presented in the following paragraphs. The nutrients are discussed in alphabetical order.

1. Chromium

Chromium participates in the control of glucose uptake by cells and thus appears to play a role in maintaining serum glucose levels (3). Dietary chromium is present as chromium III; the chromium levels for drinking water apply to total chromium. However, the chromium VI oxidation state is reduced to chromium III in the gastrointestinal track when chromium VI intakes are low (3). The data on exposure of the population to chromium in drinking water indicate that 71% of the population receive levels less than 0.01 mg/L and 29% receive levels between 0.01 mg/L and 0.1 mg/L. Only 0.001% receive concentrations greater than 0.1 mg/L (5).

Chromium intakes have not been monitored through the NHANES, CSFII, or TDS. Accordingly, the contributions from drinking water are evaluated against the adult dietary recommendation. The AI for chromium is 24 Φ g/day for adult females and 35 Φ g/day for adult males. Table 4 provides a comparison of the drinking water contribution for chromium to the dietary recommendations. No data indicate toxicity from dietary exposures to chromium, and thus the IOM did not set a UL.

Table 4. Estimated Chromium Exposure

Drinking Water (Φ g/day)	Population (%)	Food (AI) (Φ g/day)	Adult AI (%)
<1.2 ^a	71	24-35	3-5
1.2-120 ^a	29	24-35	3-500
>200 ^b	~0.001	No UL	No UL

^aDrinking water contribution was determined by multiplying the concentration by 1.2 L/day.

^bDrinking water contribution was determined by multiplying the concentration by 2 L/day.

A few duplicate diet studies of chromium intake suggest that the population intake may be marginal in some cases (3). A duplicate diet study is one in which participants collect portion sizes identical to what they consume for analysis. The collected samples are then homogenized and assayed for the analyte of interest.

The data in Table 4 indicate that chromium in drinking water can make a significant contribution to total exposure for systems that have concentrations near the MCL. Individuals exposed at or above the MCL are receiving 5 to 10 times the dietary requirement from drinking water, but only a small portion of the U.S. population is likely to be exposed at these levels. For 71% of the population, chromium contributions to total intake are minimal (3% to 5%).

2. Copper

Copper is an important constituent of a number of enzyme systems, including those responsible for utilization of iron, protection against free-radical oxygen species, and maturation of collagen

(3). It is sometimes added to impounded surface water to prevent the growth of algae, but its presence in drinking water is largely the result of corrosion of metallic copper used in the distribution system. Copper concentrations in drinking water fluctuate as a result of variations in water characteristics such as pH, hardness, and water chemistry.

The copper concentration of drinking water in the United States is measured at the tap and is reported to the State only under conditions where greater than 10% of the samples exceed the regulatory action level of 1.3 mg/L. Accordingly, the U.S. EPA does not have monitoring data for copper that are comparable to those for some other regulated mineral nutrients. In the United States, the median values for first-draw 90th percentile exceedances from 1991 to 1999 were slightly greater than 2 mg/L (7307 samples). Ten percent of the samples with exceedances had copper concentrations greater than 5 mg/L, and 1% were greater than 10 mg/L (8). Data from the NIRS indicate that 79% of the samples from groundwater systems had detections; the median concentration was 0.02 mg/L. The NIRS samples were taken at the entry to the distribution system and do not represent at-the-tap samples.

Results from a number of studies in Canada and the United States indicate that copper levels in drinking water can range from 0.005 to >30 mg/L (8,9,10). Levels of copper in running or fully flushed water tend to be low, whereas those in standing or partially flushed water samples are more variable and can be substantially higher. In four Nova Scotia communities, the first-draw water concentrations were greater than 1 mg/L in 53% of the homes (11). In a study from Sweden, the 10th percentile copper concentration in 4703 samples of unflushed water from homes was 0.17 mg/L, and the 90th percentile value was 2.11 mg/L (12). The median concentration was 0.72 mg/L.

Data on copper from the diet are available from the NHANES III, CSFII, and TDS. The TDS data indicate lower copper intakes than NHANES III and CSFII (Table 2) and were not used for Table 5. Since complete data on copper in drinking water are not available from the United States, the Pettersson and Rasmussen (12) data from Sweden are used to compare copper intakes from drinking water with those from the diet (Table 5). It is important to note that the drinking water guideline for copper in Sweden is 2 mg/L, which is greater than the 1.3 mg/L action level in the United States.

Table 5. Estimated Copper Exposure

Drinking Water (mg/day)	Homes (%)	Food^a (mg/day)	Food Intake (%)
0.2 ^b	10	0.6-0.7 1.1-1.2	29-33 17-18
>0.2-0.9 ^b	40	0.6-0.7 1.1-1.2	29-150 17-82
0.9-2.5 ^b	40	0.6-0.7 1.1-1.2	129-417 75-227
>4.22 ^c	10	2.0-2.1	>200

^aWhere there are two entries in the food column, the first applies to the 5th percentile dietary intake and the second to the 50th percentile dietary intake.

^bDrinking water contribution was determined by multiplying the concentration by 1.2 L/day.

^cDrinking water contribution was determined by multiplying the concentration by 2 L/day.

The values in Table 5 show that drinking water can supply a considerable portion of the daily copper intake for a substantial portion of the population. However, the copper intake from the combination of food and drinking water is unlikely to exceed the UL of 10 mg/L in most, but not all, instances. Drinking water concentrations greater than 4 mg/L, when combined with the 95th percentile dietary intakes, could equal or exceed the UL for copper.

3. Fluoride

Fluoride plays a role in the development of tooth enamel in young children and possibly in strengthening the bone matrix throughout life (1). In many areas of the United States, fluoride is added to drinking water as part of a program to reduce the incidence of dental caries. Because of considerable public interest, the U.S. EPA analyzed the population exposed at the minimum level recommended for fluoridation (0.7 mg/L) and the U.S. EPA Secondary Maximum Contaminant Level (SMCL) of 2 mg/L, in addition to systems exposed above the MRL and MCL (5). The SMCL was established to protect against moderate and severe dental fluorosis in young children.

The data on exposure of the population to fluoride indicate that only 3% of the population receive levels less than 0.1 mg/L, 44% receive average levels between 0.1 and 0.7, 51% are exposed to levels between 0.7 and 2 mg/L, and 1.8% are exposed to average levels between 2 and 4 mg/L (5). Only 0.09% of the population receive drinking water with average concentrations greater than 4 mg/L.

Fluoride intakes have not been monitored through the NHANES, CSFII, or TDS. Accordingly, the contributions from drinking water are evaluated against the dietary recommendations (AI). The AI for fluoride is 3 mg/day for adult females and 4 mg/day for adult males. Table 6 provides a comparison of the drinking water contribution for fluoride with the dietary recommendations. The UL for adults is 10 mg/day.

Table 6. Estimated Fluoride Exposure

Drinking Water (mg/day)	Population (%)	Food (AI) (mg/day)	Adult AI (%)
<0.12 ^a	3	3-4	3-4
>0.12-0.84 ^a	44	3-4	3-28
>0.84-2.4 ^a	51	3-4	21-80
>2.4-4.8 ^a	1.8	3-4	60-160
>8 ^b	<0.09	10 (UL)	80

^aDrinking water contribution was determined by multiplying the concentration by 1.2 L/day.

^bDrinking water contribution was determined by multiplying the concentration by 2 L/day.

The data presented in Table 6 show that fluoride in drinking water can make a significant contribution to total exposure for most individuals, especially those living in areas that are fluoridated. The major contribution of fluoride in drinking water is recognized in all surveys of dietary fluoride intake (1). However, even with a concentration of 4 mg/L and a drinking water intake of 2 L/day, the dietary adult UL for fluoride is not exceeded, and only a small percentage of the population is exposed to levels in excess of 4 mg/L.

Because of their increased susceptibility to dental fluorosis at ages younger than 8 or 9 years, children are of particular interest with regard to fluoride exposure. Accordingly, it is important to look at the ULs of intake for this group. The average drinking water intake for children during the period of dentition for the permanent teeth is 528 mL/day (7) to 600 mL/day

(1). The average drinking water intake for children aged 1 to 10 years is 528 mL/day, and 600 mL is the average formula intake for infants aged 6 months to 1 year. The UL values for children in the age group of concern are 0.9 mg/day for infants aged 6 months to 1 year, 1.3 mg/day for children aged 1 to 3 years, and 2.2 mg/day for children aged 4 to 8 years (1). Accordingly, infants aged 6 months to 1 year can ingest 600 mL/day of formula prepared from drinking water containing 1.5 mg/L fluoride but not higher concentrations without exceeding the UL for this age group. Children in the 1- to 9-year-old age group will not exceed the AI for their respective age group if they ingest water at or below the U.S. EPA SMCL of 2 mg/L at the average drinking water intake for this group—even with a 90th percentile intake of 1 L/day for the 3- to 9-year-old age group. The U.S. EPA requires public notification for systems that exceed the SMCL and recommends an alternative drinking water source for children younger than 9 years.

4. Iron

Historically, iron was one of the first trace minerals to receive an RDA because of its critical role in the synthesis of hemoglobin and other heme proteins (3). Accordingly, there is a considerable amount of information on iron intake from foods. Fewer data are available on the concentrations of iron in drinking water. Iron contamination of water often results from its presence in the earth's crust. Iron also can gain access to drinking water from the corrosion of cast iron pipes and the use of iron salts as coagulants in treatment (13).

Iron is not regulated by the U.S. EPA and has not been a subject of unregulated contaminant monitoring. However, iron was monitored in the NIRS and was detected in 75% of the groundwater systems sampled. The minimum detection level was 0.009 mg/L, and the maximum was 7.4 mg/L. The median iron concentration was 0.060 mg/L, and the 99th percentile detection value was 3.3 mg/L. Note that the detection level is variable and thus may cause an underestimation of the systems with detections. There is a U.S. EPA SMCL of 0.3 mg/L to protect against the effects of iron on the taste and color of drinking water. The SMCL value, however, is not enforceable unless a State chooses to make the secondary value a primary standard under State law.

Although data on percentages of the population exposed to varying levels of iron are not available, it is possible to make some judgment regarding the iron that can be contributed to daily dietary intake from drinking water by using the median of the detections from the NIRS and the 99th percentile value as an upper level benchmark.

Dietary iron has been monitored through the NHANES III, CSFII, and TDS (Table 1). There is some variability in the data, and the TDS estimates for the 5th and 50th percentile dietary intakes fall below those from NHANES III and CSFII estimates (Table 1). Accordingly, they were not used for Table 7.

The RDA for iron is 18 mg/day for females of childbearing age (to account for replenishment of menstrual losses) and 8 mg/day for males. Individuals at the lower end of the population exposure curve (5%) fail to consume recommended levels and would benefit from iron in drinking water. The iron from average drinking water intake could increase the food exposure by only 1% but would increase intake by about 5% at levels close to the SMCL. Drinking water intake of iron at concentrations near the SMCL can make a small contribution to total intake for individuals with low dietary intakes.

Table 7. Estimated Iron Exposure

Drinking Water (mg/day)	Systems (%)	Food ^a (mg/day)	Food Intake (%)
<0.009	25	7-8	<1
		14	<1
<0.07 ^b	38	7-8	1
		14	<1
0.07-4 ^b	36	7-8	1-57
		14	<1-29
>6.6 ^c	1	26-27	>24-25

^aWhere there are two entries in the food column, the first applies to the 5th percentile dietary intake and the second to the 50th percentile dietary intake.

^bDrinking water contribution was determined by multiplying the concentration by 1.2 L/day.

^cDrinking water contribution was determined by multiplying the concentration by 2 L/day.

The 50th percentile dietary intake group has an estimated daily iron intake that ranges from 10 to 14 g. This is adequate to meet the dietary needs of males but not females. An added 3 to 4 mg/day from 1.2 L of drinking water would be adequate to raise the intake for females too close to the RDA. The 95th percentile dietary intake is 25 to 28 mg/day. The 0.6 mg/day that would be contributed by ingesting 2 L of water at the U.S. SMCL would not increase total iron intake to a level that would exceed the UL of 45 mg/day. Concentrations of iron in drinking water at levels of 2 to 3 mg/L might pose a problem for individuals who suffer from iron storage disease (hemochromatosis) (3).

5. Manganese

Manganese is a cofactor for a number of enzyme systems involved in carbohydrate, amino acid, and lipid metabolism (3). It is widely distributed in the diet, especially for those following a vegetarian regime. Data from the NIRS indicate that 45% of the population are exposed to manganese through their drinking water at concentrations less than 1 Φg/L. Fifty-two percent are exposed at concentrations between 1 Φg/L and 300 Φg/L, and 3% are exposed at concentrations greater than 300 Φg/L (4,14). The median value for the detections was 10 Φg/L, and the 99th percentile value was 630 Φg/L.

Dietary manganese intakes have been monitored only through the TDS. These estimates suggest that the 5th percentile dietary intake is about 490 Φg/day. Average intake is about 1.7 mg/day, and the 95th percentile dietary intake is about 4.8 mg/day. The adult RDA for manganese is 1.6 mg/day for females and 2.2 mg/day for males. The adult upper limit is 11 mg/day. The data for manganese indicate that there is considerable variability in dietary intake and that average intakes are close to dietary requirements. However, about 50% of the population receive less than the RDA through their food supply. Table 8 provides a comparison of the drinking water contribution for manganese to the dietary recommendations.

The data presented in Table 8 suggest that manganese in drinking water can make a significant contribution to total intake for those at the lower end of the food intake distribution curve when concentrations in water approach the HRL. However, such exposures are infrequent given that the median of all detections was 10 Φg/L.

Table 8. Estimated Manganese Exposure

Drinking Water (Φg/day)	Population (%)	Food ^a (Φg/day)	Food Intake (%)
<1.2 ^b	45	490	<1
		1700	<1
1.2-360 ^b	52	490	<1-74
		1700	<1-21
>6002 ^c	3	4800	>13

^aWhere there are two entries in the food column, the first applies to the 5th percentile dietary intake and the second to the 50th percentile dietary intake.

^bDrinking water contribution was determined by multiplying the concentration by 1.2 L/day.

^cDrinking water contribution was determined by multiplying the concentration by 2 L/day.

Manganese concentrations greater than the HRL are unlikely to have an adverse impact, even on those in the 95th percentile dietary intake category. The combination of 2L of water at the HRL (600 Φg/day) and the 95th percentile dietary intake (4800 Φg/day) are less than the UL of 11,000 Φg/day. However, a 2 L/day intake of water from the 1% of systems with the highest manganese concentrations (>630 Φg/L), when combined with the 95th percentile dietary intake, would exceed the UL for manganese. The critical effect on which the UL is based is an increase in serum manganese levels and in the activity of manganese-dependent superoxide dismutase with a lowest-observed-adverse-effect level of 15 mg/day (3). This effect is considered marginally adverse.

6. Selenium

Selenium is a key component of several important enzymes, including glutathione reductase, iodothyronine deiodinase, and thioredoxin reductase (2). It is present in foods primarily as selenomethionine and selenocysteine; selenium in drinking water is more likely to be present as selenite or selenate ions (15). The data on exposure of the population to selenium in drinking water indicate that 77% of the population receive levels less than 5 Φg/L and 23% receive levels between 5 and 50 Φg/L (5). Only 0.002% receive concentrations greater than 50 Φg/L.

Dietary selenium intakes have been monitored through the CSFII and TDS. The estimates from these studies (Table 1) indicate that the 5th percentile dietary intake is about 57 Φg/day. The average intake is about 106 Φg/day, and the 95th percentile intake is about 193 Φg/day. The adult RDA for selenium is 55 Φg/day for females and males; the adult UL is 400 Φg/day. The dietary data for selenium indicate that the diet contains adequate quantities to satisfy requirements, even for individuals at the low end of the population intake distribution. Table 9 provides a comparison of the drinking water contributions for selenium to the dietary recommendations.

The data presented in Table 9 indicate that selenium in drinking water does not make a significant contribution to total selenium intake for most of the population. For example, selenium is 11% or less than the intake from foods in 77% of the drinking water systems. However, for those receiving concentrations near the MCL, the selenium in drinking water can provide one-half or more of the total dietary intake. Selenium concentrations greater than the MCL are unlikely to have adverse impacts, even on those in the 95th percentile dietary intake category. The combination of 2L of water at the MCL (100 Φg/day) and the 95th percentile dietary intake (193 Φg/day) is less than the UL of 400 Φg/day.

Table 9. Estimated Selenium Exposure

Drinking Water (Φg/day)	Population (%)	Food ^a (Φg/day)	Food Intake (%)
<6 ^b	77	57	11
		106	6
6-60 ^b	23	57	11-105
		106	6-57
>100 ^c	0.002	193	>52

^aWhere there are two entries in the food column, the first applies to the 5th percentile dietary intake and the second to the 50th percentile dietary intake.

^bThe drinking water contribution was determined by multiplying the concentration by 1.2 L/day.

^cThe drinking water contribution was determined by multiplying the concentration by 2 L/day.

7. Sodium

Sodium is the principal electrolyte found in extracellular fluid. The balance between the concentrations of sodium and potassium (the principal intracellular electrolyte) is critical in the transmission of electrical impulses across the cell membrane (16). Sodium levels in serum also play a role in maintaining cellular osmotic pressure within mammalian systems.

Sodium is widely distributed in drinking water; it has been detected in almost all surface and groundwater systems evaluated. However, the levels are minimal compared with those in the diet. All samples in the NIRS contained sodium. For 82% of the population, the concentrations fell between 0.9 and 60 mg/L; for 10%, the levels fell between 60 and 120 mg/L; and for 8%, the levels were greater than 120 mg/L, the HRL benchmark. The 99% concentration for all samples was 517 mg/L, and the median concentration was 16.6 mg/L.

Data on surface water concentrations of sodium are minimal, but data from five States (Alabama, California, Illinois, New Jersey, and Oregon) were analyzed by the U.S. EPA (4,17). With the exception of the State of California, 90% or more of the population received drinking water with less than 60 mg/L. In California, only 23% received water with levels below 60 mg/L. However, even in California, the concentration exceeded 120 mg/L for only 1.5% of the population.

Only limited data could be identified for dietary exposure to sodium. The data from the 1982-1991 TDS showed an average intake for women (aged 25 to 30 years) of 1950 mg/day; men in the same age group had an intake of 2986 mg/day (6). These values are likely to be an underestimate of actual intake since they do not include discretionary salt added at the table. The data support the widely accepted assumption that sodium intake for many in the population exceeds the recommended 2500 mg/day (16).

The data in Table 10 indicate that drinking water makes a minimal contribution to total dietary exposure to sodium, even for the small portion of the population who receive water with levels above 120 mg/L. The 99% concentration from groundwater was 519 mg/L. With a 2 L/day intake of drinking water, the sodium from water would be 32% (males) to 52% (females) of that from the average diet and could be of concern for a person with salt-sensitive hypertension. However, the adverse taste of water with this sodium concentration would be likely to minimize intake. The 99% concentrations for the surface water systems ranged from 150 to 379 mg/L.

Table 10. Estimated Sodium Exposure

Drinking Water (mg/day)	Population (%)	Food ^a (mg/day)	Average Intake (%)
<1.1 ^b	0	2000-3000	-4 ^c
1.1-72 ^b	82	2000-3000	<1-4
72-144 ^b	10	2000-3000	2-7
>240 ^d	8	2000-3000	>8-12

^aAverages for males and females (6).

^bDrinking water contribution was determined by multiplying the concentration by 1.2 L/day.

^cNo percentage of the population at that level.

^dDrinking water contribution was determined by multiplying the concentration by 2 L/day.

8. Zinc

Zinc is a component of more than 200 enzymes that are critical to processes such as those involved in DNA replication and gene expression (3). As with iron, there is a considerable amount of information on zinc intake from foods, but fewer data are available on the concentrations in drinking water.

Zinc is not regulated by the U.S. EPA and has not been a subject of unregulated contaminant monitoring. Zinc was included in the NIRS. It was detected in 87% of the samples, with a median detection of 0.2 mg/L and a maximum of 0.65 mg/L. Another survey (18) cited by the ATSDR (19) provided some information on the zinc found in tapwater in the United States. The minimum value reported was 0.025 mg/L, and the median value was 0.114 mg/L. Seventy-five percent of the samples contained less than 0.236 mg/L, and the maximum was 1.447 mg/L.

Zinc contamination of water can result from its presence in the earth's crust, leaching from galvanized materials for transport or storage of drinking water, and the addition of zinc orthophosphate products for corrosion control. The concentration of zinc that can be added to water for corrosion control is limited to 2 mg/L (13). There is an SMCL of 5 mg/L to protect against adverse taste effects.

As with iron, data on the percentage of the population exposed to varying levels of zinc through drinking water are not available. However, it is possible to make some judgment using the data of Greathouse and Osborne (18) and the SMCL as an upper level benchmark.

Zinc in the diet has been monitored through the NHANES III, CSFII, and TDS (Table 1). As with iron, the TDS estimates for the 5th and 50th percentile dietary intakes fall below NHANES III and CSFII estimates and were not used for Table 11. In most cases, zinc intake from drinking water does not make a significant contribution to total exposure. For PWSs that treat for corrosion control with zinc orthophosphates, the zinc from drinking water can increase that from food by 24% for individuals with an average zinc intake and by 40% for those in the 5th percentile dietary intake. At concentrations near the SMCL, zinc can make a significant contribution to total intake, increasing it by 50% or more.

The RDA for zinc is 8 mg/day for females and 11 mg/day for males. Individuals at the lower end of the population exposure curve fail to consume recommended levels and would benefit from zinc in drinking water where zinc orthophosphate is used for corrosion control or at levels close to the SMCL. These concentrations would increase zinc food intakes (3-6 mg/day) by about 2.5 to 6 mg. The 50th percentile population group has an estimated daily zinc intake that

ranges from 7 to 11 mg/day and would not benefit as much from zinc contributed by drinking water. The 95th percentile dietary intake of zinc is 18 to 19 mg/day. The 10 mg/day that would be contributed by ingesting 2 L/day of water at the SMCL would not increase the total zinc intake to a level that would exceed the UL of 40 mg/day.

Table 11. Estimated Zinc Exposure

Drinking Water (mg/day ^b)	Systems (%)	Food ^a (mg/day)	Food Intake (%)
0.03-0.14 ^c	50	6 10-11	<1-2 – 1
0.14-0.28 ^c	25	6 10-11	2-5 1-3
0.6-2.9 ^d	25	18-19	3-16

^aWhere there are two entries in the food column, the first applies to the 5th percentile dietary intake and the second to the 50th percentile dietary intake.

^bGreathouse and Osborne (18).

^cDrinking water contribution was determined by multiplying the concentration by 1.2 L/day.

^dDrinking water contribution was determined by multiplying the concentration by 2 L/day.

V. CONCLUSIONS

Although all of the minerals from drinking water evaluated in this report (chromium, copper, fluoride, iron, manganese, selenium, sodium, and zinc) can make significant contributions to dietary intake for some segments of the population, the affected population is generally small, and the contributions of potable water are most significant as the concentrations approach the MCL or HRL. This situation is fairly uncommon except in areas that are geologically rich in the mineral in question or, more importantly, when there is a source of the mineral from drinking water treatment chemicals (fluoride, iron, zinc) or as a result of leaching from drinking water contact materials (copper, zinc).

Individuals who would receive the greatest benefit from the presence of minerals in drinking water are those individuals with marginal intakes from food sources. In the United States, the 50th percentile dietary intakes from food appear to be adequate in most cases, with the exception of iron intakes by women. Accordingly, the intake from drinking water does not have a great impact on total exposure or physiological response.

The situation may well be very different in areas of the world where food is scarce or for those who do not benefit from the nutrient fortification programs that have been established in the United States. In cases where average intakes of mineral nutrients are below recommended levels, the minerals contributed by drinking water would become proportionally more important than indicated by U.S. data. From a toxicological perspective, the comparisons of the upper intakes from water plus food did not exceed the dietary UL recommendation for adults. This might partially be a reflection of the nature of the available data. For example, in a few cases where data from the upper extremes of exposure are available (copper and manganese), some individuals could be exposed above the UL.

Some sensitive population issues must be considered when examining the data presented in this report. Individuals with Wilson's disease must restrict their dietary copper intake, individuals with hemochromatosis have similar limitations on total dietary iron, and salt-sensitive hypertensive individuals must take measures to limit their sodium intake. Children are sensitive to dietary fluoride during the years of tooth formation, and levels of fluoride in drinking water near the SMCL (2 mg/L) and MCL (4 mg/L) can cause dental fluorosis in cases where drinking water intakes are higher than the average during this time period.

This report should be regarded as a preliminary effort to compare the contribution of waterborne minerals to overall nutritional health and well-being. Additional studies must be undertaken, especially in those areas with marginal intakes of these minerals from foods and/or high concentrations in drinking water. Programs that may be established to fortify desalinated or demineralized water must consider the effects on sensitive populations as well as the beneficial aspects of such measures.

References

1. Dietary reference intakes for calcium, phosphorous, magnesium, vitamin D, and fluoride. Institute of Medicine. National Academy of Sciences. National Academy Press. Washington, DC, 1997.
2. Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. Institute of Medicine. National Academy of Sciences. National Academy Press. Washington, DC, 2000.
3. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. A Report of the Panel on Micronutrients, Subcommittees on Upper Reference Levels of Nutrients and of Interpretation and Use of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. National Academy Press. Washington, DC, 2001.
4. Analysis of national occurrence of the 1998 contaminant candidate list (CCL) regulatory determination priority contaminants in public water systems. Office of Water. EPA 815-D-01-002. Washington, DC, 2002.
5. Occurrence estimation methodology and occurrence findings report for the six-year review of existing national primary drinking water regulations. Office of Water. EPA-815-R-03-006. Washington, DC, 2003.
6. Pennington JA, Schoen SA. Total Diet Study: Estimated dietary intakes of nutritional elements 1982-1991. *Int J Vitam Nutr Res* 1996;66:350-362.
7. Estimated per capita water ingestion in the United States. Office of Water. EPA-822-00-008. Washington, DC, 2000.
8. Copper in drinking water. National Research Council (NRC). National Academy of Sciences. National Academy Press. Washington, DC, 2000.
9. Maximum contaminant level goals and national primary drinking water regulations for lead and copper; final rule. *Federal Register* 56(110), 26460-26564. U.S. Environmental Protection Agency, 7 June 1991.
10. Health Canada. Copper. In: *Guidelines for Canadian drinking water quality. Supporting documentation*. Ottawa, Ontario, 1992.
11. Toxicological profile for copper (draft for public comment). U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry (ATSDR) (Subcontract No. ATSDR-205-1999-00024). Atlanta, GA, 2002.
12. Pettersson R, Rasmussen F. Daily intake of copper from drinking water among young children in Sweden. *Environ Health Perspect* 1999;107(6):441-446.
13. Drinking water treatment chemicals - health effects. American National Standard/National Science Foundation (NSF) international standard for drinking water additives. ANSI/NSF 60 - 2000. NSF International, Ann Arbor, MI, 2000.
14. Health effects support document for manganese. Office of Water. EPA-822-00-008. Washington, DC, 2003.
15. Toxicological profile for selenium (draft for public comment). U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry (ATSDR) (Subcontract No. ATSDR-205-1999-00024). Atlanta, GA, 2002.
16. Recommended dietary allowances. National Research Council. National Academy of Sciences. National Academy Press. Washington, DC, 1989.

17. Drinking water advisory: consumer acceptability advice and health effects analysis on sodium. Office of Water. EPA 822-R-03-006. Washington, DC, 2003.
18. Greathouse DG, Osborne RH. Preliminary report on nationwide study of drinking water and cardiovascular diseases. *J Environ Path Toxicol Oncol* 1980;4:65-76 (as cited in ATSDR 1994).
19. Toxicological profile for zinc. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry (Subcontract No. ATSDR- 205-88-0608). Atlanta, GA, 1994.

7. MINERAL ELEMENTS RELATED TO CARDIOVASCULAR HEALTH

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I. INTRODUCTION

Consideration of the characteristics of water as determinants of disease risk is not a new idea. Hippocrates is quoted: "We must also consider the qualities of the waters, for as they differ from one to another in taste in weight, so also do they differ much in their qualities" (1). Indeed, the science of epidemiology traces its origin to the 19th century work of Snow who mapped the incidence of cholera in London, showing it to be much higher in areas supplied with a particular water source (2).

II. NUTRITIONAL DETERMINANTS OF HEART DISEASE RISK

Keys (3) was among the first to notice the great variation in heart disease death rates among various nations. The death rate for men in Finland was 16 times that in Taiwan. Times change and methods vary, but differences still are substantial (4). For example, the male death rate for ischemic heart disease in Scotland is nearly nine times as great as that in Japan which, in turn, is more than five times that in Guatemala.

Ischemic heart disease (IHD) is often thought of as a hereditary illness because some families have several affected members and other families have none. It seems unlikely, however, that most ischemic heart disease is hereditary for two reasons. First, in the wealthier nations, ischemic heart disease is far too common to be explained on the basis of heredity; nearly one-fourth of all deaths in the US are from IHD (5) (hereditary illnesses typically occur at prevalences <5 per 1000 live births (6). Second, emigrants from low to high IHD risk nations experience an increase IHD risk (7, 8, 9, 10, 11). This phenomenon is best demonstrated by comparing people of Japanese heritage some of whom immigrated to the US: serum cholesterol, one of the better predictors of heart disease risk, was lowest among farmers in Koga, was greater among doctors in Fukouka and men in Hawaii, and greatest among Japanese Americans born in Los Angeles of immigrant parents (7).

It is now clear that dietary trace elements are associated with heart disease risk. Knox (12) found a negative correlation between dietary calcium intake and heart disease risk in England and Wales. Varo (13) found a highly positive correlation between death rates for ischemic heart disease and the dietary ratio of calcium to magnesium in the European Union. In fact, Finnish children with the highest concentrations of cholesterol in serum, and presumably the highest risk of IHD, consumed significantly less calcium than those with the lowest serum concentrations of cholesterol (14). One of us found that the mortality rate for coronary heart disease in the United States was correlated positively with the ratio of zinc to copper in milk consumed in 47 cities (15). Therefore, it is likely that at least part of the geographic difference in risk may be related to

Environmental measurements of trace elements also are associated with risk. Valentine and Chambers (16) found the risk of death due to arteriosclerotic heart disease was proportional to the concentration of zinc in reservoirs storing water for nine study areas in Houston. Kodavanti et al. (17) have reviewed associations between cardiovascular morbidity and mortality and air pollution indices, and have implicated particulate matter containing highly bioavailable zinc. They also have produced cardiovascular pathology in rats exposed to similar particles by inhalation. People who eat diets low in copper may be particularly susceptible to harm from air pollution high in zinc (18).

III. WATER AND HEART DISEASE

Kobayashi (19) made the first observation on the relationship between the chemistry of river water and the risk of vascular disease, a phenomenon that has come to be called the "water factor." A literature search revealed that the bulk of the data show lower risk with harder water (20, 21). Crawford (22) concluded that the correlation may be causal because of findings from English and Welsh towns which experienced increases in heart disease rates after reducing the hardness of the water supplies. Interest in the hard water phenomenon continues (23, 24, 25, 26) although mechanisms are ill-defined.

IV. OTHER ILLNESSES RELATED TO WATER MINERAL CONTENT

Sparrow et al. (27) found pulmonary function to be positively correlated with the concentration of copper in the drinking water in homes of nonsmokers. This observation may be clarified by the finding that lungs of rats (28) and pigs (29) deficient in copper are anatomically similar to those of emphysema patients. Cadmium, lead, and tin have no known nutritional benefits; however, each has been indicated in the etiology of essential hypertension. Chronic exposures to low levels of cadmium increased blood pressure in rats (30, 31); hypertension in people is more likely at environmental than industrial levels of cadmium (32). Blood cadmium concentration is directly related to risk of hypertension in humans (33). The risk of hypertension appears to be more strongly associated with lead exposures at industrial levels (34, 35) than environmental ones (36, 37, 38, 39, 40).

V. HARDNESS GOOD OR SOFTNESS BAD?

Several researchers have shown inverse associations between hard water and IHD risk (Water and Heart Disease, above). Such epidemiologic associations, however, cannot distinguish between the prospect of something harmful in soft water or something protective in hard water. Experimental results would support the latter hypothesis, as they have indicated that calcium (and/or magnesium) can be protective against heart disease. To date, six experiments (41, 42, 43, 44, 45, 46) involving a total of 145 subjects have shown decreases in the concentration of cholesterol in serum of men and women ingesting calcium salts (usually carbonate) as supplements to their usual diets. The daily doses of calcium were in the 1-2 g range.

Some 34 elements have been found to show epidemiologic relationships with ischemic heart disease or to the metabolism of cholesterol or other lipids (40, 47) (Figure 1). This chart has been revised several times; earlier articles (48, 49, 50) include numerous references to epidemiology and experiment. Shaded elements are those that may act by either enhancing or inhibiting copper, deficiency of which can produce a wide variety of anatomical, chemical, and physiological pathology in the cardiovascular system (51).

Figure 1. Elements implicated in atherosclerosis or ischemic heart disease by epidemiology or experiment.

Elements of Atherosclerosis																	
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3	Li	4															
5	Na	6	Mg														
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The mechanisms by which particular elements or their compounds may affect heart disease risk are not clear, but it is likely that they involve effects on enzymes, hormones, and messenger molecules. After all, as Mildvan (52) observed, more than 27% of known enzymes contain mineral elements and/or require minerals for activity. It has been suggested that chromium may produce some of its effects by potentiating insulin (53); zinc deprivation decreased serum thymulin and interleukin-2 (54); and prostaglandin metabolism appears to be modified by dietary copper (55, 56).

Other mechanisms may involve the complexity of interactions among the various mineral elements. For example, zinc is known to inhibit copper utilization (57, 58, 59, 60) and increase plasma cholesterol (57, 61), and cadmium can induce hypercholesterolemia that can be relieved by extra copper (62). Lead produced increased urinary losses of copper (63) and can antagonise copper in hematopoiesis (64). Pekelharing et al. (65) found that amounts of tin similar to those found in human diets can decrease copper status.

Calcium can modify the utilization of other dietary elements. Romasz et al. (66) fed rats a wide range of dietary calcium; as dietary calcium increased, the concentration of cholesterol in serum decreased, and the concentrations of copper and zinc in liver increased and decreased, respectively, although the dietary concentration of the trace elements was constant. Reeves and Chaney (67, 68) found that a low calcium intake of rats caused increased absorption and retention of cadmium, thereby increasing the potential for cadmium intoxication.

VI. TRACE ELEMENTS IN WATER SUPPLIES

Calcium and magnesium are the main elements that give water its hardness. The correlation coefficient between calcium and hardness in water is about 0.96 (58). Calcium in hard water can

be an important dietary supplement (58) because hard water can contribute 175-180 mg of calcium daily (58). Calcium and magnesium in water also are correlated (c0.8) as are magnesium and hardness (c0.9) (58). The inverse correlation between coronary heart disease mortality and magnesium in water is similar to that with calcium (30, 69, 70).

Lower intakes of dietary magnesium (less than 186 mg daily) are associated with higher risk of coronary heart disease in the Honolulu Heart Program (71). Higher magnesium intakes may improve cholesterol metabolism and prevent cardiac arrhythmia. Low dietary magnesium increased the total concentration of cholesterol in the blood of rats and monkeys (72, 73). A "placebo" containing magnesium seemed to produce a decline in the concentration of cholesterol in the sera of men and women (44). People who live where the water is soft may be in jeopardy for cardiac arrhythmia if they eat diets low in magnesium (74, 71).

Most public water supplies do not contain enough copper to be of appreciable nutritional significance. A survey of the water supplies of the 100 largest US cities (75) found that 94% contained less than 100 µg copper per liter. At typical rates of consumption (a liter per day), this would add less than 0.1 mg copper to daily intakes. However, water chemistry changes between municipal reservoirs and consumers' taps where greater amounts of the element may be available. Angino (76) found that 16% of 284 US water samples contained enough copper to add at least 0.2 mg of copper to the daily intakes, and 6% would add 0.5 mg of copper to those intakes. Accordingly, drinking water (1 L per day) in Boston, MA, was estimated to provide 0.46 mg copper daily (27). A study of the drinking water available in Seattle, WA (77), showed that source to supply residents with much more copper: 1.3-2.2 mg per day. Copper supplements this large are easily tolerable (78, 79, 80) and may be beneficial considering that the Western diet often is low in copper (81) and that people with cardiovascular disease have been found to have decreased copper in hearts and arteries (51, 82) and decreased activities of enzymes dependent on copper (82). A diet low in copper can increase cholesterol in plasma (78).

VII. CONCLUSION

In most cases, drinking and cooking water may be of only minor importance to the trace element nutrition of individuals. In some cases, and particularly for individuals dependent on foods and food systems that do not provide adequate amounts of calcium and copper, some water sources by virtue of their hardness and/or contributions of copper piping, can provide significant amounts of those elements. Available information indicates that such sources can be beneficial. We conclude that hard water is good because it contains nutrients valuable in themselves and because these nutrients can decrease impact of toxic elements in the environment.

To minimize heart disease risk, the ideal water should contain sufficient calcium and magnesium to be moderately hard. No effort should be made to eliminate trace elements such as copper and iron where these elements are in short, dietary supply. Elements such as cadmium and lead, which can accumulate in the body, should be minimized.

References

1. Adams F. Hippocratic writings. In: Adler M, ed. Great Books of the Western World, vol. 9, Chicago: Encyclopedia Britannica, Inc., 1952.
2. Frost WH. Snow on Cholera, New York:Hafner Publishing Company, 1965:86.
3. Keys A. Coronary heart disease the global picture. *Atherosclerosis* 1975;22:149-192.
4. Anon. 1985 Demographic Yearbook. 37th Issue, Table 2 ed. NewYork:United Nations, 1987b:847-867.
5. Anon. (1987a) Vital Statistics of the United States, Vol. II, Mortality, Part A, 1984 DHHS Pub. No. (PHS) 87-1122. Table 1-6. Hyattsville:Public Health Service, 1987a.
6. Cleave TL, Campbell GD. Diabetes, Coronary Thrombosis, and the Saccharine Disease, 1st ed. Bristol:John Wright & Sons Ltd, 1966:2-3.
7. Keys A, Kimura N, Kusukawa A, et al. Lessons from serum cholesterol studies in Japan, Hawaii and Los Angeles. *Ann Intern Med* 1958;48:83-94.
8. Toor M, Katchalsky A, Agmon J, Allalouf D. Atherosclerosis and related factors in immigrants to Israel. *Circulation* 1960;22:265-279.
9. Brown J, Bourke GJ, Gearty GF, et al. Nutritional and epidemiologic factors related to heart disease. *World Rev Nutr Diet* 1970;12:1-42.
10. Hankin J, Reed D, Labarthe D, et al. Dietary and disease patterns among Micronesians. *Am J Clin Nutr* 1970;23:346-357.
11. Harding S. Mortality of migrants from the Indian subcontinent to England and Wales: effect of duration of residence. *Epidemiology* 2003;14:287-292.
12. Knox EG. Ischaemic-heart-disease mortality and dietary intake of calcium. *Lancet* 1973;1:1465-1467.
13. Varo P. Mineral element balance and coronary heart disease. *Int J Vitam Nutr Res* 1974;44:267-273.
14. Räsänen L, Wilska M, Kantero RL, et al. Nutrition survey of Finnish rural children. IV. Serum cholesterol values in relation to dietary variables. *Am J Clin Nutr* 1978;31:1050-1056.
15. Klevay LM. The ratio of zinc to copper in milk and mortality due to coronary heart disease: an association. In: Hemphill DD, ed. Trace Substances in Environmental Health-VIII, Columbia:University of Missouri Press, 1974:9-14.
16. Valentine JL, Chambers LA. Distribution of trace elements in the Houston environment: relationship to mortality from arteriosclerotic heart disease. *Tex Rep Biol Med* 1976;34:331-339.
17. Kodavanti UP, Moyer CF, Ledbetter AD, et al. Inhaled environmental combustion particles cause myocardial injury in the Wistar Kyoto rat. *Toxicol Sci* 2003;71:237-245.
18. Klevay L. *Toxicol Sci* (letter to editor) 2003;74:228-229.
19. Kobayashi J. On geographical relationship between the chemical nature of river water and death-rate from apoplexy. *Berichte der Ohara Institute* 1957;11:12-21.

20. Sharrett AR, Feinleib J. Water constituents and trace elements in relation to cardiovascular diseases. *Prev Med* 1975;4:20-36.
21. Klevay LM. The influence of copper and zinc on the occurrence of ischemic heart disease *J Environ Pathol Toxicol* 1980a;4:281-287.
22. Crawford MD. Hardness of drinking-water and cardiovascular disease. *Proc Nutr Soc* 1972;31:347-357.
23. Lacey RF, Shaper AG. Changes in water hardness and cardiovascular death rates. *Int J Epidemiol* 1984;13:18-24.
24. Nerbrand C, Svärdsudd K, Ek J, Tibblin G. Cardiovascular mortality and morbidity in seven counties in Sweden in relation to water hardness and geological settings. The project: myocardial infarction in mid-Sweden. *Eur Heart J* 1992;13:721-727.
25. MacPherson A, Bacso, J. Relationship of hair calcium concentration to incidence of coronary heart disease. *Sci Total Environ* 2000;255:11-19.
26. Kousa A, Moltchanova E, Viik-Kajander M, et al. Geochemistry of ground water and the incidence of acute myocardial infarction in Finland. *J Epidemiol Community Health* 2004;58:136-139.
27. Sparrow D, Silbert JE, Weiss ST. The relationship of pulmonary function to copper concentrations in drinking water. *Am Rev Respir Dis* 1982;126:312-315.
28. O'Dell BL, Kilburn KH, McKenzie WN, Thurston RJ. The lung of the copper-deficient rat. A model for developmental pulmonary emphysema. *Am J Pathol* 1978;91:413-432.
29. Soskel N, Watanabe S, Hammon E, et al. A copper-deficient, zinc-supplemented diet produces emphysema in pigs. *Am Rev Respir Dis* 1982;126:316-325.
30. Schroeder HA, Nason AP, Mitchener M. Action of a chelate of zinc on trace metals in hypertensive rats. *Am J Physiol* 1968;214:796-800.
31. Perry HM, Jr., Erlanger M, Perry EF. Hypertension following chronic, very low dose cadmium feeding. *Proc Soc Exp Biol Med* 1977;156:173-176.
32. Kopp SJ, Gonek T, Perry HM, Jr, et al. Cardiovascular actions of cadmium at environmental exposure levels. *Science* 1982;217:837-839.
33. Thind GS, Fischer GM. Plasma cadmium and zinc in human hypertension. *Clin Sci Mol Med* 1976;51:483-486.
34. Egeland GM, Burkhardt GA, Schnorr TM, et al. Effects of exposure to carbon disulphide on low density lipoprotein cholesterol concentration and diastolic blood pressure. *Br J Ind Med* 1992;49:287-293.
35. Maheswaran R, Gill JS, Beevers DG. Blood pressure and industrial lead exposure. *Am J Epidemiol* 1993;137:645-653.
36. Kromhout D, Wibowo AA, Herber RF, et al. Trace metals and coronary heart disease risk indicators in 152 elderly men (the Zutphen Study). *Am J Epidemiol* 1985;122:378-385.
37. Kromhout D. Blood lead and coronary heart disease risk among elderly men in Zutphen, The Netherlands. *Environ Health Perspect* 1988;78:43-46.
38. Staessen J, Sartor F, Roels H, et al. The association between blood pressure, calcium and other divalent cations: a population study. *J Hum Hypertens* 1991;5:485-494.

39. Dolenc P, Staessen JA, Lauwerys R, Amery A. Short report: low-level lead exposure does not increase the blood pressure in the general population. Cadmibel Study Group. *J Hypertens* 1993;11:589-593.
40. Klevay LM. Copper and other chemical elements that affect the cardiovascular system. In: Chang LW, Magos L, Suzuki T, eds. *Toxicology of Metals*, 1st ed. Boca Raton: CRC Lewis, 1996:921-928.
41. Yacowitz H, Fleischman AI, Bierenbaum ML. Effects of oral calcium upon serum lipids in man. *Br Med J* 1965;1:1352-1354.
42. Maibach E. Die Beeinflussung des Gesamtcholesterins der β -Lipoproteide und Gesamtlipide des Serums durch orale und parenterale Calciumzufuhr. *Schweizerische medizinische* 1967;97:418-421.
43. Maibach E. Über die Beeinflussung des Gesamtcholesterins und der Gesamtlipide im Serum des Menschen durch orale Kalziumzufuhr. *Wiener medizinische Wochenschrift* 1968;118:1059-1062.
44. Carlson LA, Olsson AG, Oro L, Rossner S. Effects of oral calcium upon serum cholesterol and triglycerides in patients with hyperlipidemia. *Atherosclerosis* 1971;14:391-400.
45. Bierenbaum ML, Fleischman AI, Raichelson RI. Long term human studies on the lipid effects of oral calcium. *Lipids* 1972;7:202-206.
46. Albanese AA, Edelson AH, Woodhull ML, et al. Effect of calcium supplement on serum cholesterol, calcium, phosphorous and bone density of "normal, healthy" elderly females. *Nutrition Reports International* 1973;8:119-130.
47. Klevay LM. Elements of ischemic heart disease. *Perspect Biol Med* 1977a;20:186-192.
48. Klevay LM. The role of copper and zinc in cholesterol metabolism. In: Draper HH, ed. *Advances in Nutrition Research*, vol. 1, 1st ed. New York: Plenum Publishing Corp., 1977b:227-252.
49. Klevay L. The role of copper, zinc, and other chemical elements in ischemic heart disease. In: Rennert OM, Chan WY, eds. *Metabolism of Trace Metals in Man*, vol. 1. Boca Raton, FL: CRC Press, 1984:129-157.
50. Klevay LM. Elements of atherosclerosis. In: Reis MF, Pereira JM, Machado AA, Abdulla M, eds. *Trace Elements in Medicine, Health and Atherosclerosis*. London: Smith-Gordon, 1995:9-14.
51. Klevay LM. Trace element and mineral nutrition in disease: Ischemic heart disease. In: Bogden JD, Klevay LM, eds. *Clinical Nutrition of the Essential Trace Elements and Minerals: The Guide for Health Professionals*, 1st ed. Totowa, NJ: Humana Press Inc., 2000:251-271.
52. Mildvan AS. Metals in enzyme catalysis. In: Boyd PD, ed. *The Enzymes*, 2nd ed., 1970:445-536.
53. Pi-Sunyer FX, Offenbacher EG. (1984) Chromium. In: Olson RE, Broquist HP, Chichester CO, Darby WJ, Kolbye AC, Jr, Stalvey RM, eds. *Present Knowledge in Nutrition*, 5th ed. Washington, DC: The Nutrition Foundation, Inc., 1984:571-586.
54. Prasad AS, Meftah S, Abdallah J, et al. Serum thymulin in human zinc deficiency. *J Clin Invest* 1988;82:1202-1210.

55. Mitchell LL, Allen KG, Mathias MM. Copper deficiency depresses rat aortae superoxide dismutase activity and prostacyclin synthesis. *Prostaglandins* 1988;35:977-986.
56. Allen KGD, Lampi KJ, Bostwick PJ, Mathias MM. Increased thromboxane production in recalcified challenged whole blood from copper-deficient rats. *Nutr Res* 1991;11:61-70.
57. Klevay LM. Hypercholesterolemia in rats produced by an increase in the ratio of zinc to copper ingested. *Am J Clin Nutr* 1973;26:1060-1068.
58. Klevay LM. Coronary heart disease: the zinc/copper hypothesis. *Am J Clin Nutr* 1975;28:764-774.
59. Underwood EJ. *Trace Elements in Human and Animal Nutrition* 4th ed. New York:Academic Press, 1977:61, 226, 231.
60. Klevay LM. Interactions of copper and zinc in cardiovascular disease. *Ann N Y Acad Sci* 1980b;355:140-151.
61. Klevay LM, Pond WG, Medeiros DM. Decreased high density lipoprotein cholesterol and apoprotein A-I in plasma and ultrastructural pathology in cardiac muscle of young pigs fed a diet high in zinc. *Nutr Res* 1994;14:1227-1239.
62. Bordas E, Gabor S. Die Cholesterinämie unter der Auswirkung der assoziierten verabreichung von Kadmium, Kupfer und Cholesterin. *Revue Roumaine de Biochimie* 1982;19:3-7.
63. Victory W, Miller CR, Goyer RA. Essential trace metal excretion from rats with lead exposure and during chelation therapy. *J Lab Clin Med* 1986;107:129-135.
64. Klauder DS, Petering HG. Anemia of lead intoxication: a role for copper. *J Nutr* 1977;107:1779-1785.
65. Pekelharing HL, Lemmens AG, Beynen AC. Iron, copper and zinc status in rats fed on diets containing various concentrations of tin. *Br J Nutr* 1994;71:103-109.
66. Romasz RS, Lemmo EA, Evans JL. Diet calcium, sex and age influences on tissue mineralization and cholesterol in rats. *Proceedings on Trace Substances in Environmental Health* 1977;11:289-296.
67. Reeves PG, Chaney RL. Mineral status of female rats affects the absorption and organ distribution of dietary cadmium derived from edible sunflower kernels (*Helianthus annuus* L.). *Environ Res* 2001;85:215-225.
68. Reeves PG, Chaney RL. Nutritional status affects the absorption and whole-body and organ retention of cadmium in rats fed rice-based diets. *Environ Sci Technol* 2002;36:2684-2692.
69. Schroeder HA. Relation between mortality from cardiovascular disease and treated water supplies. *JAMA* 1960;172:1902-1908.
70. Schroeder HA, Kraemer LA. Cardiovascular mortality, municipal water, and corrosion. *Arch Environ Health* 1974;28:303-311.
71. Abbot RD, Ando F, Masaki KH, et al. Dietary magnesium intake and the future risk of coronary heart disease (the Honolulu Heart Program). *Am J Cardiol* 2003;92:665-669.
72. Hellerstein EE, Nakamura M, Hegsted DM, Vitale JJ. Studies on the interrelationships between dietary magnesium, quality and quantity of fat, hypercholesterolemia and lipidosis. *J Nutr* 1960;71:339-346.

73. Vitale JJ, Velez H, Guzman C, Correa P. Magnesium deficiency in the Cebus monkey. *Circ Res* 1963;12:642-650.
74. Klevay LM, Milne DB. Low dietary magnesium increases supraventricular ectopy. *Am J Clin Nutr* 2002;75:550-554.
75. Durfor CN, Becker E. Public water supplies of the 100 largest cities in the United States, 1962. In: Geological Survey Water-Supply Paper No. 1812. Washington:U.S. Government Printing Office, 1964:68.
76. Angino EE. Geochemistry of drinking water as affected by distribution and treatment. In: Angino EE, Sandstead HH, Comstock GW, Corbett RG, Strong JP, Voors AW, eds. *Geochemistry of Water in Relation to Cardiovascular Disease*. Washington DC: National Academy of Sciences, 1979:3-13.
77. Sharrett AR, Carter AP, Orheim RM, Feinleib M. Daily intake of lead, cadmium, copper, and zinc from drinking water: The Seattle Study of Trace Metal Exposure. *Environ Res* 1982;28:456-475.
78. Klevay LM, Inman L, Johnson LK, et al. Increased cholesterol in plasma in a young man during experimental copper depletion. *Metabolism: Clinical and Experimental* 1984;33:1112-1118.
79. Araya M, McGoldrick MC, Klevay LM, et al. Determination of an acute no-observed-adverse-effect level (NOAEL) for copper in water. *Regul Toxicol Pharmacol* 2001;34:137-145.
80. Araya M, Chen B, Klevay LM, et al. Confirmation of an acute no-observed-adverse-effect and low-observed-adverse-effect level for copper in bottled drinking water in a multi-site international study. *Regul Toxicol Pharmacol* 2003;38:389-399.
81. Klevay LM. Lack of a recommended dietary allowance for copper may be hazardous to your health. *J Am Coll Nutr* 1998;17:322-326.
82. Klevay LM. Advances in cardiovascular-copper research. In: *First International Bio-minerals Symposium: Trace Elements in Nutrition, Health and Disease*, Montreal, Canada:Institut Rosell, 2002:64-71.

8. STUDIES OF MINERALS AND CARDIAC HEALTH IN SELECTED POPULATIONS

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I. INTRODUCTION

Cardiovascular diseases are, as a group, the leading cause of death in western countries. Sudden death from cardiovascular disease accounts for over 300,000 deaths per year in the U.S. (1). Because of the importance of cardiovascular disease, major efforts have been made to identify risk factors and to take steps to reduce these risks.

There is an increasing body of evidence that drinking water hardness and elevated concentrations of certain minerals in hard water may reduce the risk of cardiac death and, in particular, the risk of sudden cardiac death. Recent interest has focused on deficits in dietary magnesium. In developed countries, these deficits are potentially compounded by use of medications, such as diuretics, that further reduce body stores of magnesium (2). There is also concern that increased use of calcium supplements to prevent osteoporosis may alter the ratio of calcium to magnesium intake, further exacerbating the deficiency in magnesium intake. Since calcium and magnesium compete for absorption, there is concern that increasing calcium intake without also increasing magnesium intake can result in a deficit of magnesium. The optimal ratio of calcium to magnesium is unknown. In this chapter, the plausibility of a relationship between waterborne and dietary magnesium ingestion and cardiac disease is discussed, primarily in terms of persons who are on magnesium therapy or participate in rigorous exercise. In particular, can studies of these two high-risk populations provide evidence for or against the hypothesis of a causal relationship between water hardness and the risk of cardiovascular disease?

II. MAGNESIUM DEFICIENCY

In theory, it should be relatively easy to determine whether a population has a deficit in magnesium or calcium intake and whether drinking water levels of either mineral significantly affect total intake. However, of more direct interest for public health intervention is whether individuals who have certain heart diseases have a deficiency of magnesium body stores or whether they have too much calcium intake relative to their magnesium intake. It is difficult to identify magnesium deficiencies because serum and tissue magnesium levels are not correlated. Perhaps, the lack of a correlation is because magnesium can readily move between bone, muscle, soft tissues, and other body compartments. About 53% of the total body stores of magnesium are in the bone, 27% in muscle, 19% in soft tissue, 0.5% in erythrocytes and 0.3% in serum (2), but it is difficult to measure tissue levels and assess magnesium deficiency levels in any individual. This difficulty limits efforts to relate magnesium deficiency to heart disease. Another major problem in assessing magnesium deficiencies is that magnesium interacts with both calcium and potassium, so that a deficiency or excess of one can affect the others. The effect of adequate magnesium intake is to maintain cellular levels of both magnesium and potassium. Magnesium is needed for the sodium/potassium pump. A magnesium deficiency may impair the ability of cells to pump sodium out of the cell and to pump potassium into the cell. Prescription diuretics can deplete magnesium and potassium (3).

Magnesium and calcium are also antagonistic for blood coagulation. Magnesium inhibits coagulation while calcium promotes the process. It is possible that calcium to magnesium ratios of much greater than 2 to 1 can interfere with coagulation as well as other processes (3).

In clinical and population studies where magnesium tissue levels can be measured, evidence of hypomagnesemia is commonly found. Hypomagnesemia occurs in about 65% of intensive care unit patients (4) and in 11% of the general population (5). The clinical manifestations of hypomagnesemia include neuromuscular hyperactivity, psychiatric disturbances, calcium/potassium abnormalities and cardiac effects (6). An experimental study of magnesium depletion in humans found that plasma magnesium levels fell to 10%-30% of previous levels. The primary symptoms of the depletion were neurologic signs (e.g. Trousseau sign, personality change, tremor and fasciculation), however, anorexia, nausea and apathy were also reported. All symptoms reverted to normal following reinstitution of magnesium (7).

Other clinical data support a relationship between magnesium and cardiovascular function. Deficiencies in magnesium have been shown to cause an increase in cardiac arrhythmias (8). Lower levels of magnesium were found in the heart muscle of persons who died suddenly from ischemic heart disease compared to people who died from other causes (9). Supplementing magnesium intake for patients with arrhythmias often controls the arrhythmias.

1. Protective Effects of Magnesium

Epidemiological studies have repeatedly indicated that a benefit of magnesium is to reduce the occurrence of sudden death from cardiovascular disease. Singh (10) conducted an intervention study using two cohorts at high risk of cardiovascular disease morbidity and mortality. One cohort (206 subjects) was given a magnesium-enriched diet and the other (194 subjects) remained on their usual diet. The magnesium-enriched diet contained 1,142 mg/day whereas the usual diet contained 418 mg/day of magnesium. The high magnesium diet included 880 mg/day calcium whereas the low magnesium diet included 512 mg/day of calcium. The occurrence of sudden death was 1.5 times more common in the usual-diet group. This finding is consistent with prior studies showing low intake of magnesium is associated with arrhythmias (8,9).

A recent study (11) tracked 7,172 men in the Honolulu Health Program. Baseline measurements were made between 1965 and 1968. Over a 30-year period follow-up 1,431 men developed coronary heart disease. There was a statistically significant increased risk of coronary heart disease in men in the lowest versus the highest quintiles of baseline magnesium intake after adjusting for other dietary and non-dietary cardiovascular disease risk factors both of which were also ascertained at baseline. They did not present data on both calcium and magnesium intake for the various quintiles, making it impossible to determine the calcium to magnesium ratio. An interesting finding, however, was that systemic hypertension decreased with increasing magnesium intake. Unfortunately, in assessing the effects of both calcium and magnesium, some papers have adjusted for blood pressure, which appears to be an intermediate outcome of increased magnesium intake. By adjusting for such an intermediate outcome one can falsely conclude that calcium is protective but that magnesium has no effect on heart disease risks. In reality the effect of magnesium on heart disease could be through its effect on lowering blood pressure (12).

Two case-control studies reported protective effects of magnesium for cardiovascular diseases in women (13) and for men and women (14). Since the case-control and cohort design provide persuasive evidence of a causal relationship, these studies are particularly important, and their results significantly increase the level of confidence in the relationship between magnesium exposure and cardiovascular disease. The highest quartile received 9.9 mg/l or more drinking

water magnesium versus less than or equal to 3.4 mg/l magnesium in the lowest or comparison group. The odds ratio for the highest exposure group was 0.70 (95% C.I. 0.50-0.99).

2. Magnesium Therapy

Another approach to assessing the contribution of magnesium to cardiac health is to examine the therapeutic effects of administering magnesium. Although these magnesium levels are much higher than found in water or the diet, the studies can provide supportive evidence of protective effects and possible adverse effects at deficient levels. Magnesium therapy has been tested as a treatment for people with a known or suspected myocardial infarction. A review (15) of randomised clinical trials of the role of magnesium in reducing mortality from acute myocardial infarction reported a statistically significant reduced relative risk, an odds ratio of 0.61 (95% C.I. 0.48-0.76). The Leicester Intravenous Magnesium Intervention Trial of suspected myocardial infarction (16) used a double-blind protocol that started injection before any thrombolytic therapy was used. They found a 21% reduction in mortality from ischaemic heart disease (95% C.I. 5%-35%) and a 16% reduction in all cause mortality (95% C.I. 75-9%). However, another trial (ISIS-4 (17)) randomly assigned approximately 2000 people to receive magnesium therapy following an acute myocardial infarction [magnesium sulfate for 24 hours (8 mmol initial bolus, followed by 72 mmol)]. Unlike the earlier studies (15,16), this trial found no benefit from magnesium therapy given the dosage, timing and mode of administration.

Even in the absence of hypomagnesemia, magnesium is often used for treatment of pre-eclampsia (18, 19) and asthma (20). It is also an accepted therapy for cardiac arrhythmias (2). However, there are questions whether much of the benefit of the magnesium therapy results from correcting magnesium deficiency caused by other therapies such as digitalis and diuretics. Unfortunately, the success of magnesium in treating patients for these diseases does not provide sufficient evidence that it would be successful in preventing the diseases. We do not know the mode of action for its effectiveness and thus, do not know whether the effectiveness of therapeutic magnesium results from correcting a deficiency in body stores of magnesium or some other reason.

III. CALCIUM, COPPER, AND ZINC DEFICIENCIES

The relationship between minerals, trace elements and cardiovascular outcomes appears to be rather complex. High levels of serum calcium have been positively correlated with adverse cardiovascular outcomes (21), but a deficiency of calcium is also related to an elevated risk of hypertension (22). Elevated serum copper levels have been suggested as a risk factor for cardiovascular disease (19). There may be relationships between absorption of magnesium and each of these other elements. One study that considered serum levels of many of these elements found that only high serum copper and low serum zinc were associated with an increased risk of cardiovascular mortality. No associations with serum calcium or magnesium and mortality risk were apparent in this study (23). However, as discussed earlier, serum levels may not be good indicators of cellular levels of these elements (23). Furthermore calcium and magnesium serum levels may fluctuate more than cellular levels.

IV. MAGNESIUM, STRENUOUS EXERCISE, AND SUDDEN CARDIAC DEATH

In this case, the question is whether water hardness or elevated dietary magnesium intake can reduce the risk of sudden cardiac death among people involved in modest to rigorous exercise. This is important because there is considerable evidence that exercise reduces the risk of premature mortality and physicians encourage most of their patients to maintain a program of

regular exercise (24). However, during exercise there is also an increase risk of sudden death (25). Inactive men have a 56-fold increased risk of death during periods of vigorous exercise than during other periods (26).

There are a number of articles reporting sudden deaths during marathon races, while playing squash or during other sporting events. Studies of sudden deaths of males during athletic events have generally found that the deaths were triggered rather than caused by the exercise (26). In general, cardiac abnormalities were found that could explain the death (27). The situation is less clear for women. The majority of sudden cardiac deaths in women occur in the absence of obvious risk factors. Furthermore, the rate of sudden cardiac deaths among women is increasing. There have, unfortunately, been few rigorous studies of mineral intake or serum or cellular mineral levels of women suffering sudden cardiac death.

There are also studies of the effects of strenuous exercise on non-fatal events. An interesting analysis of the metabolic effects of strenuous exercise was conducted in Israel (28). Healthy young men received 6 months of physical training. They participated in a rigorous march and were screened for a large number of metabolic parameters. Of all the parameters measured, the primary change was in serum magnesium concentration. Although serum magnesium did not change immediately following the march, it declined at 72 hours, and it remained lower at 18 days and at 3 months. Another study by the same authors (29) found the same change in serum magnesium in a different group of young males participating in vigorous exercise. A study conducted by Corrado (30) found that young athletes in Padova, Italy had 2.5 times the risk of sudden death than non-athletes. This occurred despite routine medical and ECG screening of these young athletes. Stendig-Lindberg (31) speculated that sudden death in athletes during exertion is 'mediated' by the effects of persistent magnesium deficiency.

Given both the added risks and benefits of exercise on health, more information is needed to better understand the physiological effects of exercise and to identify both risk factors and approaches to minimize the health risks from exercise. Considering the limited data available, people involved in moderate to vigorous exercise may be at risk of mineral imbalances, particularly magnesium. An added concern is that the U.S. Centers for Disease Control and Prevention (www.cdc.gov/od/oc/media/pressrel/r010301.thm) reported that sudden cardiac deaths are increasing in young people, especially young women. Reasons for the increase are unknown at this time.

V. CONCLUSIONS

There are many potential implications from the studies of minerals in drinking water and health effects. The most convincing findings, to date, have been relationships between the occurrence of sudden cardiac death and deficits in magnesium intake. Sudden death is a significant cause of cardiovascular death, and many of these deaths are believed to be related to arrhythmias and coronary artery vasospasm. Thus, the benefits of magnesium in hard water are likely to be significant.

The problem with the current body of evidence is the complexity of the interrelationship between potassium, calcium and magnesium intake and other risk factors for cardiac death (i.e., the web of causation). The interpretation of current study results allows several conflicting hypotheses to be consistent with the available data, and it is possible to convince oneself that magnesium is an important as well as an unimportant risk factor for cardiovascular risks. For example, the Task Force on Sudden Cardiac Death of the European Society of Cardiology (32) reported that some studies of supplemental magnesium administration showed a 45% reduction in all-cause mortality, with most of the reduction due to a reduce risk of death from congestive heart

failure. However, the Task Force also cautioned that more recent studies have not been able to confirm earlier findings showing a 45% reduction in mortality. The Task Force suggested that differences in observed results between the earlier and later studies may be due to delayed initiation of the magnesium therapy in the later studies. Even though not all studies show a benefit, many indicate that small increases in magnesium intake may result in reduced risks of sudden cardiac death. If so, it is possible that relatively modest increases in water or food magnesium levels might result in considerable benefits with minimal risks of adverse effects.

For any large-scale intervention program where magnesium is added to drinking water, one must also consider the possibility that some persons may be harmed by the addition of magnesium to the diet. However, high dose intravenous administration for individuals with heart disease is considered to be safe (33) suggest that low-dose supplementation of magnesium in drinking water is likely to have a significant margin of safety. In considering possible magnesium supplementation, Eisenberg et al. (1) raise several important concerns including: how should the supplementation occur (e.g., through drinking water or food or by treating individuals) and how long must it be conducted before a benefit is apparent? Legal and liability issues with magnesium supplementation of water or food should also be considered. Given the special health risks of people over age 40 who participate in vigorous sports, the balancing of risks and potential benefits from magnesium supplementation may be different than for the general population. Also, since supplementation could be done for specific individuals, it may be easier to exclude individuals who may suffer adverse health effects from magnesium supplementation. Although this might best be accomplished through dietary supplementation, ensuring that sufficient magnesium is in the drinking water would more effectively reach a large number of people with a minimum of cost. An important question, however, is what are the minimum and maximum levels of magnesium that should be considered for drinking water? Additional low-cost observation studies should be conducted to expand the available data on the protective effects of magnesium. Randomised placebo-controlled trials of magnesium supplementation may also be feasible, especially in high-risk populations. These studies could provide the information needed to plan future large-scale efforts to more conclusively resolve the relationships between water hardness, magnesium intake and cardiovascular risks and assist public health officials in selecting optimum, safe levels that could be added to demineralised water.

References

1. Eisenberg MJ. Magnesium deficiency and sudden death. *Am. Heart J* 1992; 124 (2):544-549.
2. McLean RM. Magnesium and its therapeutic uses: A review. *Am J Medicine* 1994; 96:63-75.
3. Martin B, Milligan K. Diuretic-associated hypomagnesemia in the elderly. *Arch Intern Med* 1987;147:1768-71.
4. Fink EB. Magnesium deficiency: Etiology and clinical spectrum. *Acta Med Scand* 1981; 647(Suppl):125-37.
5. Ryzen E, Wagers PW, Singer FR, Rude RK. Magnesium deficiency in a medical ICU population. *Crit Care Med* 1985; 13:19-21.
6. Wong ET, Rude RK, Singer FR, Shaw ST. A high prevalence of hypomagnesemia in hospitalised patients. *Am J Clin Pathol* 1983; 79:348-52.
7. Shils ME. Experimental human magnesium deletion. *Medicine* 1969; 48(1):61-85.
8. Reinhart RA. Clinical correlates of the molecular and cellular actions of magnesium on the cardiovascular system. *Am Heart J* 1991; 121 (5), 1513-1521.
9. Chipperfield B, Chipperfield JF. Differences in metal content of the heart muscle in death from ischemic heart disease. *Am Heart J* 1978; 95:732-737.
10. Singh, R.B. Effect of dietary magnesium supplementation in the prevention of coronary heart disease and sudden cardiac death. *Magnes Trace Elem* 1990; 9 (3):143-151.
11. Abbot RD, Ando F, Masaki KH, Tung KH, Rodriguez BL, Petrovitch H, Yano K, Curb JD. Dietary magnesium intake and the future risk of coronary heart disease (The Honolulu Heart Program). *Am J Cardiol* 2003; 92:665-669.
12. Iso H, Stampfer MJ, Manson JE, Rexrode K, Hennekens CH, Colditz GA, Speizer FE, Willett WC. Prospective study of calcium, potassium, magnesium intake and risk of stroke in women. *Stroke* 1999; 30(9):1772-1779
13. Rubenowitz, E., Axelsson, G., Rylander, R. Magnesium and calcium in drinking water and death from acute myocardial infarction in women. *Epidemiol* 1999;10 (1): 31-36.
14. Rubenowitz, E., Molin, I., Axelsson, G., Rylander, R. Magnesium in drinking water in relation to morbidity and mortality from acute myocardial infarction. *Epidemiol* 2000; 11 (4): 416-421.
15. Teo KK, Yusuf S. Role of magnesium in reducing mortality in acute myocardial infarction. A review of the evidence. *Drugs* 1993; 46:347-359.
16. Woods KL, Fletcher S. Long-term outcome after intravenous magnesium sulphate in suspected acute myocardial infarction: the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2) *Lancet* 1994; 343:816-819.
17. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group: ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. *Lancet* 1995; 345: 669-685.
18. Sadeh M. Action of magnesium sulfate in the treatment of preeclampsia-eclampsia. *Stroke* 1989; 20:1273-1275.
19. Iskra M, Patelski J, Majewski W. Concentration of calcium, magnesium, zinc and copper in relation to fatty acids and cholesterol in serum of arteriosclerotic men. *J Trace Electrolytes Health Dis* 1993; 7:185-188.
20. Okayama H, Aikawa T, Okayama M, Sasaki H, Mue S, Takishima T. Bronchodilating effect of intravenous magnesium sulfate in bronchial asthma. *JAMA* 1987; 257:1076-1078.

21. Lind L, Jakobsson S, Lithell H, Wengle B, Ljunghall S. Relation of serum calcium concentration to metabolic risk factors for cardiovascular disease *Br Med J* 1988;729:960-963.
22. Cutler JA, Brittain E. Calcium and blood pressure: an epidemiologic perspective. *Am J Hyperten* 1990; 3:137S-146S.
23. Reunanen A, Knekt P, Marniemi J, Maki J, Maatela J, Aromaa A. Serum calcium, magnesium, copper and zinc and risk of cardiovascular death. *Eur J Clin Nut* 1996; 50:431-437.
24. Carter L, Phillips W. Structural changes in exercising middle-age males during a 2-year period. *J Appl Physiol* 1969; 27:787-794.
25. Northcote RH. Vigorous exercise and cardiovascular death: a perspective. *J Royal Soc Med* 1985; 78:889-890.
26. Siscovick DS, Weiss NS, Fletcher RH, Lasky T. The incidence of primary cardiac arrest during vigorous exercise. The incidence of primary cardiac arrest during vigorous exercise. *NEJM* 1984; 311:874-877.
27. Marion BJ. Sudden death in young athletes. *NEJM* 2003; 349:1064-1075S.
28. Stendig-Lindberg G, Shapira Y, Graff E, Schonberger E, Wacker WE. Delayed metabolic changes after strenuous exertion in trained young men. *Magnesium Res* 1989; 2(3):211-218.
29. Stendig-Lindberg G, Wacker WE, Shapiro Y. Long term effects of peak strenuous effort on serum magnesium, lipids, blood sugar in apparently healthy young men. *Magnesium Res* 1991; 4(1):59-65.
30. Corrado D. presentation at the 2001 American Heart Association meeting in Anaheim, CA.31. Stendig-Lindberg G. Sudden death of athletes: is it due to long-term changes in serum magnesium, lipids and blood sugar. *J Basic Clin Physiol Pharmacol* 1992; 3(2):153-64.
31. Priori SG, Aliot E, Blomstrom-Lundqvist C, Bossaert L, Brithardt G, Brugada P, Camm AJ, Cappato R, Cobbe SM, DiMario C, Maron BJ, McKenna WJ, Pedersen AK, Ravens U, Schwartz PJ, Trusz-Gluza M, Vardas P, Wellens HJJ, Zipes DP. Task force on sudden cardiac death of the European Society of Cardiology. *Eur Heart J* 2001; 22:1374-1450.
32. Horner SM. Efficacy of intravenous magnesium in acute myocardial infarction in reducing arrhythmias and mortality. *Circulation* 1992; 86(3):775-779.

9.

HOW TO INTERPRET EPIDEMIOLOGICAL ASSOCIATIONS

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I. INTRODUCTION

Cardiovascular disease is among the leading causes of morbidity and mortality in industrialized countries. Hypertensive disease, smoking, excessive alcohol consumption, diet, and physical inactivity have been identified as risk factors, but they do not entirely explain the worldwide variability of cardiovascular disease (1,2). It has long been suspected that cardiovascular disease mortality may be associated with geochemical constituents, especially water hardness.

Our knowledge of the association of cardiovascular disease with water hardness is based largely on observational epidemiological studies that have been conducted over the past half century. The hypothesis is that hard water or minerals, such as calcium and magnesium found in hard water, may help decrease cardiovascular risks or constituents associated with soft waters (e.g., corrosion products from distribution pipes, sodium from home softening units) may increase the risk.

Concern about a water factor can be traced to research reported in the 1950s. In 1956, Enterline and Stewart (3) called attention to the marked geographical variation in death rates from heart disease for the United States during the period 1949–1951 and suggested that place of residence might be an important risk factor. In 1957, Kobayashi (4) reported an association of mortality from apoplexy in Japan and the acidity of river water (i.e., the ratio of sulfates to carbonates). After meeting with Kobayashi, Schroeder sought to confirm the findings in the United States using the 1949–1951 mortality statistics (5,6). Since drinking water hardness was the most widely available water quality measure in the United States, Schroeder (7,8,9) evaluated its relationship to death rates on a state-by-state basis (Comstock 1979). In 1960, Schroeder (7,8) reported statistically significant inverse (protective) correlations between water hardness and deaths from all causes ($r=-0.36$), all cardiovascular diseases ($r=-0.56$), coronary heart disease ($r=-0.31$), other cardiovascular diseases ($r=-0.36$), and stroke ($r=-0.33$). In a second study of 163 metropolitan areas of the United States, Schroeder (9) also found an inverse association between coronary heart disease mortality rates for white males 45–64 years of age and water hardness ($r=-0.29$), magnesium ($r=-0.30$), and calcium ($r=-0.27$). In the years since these landmark studies, epidemiologists around the world have studied the association between water hardness and cardiovascular disease. Results of these epidemiological studies are reviewed in subsequent chapters (see Calderon and Craun, Monarca and Donato, Kozisek, and Frost). This chapter discusses epidemiological study designs and other important aspects of the studies to help readers better interpret the observed associations.

II. TYPES OF EPIDEMIOLOGICAL STUDIES

Observational epidemiological studies can be descriptive or analytical (Table 1).

Table 1. Types of observational epidemiological studies*

Descriptive Studies	Analytical Studies
Disease Surveillance/Surveys	Cross-sectional
Ecological	Longitudinal
	- Cohort or Follow-up
	- Case-Control

*Adapted from Monson (1990)

Descriptive epidemiology is primarily used to summarize disease information, assess geographical or temporal patterns of disease, and develop hypotheses about disease etiologies. Ecological studies, sometimes called geographical, correlation, group, or aggregate studies, are used to explore possible relationships between available health statistics (e.g., cardiovascular disease mortality) and geographical location, population characteristics, or environmental and water quality measures (e.g., water hardness). Investigators often conduct these studies to help develop hypotheses for further evaluation with analytical studies. Because ecological studies consider exposures and outcomes determined in the aggregate for groups of people, they rely on available statistics. Thus, they are relatively inexpensive and easy to conduct. However, the observed associations should be viewed with caution (10,11,12,13). Since the health, exposure, and demographic measures characterize population groups, inferences from associations observed in an ecological study may not necessarily pertain to the individuals within the group, especially when outcomes from long-term exposures are studied. Population migration and other demographic changes may have occurred, and group exposures (e.g., water quality) and health statistics may not be consistent over the relevant study period. For example, migration into the study area by older people may increase the mortality rates, but the increase may reflect exposures at previous residences. Neither theoretical nor empirical analyses have offered consistent guidelines for the interpretation of ecological analyses. However, ecological analyses have a distinct advantage because of their statistical power to detect small risks. If information is available to adequately assess population characteristics, relevant exposures, and the health outcome of interest, these studies can help identify potential problems. This design is especially useful for environmental health studies.

Many ecological studies have assessed the association between water hardness and cardiovascular disease mortality. In these studies, investigators considered the available population information about mortality, water exposures, and demographic characteristics. Although many studies considered water hardness, some considered calcium and magnesium, the principal constituents that contribute to the water hardness. Several community-intervention studies evaluated mortality changes associated with water hardness changes.

Analytical studies are used to test specific hypotheses, and they can provide a quantitative estimate of the relative risk and other information to help scientists assess causality (14). Information about disease, exposures, and important behaviours or characteristics is obtained from each study participant. Analytical studies can be either longitudinal or cross-sectional (Table 1). In the cross-sectional study, information about exposure and disease relate to the same time period. These studies are most useful for studying diseases with a short latency period. The longitudinal study allows a time sequence to be inferred between an exposure and disease. Two distinct, opposite approaches are used. The cohort or follow-up study begins with an exposure or

characteristic of interest and evaluates disease consequences of the exposure or characteristic. The case-control study begins with a disease or health condition of interest and evaluates previous exposures of interest and risk factors associated with the disease. Because past exposures are studied, a case-control study may be labelled a retrospective study. It is sometimes called a case-referent or case-comparison study. The case-control study is usually less costly than the cohort study, since fewer study participants are required for adequate statistical power.

To avoid selection bias in a case-control study, participants should enter the study solely on the basis of their disease status, and the investigator should have no knowledge of their exposure status. A single disease or health outcome (e.g., cardiovascular mortality) is studied. Persons with the disease or outcome are selected from a defined geographical area, hospital(s), clinic(s), or even a cohort. A comparison group of persons in which the condition or disease is absent is also selected, preferably at random from the same population from which the cases were selected. Existing or past attributes and exposures thought to be relevant in the development of the disease are determined for all participants, and the frequency of exposure is compared among persons with and without the disease. Information about the relevant exposure or behavior is obtained by interview or other means. For example, participants may be asked about their smoking habits (number of cigarettes smoked per day) or a blood specimen may be collected and analyzed for DNA adducts. A residence history is required to determine long-term drinking water exposures. Water quality information (e.g., water hardness, magnesium, or calcium levels) can then be obtained from water quality records at the appropriate water system. If information about current tap water quality is important, a sample can be collected and analyzed. The participant may also be questioned about water consumption patterns and other exposures (e.g., dietary calcium and magnesium intake). Sometimes, information must be obtained by questioning a spouse or care giver. When collecting information from participants or others, it should be recognized that it may be difficult to accurately recall exposures or events that occurred many years ago. Investigators should ensure that the quality of the information is similar for both cases and controls.

An advantage of the cohort study is that more than one health-related outcome or disease can be studied. To avoid selection bias, the cohort should be assembled solely on the presence or absence of certain characteristics, a specific event, or their exposure status (e.g., water hardness; high, moderate, or low levels of calcium or magnesium in drinking water). Morbidity or mortality incidence is determined for the diseases of interest, and rates are compared for exposed and unexposed groups in the cohort. A cohort can be based on currently-defined exposures or historical exposures and followed forward from that point in time. Thus, the approach can be prospective, retrospective, or both. For example, if a cohort were established based on known drinking water exposures to magnesium from 1980 to the present, 23 years of exposure would have already occurred. The analysis could evaluate risks associated with this period of exposure or continue to follow the cohort for two or five years and consider 25 or 30 years of exposure.

A cohort study can be conducted when a community changes its water treatment practice or water source. Either individual- or group- information can be evaluated. Community-intervention studies have helped demonstrate the effectiveness of water fluoridation in preventing dental caries, and as noted earlier, several studies have evaluated cardiovascular disease associated with changes in hardness of a community's drinking water. An advantage of this type study is that water quality is changed at all places where persons may consume water (e.g., home, school, work, restaurants) minimizing exposure misclassification bias. However, an important limitation to consider is that many years of exposure may be required to effect a change in the disease risk. Population demographics, behaviours, and other risk factors may also change during the study period and should be taken into account when analyzing the data. Also, the areas may not be optimal in terms of desired water quality or population characteristics.

III. THE EXPOSURE-DISEASE ASSOCIATION

The correlation coefficient (r) frequently reported in ecological studies does not provide reliable, quantitative information about the risk or benefit of an observed association. In contrast, analytical studies can provide an estimate of the magnitude of the risk or benefit. The basic measures are the rate difference (RD) and rate ratio (RR). The RD is a measure of the absolute difference between two rates (e.g., incidence rate of cardiovascular disease for the exposed minus the incidence rate for the unexposed in a cohort study). The RR is a relative measure of two rates (e.g., incidence rate for the exposed divided by the incidence rate for the unexposed in a cohort study). The RR is also called the relative risk. A reported RR of unity (1.0) indicates no association and no increased risk; any other value signifies either increased or decreased risk. For example, a RR of 1.8 indicates an 80 percent increased relative risk of disease; a RR of 0.8 indicates a decreased risk of 20 percent. Because participants in a case-control study are selected according to their disease status, the exposure odds ratio (OR) is determined. The OR is the odds or chance of disease among the exposed divided by the odds of disease among the unexposed. The OR is essentially equivalent to the RR (14). Another important, but often misunderstood measure, is the population attributable risk (PAR). Often computed as a percentage, the PAR provides an estimate of the incidence of a disease in a population that is associated with or attributed to the exposure or risk factor in question, provided the association is causal (15). A PAR computed for water hardness should be cautiously interpreted, since cardiovascular disease has many known and suspected risk factors. The individual PARs computed for several potential risk factors for a disease may add up to over 100% (14).

1. Random and Systematic Error

The epidemiological association should be evaluated for possible systematic and random error (Table 2). The likelihood that an observed association is due to random error is assessed by the level of statistical significance ("p" value) or the confidence interval (C.I.). The C.I. is the preferred measure because it provides a range of possible values consistent with the risk estimate. For example, a reported RR of 1.8 with a 95% C.I. of 1.6-2.0 indicates both a precise and statistically significant estimate because the C.I. is narrow and does not include 1.0. A reported RR of 2.7 with a C.I. of 0.8-14.5 indicates that the risk estimate is not statistically significant (the C.I. includes 1.0) and imprecise (a wide range of values). It should always be remembered that random error or chance can never be completely ruled out as the explanation for an observed association and that statistical significance does not imply causality, biological significance, or the lack of systematic error.

Table 2. Assessing bias for reported associations

Lack of Random Error (Precision)	Lack of Systematic Error (Validity)
Study Size and Statistical Power	Misclassification Bias
	Selection Bias
	Observation Bias
	Confounding

Systematic error affects the validity of an observed association and can occur in the design or conduct of the study. In either case, it leads to a false or spurious association and a measure of risk that departs systematically from the true value. Selection bias occurs when criteria are not comparable for enrolling cases and controls or exposed and unexposed persons into the study.

Observation bias occurs when disease or exposure information is collected differently from participants. For example, cases may selectively or differentially recall the exposure (14).

The erroneous classification of a study participant's exposure or disease will result in misclassification bias. Differential misclassification bias can result in associations that either under or over estimate the magnitude of risk. Non-differential misclassification will almost always result in not observing an association when one may actually be present, thereby under estimating the risk. In environmental epidemiological studies where the magnitude of the association is often small, accurate assessment of exposure is critical, as the impact of exposure misclassification can be severe. The imprecise estimate of water hardness in many of the cardiovascular disease studies presents a potential for misclassification bias. A confounding characteristic rather than the suspected cause or exposure may be responsible for all or much of the observed association. Confounding does not necessarily result from an error of the investigator. It is potentially present in all epidemiological studies and should be considered as a possible explanation for any observed association. Cigarette smoking may confound many associations.

Investigators may control confounding in the study design and assess it during the analysis (e.g., regression techniques and stratification). A confounder is a characteristic that can cause or prevent the disease and is associated with the exposure being evaluated. Thus, if the suspected characteristic (e.g., smoking) can be shown to have no association with exposure (e.g., water hardness), the characteristic cannot confound the association that may be observed between the exposure and the disease. Confounding can be controlled by using a technique known as matching in the design of the study. For example, controls may be selected to have similar characteristics (e.g., smoking status) as cases. In this example, all study participants will either be smokers or non-smokers. Effect modification refers to a change in the magnitude of the effect of a putative cause (14) and should not be confused with confounding. For example, if cardiovascular disease risks associated with water hardness differed among smokers and non-smokers, smoking would be considered an effect modifier.

2. Strength of an Association

An increased risk of less than 50% ($RR=1.0-1.5$) or a decreased risk of less than 30% ($RR=0.7-1.0$) is considered by many epidemiologists to be either a weak association or no association (Table 3).

Table 3. Assessing the strength of an epidemiological association *

Rate Ratio (Increased risk)	Rate Ratio (Decreased risk)	Strength of Association
1.0 - 1.2	0.9 - 1.0	None
1.2 - 1.5	0.7 - 0.9	Weak
>1.5	< 0.9	Moderate to Strong

*Adapted from Monson (1990)

Based on Monson's experience (14), it may be difficult to interpret associations with these RRs. Confounding can lead to a weak association between exposure and disease, and it is usually not possible to identify and adequately measure or control weak confounding characteristics. For weak associations, investigators should thoroughly evaluate the possibility that the association is affected by uncontrolled confounding. On the other hand, a very large increased or decreased RR is unlikely to be completely explained by an unidentified or uncontrolled confounding factor. The magnitude of a RR, however, has no bearing on the possibility that an association is due to

observation, selection, or misclassification bias. Systematic error, even in studies with a large RR, may lead to a spurious association.

IV. CAUSALITY OF AN ASSOCIATION

Epidemiologists have debated how to make causal inferences from observed associations. Even though an association is repeatedly observed, investigators may question whether the association constitutes an “empirical demonstration that serves as a valid platform for (causal) inference” or whether “the process is still steeped in uncertainty” (16). Interpretation of epidemiological results should always be made with caution and in the context of all relevant biological information about the disease. Epidemiologists generally agree that no single epidemiological study, even one with little systematic error, can provide a definitive answer about the exposure and its effect. Results from a relatively large number of studies in various geographical areas allow for a more definitive assessment of the causality of an association. However, the design, precision, and validity of the individual studies must be evaluated before the evidence for causality is considered. Epidemiologists judge the causality of an epidemiological association (16,17,18) based on the following guidelines:

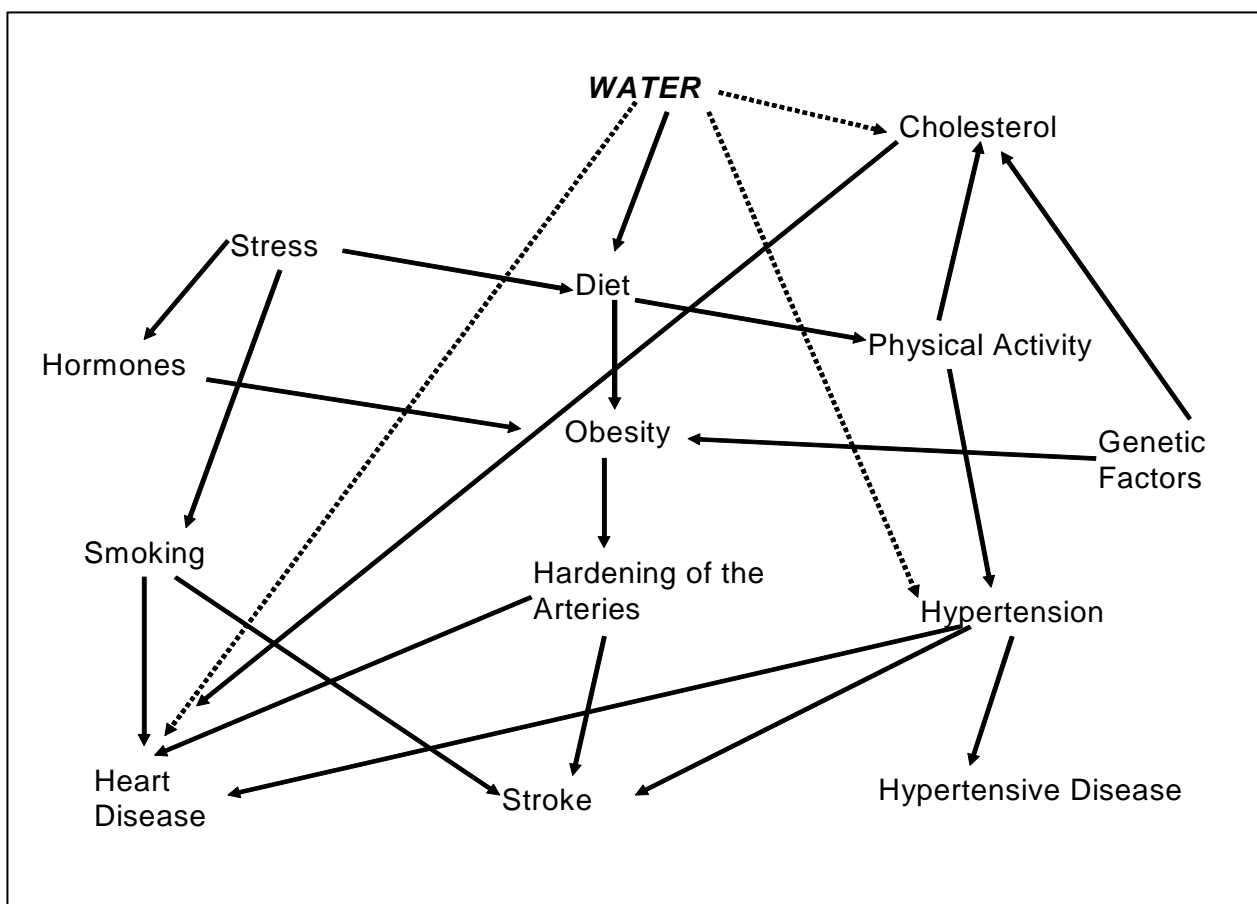
- **Temporal Association.** Exposure must precede the disease, and in most epidemiological studies this can be inferred. In studies where exposure and disease are measured simultaneously or exposure is measured after the occurrence of disease, the temporal association should be evaluated.
- **Specificity.** A supposed cause or exposure leads to a specific disease rather than to a general effect or multiple diseases. The presence of specificity argues for causality, but its absence should not rule it out.
- **Consistency.** Repeated observation of an association under different study conditions supports an inference of causality, but its absence should not rule it out.
- **Biological Plausibility.** When the association is supported by evidence from clinical research or basic sciences (e.g., toxicology, microbiology) about biological mechanisms, an inference of causality is strengthened.
- **Strength of Association.** As noted earlier, the greater the magnitude of risk or benefit, the less likely the association is to be spurious or due to confounding bias. However, a causal association should not be ruled out simply because a weak association is observed.
- **Dose-Response Relationship.** A causal interpretation is more plausible when an exposure- or dose-response gradient is found (e.g., a higher risk is associated with larger exposures).
- **Reversibility.** An observed association leads to some preventive action, and removal or reduction of the exposure should lead to a reduction of disease or risk of disease.

Scientific evidence for causality may be sparse and inconsistent, and scientists may offer conflicting opinions about causality. When environmental policy makers and regulators are confronted with epidemiological associations that suggest the need for action, they should consider the uncertainties about causality. Most regulatory actions will require a high level of certainty about the causal nature of the association. However, it should also be recognized that effective public health actions may be taken even with incomplete knowledge about causality. For example, Dr. John Snow in mapping cholera deaths in London more than one hundred and fifty years ago was able to associate increased deaths with use of the Broad Street well. This information was considered sufficient to remove the pump handle and preventing use of the well. This action was taken well before the etiological agent *Vibrio cholerae* was identified and scientists understood the importance of the transmission of cholera through water contaminated by human feces. More recently, the mounting epidemiological evidence of increased lung cancer risks among smokers prompted public health warnings about cigarette smoking in the 1960s long before specific carcinogens were identified.

V. WEB OF CAUSATION

Many diseases have multiple exposures or risk factors that cause the disease or increase the disease risk, and the disease process is often complex. This complexity is evident in an example of a conceptual model that might be used to describe the relationship between various exposures and risk factors for cardiovascular disease (Figure 1). This model, often referred to as the web of causation, places less emphasis on the role of a single agent (e.g., a water constituent) in favour of other factors that may be important in the onset of disease (19). When evaluating the role of water hardness in the etiology of cardiovascular disease, it is important to consider how various risk factors might affect not only disease but also exposure. In the example provided, a dotted line is used to suggest that additional evidence may be warranted for waterborne exposures and how these exposures may affect the disease process.

Figure 1. Example of a disease model for cardiovascular disease*



*Adapted from Rockett (1994)

VI. CONCLUSIONS

Numerous ecological and analytical studies during the past forty-five years have provided epidemiological information about health benefits associated with hard water. Results from these studies can be evaluated to assess the causality of the association and potential magnitude of the benefit. This information can help public health officials make decisions about recommendations for adding certain constituents to demineralised and desalinated waters.

References

1. Sauvant M-P, Pepin D. Drinking water and cardiovascular disease. *Food Chem Toxicol* 2002; 40:1311-1325.
2. Hornstra G, Barth CA, Galli C. et al. Functional food science and the cardiovascular system. *Bri J Nutr* 1998; 80(suppl. 1): S113-S146.
3. Enterline P, Stewart W. Geographic patterns in deaths from coronary heart disease. *Public Health Rpts* 1956; 71:849-855.
4. Kobayashi J. On geographical relationship between the chemical nature of river water and death-rate from apoplexy. *Berichte des ohara institutes fur landwirtschaftliche biologie* 1957; 11:12-21.
5. Comstock G. Water hardness and cardiovascular diseases. *Amer J Epidemiol* (1979; 110(4):375-400.
6. Comstock G. The association of water hardness and cardiovascular diseases: An epidemiological review and critique. In: *Geochemistry of Water in Relation to Cardiovascular Disease*. Washington, DC: National Academy of Sciences, 1979: 48-68.
7. Schroeder H. Relations between hardness of water and death rates from certain chronic and degenerative diseases in the United States. *J Chronic Dis* 1960;12:586-591.
8. Schroeder H. Relationship between mortality from cardiovascular disease and treated water supplies. Variations in states and 163 largest municipalities of the United States. *J Amer Med Assoc* 1960; 172:1902-1908.
9. Schroeder H. The water factor. *New Engl J Med* (1969; 280:836-838.
10. Greenland S, Robins J. Invited commentary: ecologic studies--biases, misconceptions, and counter examples. *Amer J Epidemiol* 1994; 139:747-760.
11. Greenland S, Robins J. Accepting the limits of ecologic studies. *Amer J Epidemiol* 1994; 139:769-771.
12. Piantadosi S. Invited commentary: ecologic biases. *Amer J Epidemiol* 1994; 139: 71-64.
13. Poole C. Editorial: ecologic analysis as outlook and method. *Amer J Public Health* 1994; 84: 715-716.
14. Monson R. *Occupational Epidemiology*, 2nd edition. Boca Raton, Florida: CRC Press Inc., 1990.
15. Last JM. *A Dictionary of Epidemiology*, 3rd edition. New York, Oxford, Toronto: Oxford University Press, 1995.
16. Rothman K. *Modern Epidemiology*. Boston: Little, Brown and Company, 1986: 7-21.
17. Hill A. Environment and disease: association or causation? *Proc Royal Soc Med* 1965; 58:295-300.
18. Beaglehole R, Bonita R, Kjellstrom T. *Basic Epidemiology*. Geneva: World Health Organization, 1993: 71-81.
19. Rockett I. Population and health: An introduction to epidemiology, *Population Bull* 1994; 49(3):11.

10.

WATER HARDNESS AND CARDIOVASCULAR DISEASE: A REVIEW OF THE EPIDEMIOLOGICAL STUDIES, 1957-78

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I. INTRODUCTION

Since publication of articles by Kobayashi (1) in 1957 and Schroeder in 1960 (2, 3) and 1969 (4), numerous epidemiologists throughout the world have studied the inverse (protective) association between drinking water hardness and cardiovascular disease mortality. Most investigators conducted ecological studies that considered population exposures to hard water and mortality statistics. Several community-intervention studies evaluated changes in mortality when drinking water hardness was increased or decreased. In more recent years, epidemiologists conducted analytical studies in which individual exposures and risk factors were considered.

Summarized in this chapter is the epidemiological literature published before 1979 and conclusions of scientific working groups convened by the National Academy of Sciences (NAS) and World Health Organization (WHO) during the 1970s.

II. SCIENTIFIC REVIEWS BY EXPERT GROUPS

1. National Academy of Sciences

In 1968, 1973, and 1974, the NAS-National Research Council (NRC) Subcommittee on the Geochemical Environment in Relation to Health and Disease held workshops to examine ways in which the geochemical environment might influence the processes of human health and disease. In the first two workshops, participants considered trace elements from natural sources and their essentiality. In the third workshop, participants evaluated the geographical distribution of diseases, their possible association with environmental trace elements, and sources of exposure. The diseases considered were esophageal, stomach, and colorectal cancer; cardiovascular disease including hypertension and stroke; and urolithiasis, particularly kidney stones. The report of the third workshop (5) acknowledged that “an enormous number of concise data that have been gathered together and correlated ... show distribution patterns ... of the geochemical environment that may affect health and disease” However, the report also noted that more specific exposure data were needed, especially for water constituents and that there are problems relating the health and geochemical data.

The NAS-NRC Panel on Geochemistry of Water in Relation to Cardiovascular Disease (6) also reviewed the epidemiological studies of water hardness and cardiovascular disease reaching the following conclusions:

- In general, when studies encompass large geographical areas, hard water was correlated with low cardiovascular disease mortality rates. This association was not always observed when smaller areas were considered or when the study populations were grouped by altitude or the proximity of a seacoast. Some non-cardiovascular diseases were also associated occasionally with soft water, raising the possibility that water hardness may merely be a surrogate for another risk factor(s).
- Although most studies reported correlation coefficients and not risk estimates as a function of exposure, a few studies estimated risk. Upper estimates of the risk ratios for soft compared to hard water averaged approximately 1.25 for all cardiovascular diseases and 1.2 for stroke and arteriosclerotic and hypertensive diseases.
- Autopsy studies in Canada and the United Kingdom reported low magnesium levels in various tissues (heart, diaphragm, and pectoral muscle) of persons who died from myocardial infarction compared to persons who died from accidental causes. Although the data were not consistent, similar magnesium deficits were reported in persons from soft compared to hard water areas.
- There may be a water factor associated with cardiovascular disease risk, but this is far from certain. The factor is unlikely to be water hardness or softness as such, and its effect may be weak in comparison with other known risk factors. One possible mechanism is that enough magnesium is present in some hard waters to prevent borderline magnesium deficiencies in some persons, thereby reducing their liability to sudden cardiac death as a result of arrhythmia following an infarct.
- Another review of the evidence for an association between water hardness and cardiovascular disease was conducted as part of the congressional mandate of the Safe Drinking Water Act. In 1980, the NAS-NRC Safe Drinking Water Committee (7) concluded:
- “Given the current status of knowledge regarding water hardness and the incidence of cardiovascular disease, it is not appropriate at this time to recommend a national policy to modify the hardness or softness of public water supplies. The data do not indicate clearly which (if any) additions to soft water would benefit human health.”

2. World Health Organization

The WHO Working Group on Health Significance of Chemicals Occurring Naturally in Drinking Water met in 1978 to consider the relationship between mineral content and cardiovascular disease with special reference to demineralized and desalinated water (8). This group was one of several convened by WHO to provide information for the possible revision of the drinking water guidelines. The Working Group was of the opinion that sufficient epidemiological evidence was available to support a protective association between the hardness of drinking water (particularly for calcium) and cardiovascular disease mortality but emphasized that the association was not consistently reported. Although some investigators failed to find a protective association, the Working Group felt that the inconsistent study results did not negate the weight of evidence to the contrary. Some scientists thought that the presence or absence of a certain substance or substances in drinking water might be directly associated with the differences in cardiovascular mortality. Others thought that the association was indirect. That is, the “existing epidemiological evidence suggests that the full picture may have an indirect explanation and have nothing at all to do with drinking water.” Water quality may only be an indicator of other environmental conditions that have a direct effect on heart disease.

The Working Group concluded:

- “A better understanding is required of the true nature of the association between cardiovascular mortality and the concentration of calcium and magnesium ions (and other components of hardness) in drinking water ... Should the relationship eventually prove to be a causal one, the benefits that could be derived from modifying the mineral content of drinking water would be so considerable that no opportunity should be missed to establish such studies as soon as possible ... water could be an important source of certain essential substances, especially magnesium and calcium. This applies particularly in circumstances where the mineral intake from diet alone may be deficient.”

The Working Group also made several recommendations for demineralized and desalinated water including the following:

- “The use of demineralized and/or desalinated water in a given area should be approached cautiously ... only after careful study has been made of the total mineral intake of the local inhabitants.”
- “The effects of water demineralization on health should be measured.”
- “Increased corrosion of pipes should be taken into account when proposals for the use of demineralized drinking water are examined.”

III. SUMMARY OF THE EPIDEMIOLOGICAL STUDIES

From 1957 through 1978, more than 60 epidemiological studies of water hardness and cardiovascular disease mortality were conducted throughout the world. All were ecological studies where mortality statistics and drinking water quality measures were obtained from readily available information about the population groups being studied. A number of investigators including Punsar (9), Neri *et al.* (10, 11), Sharrett and Feinleib (12), Sharrett (13) and Comstock (14, 15) reviewed these studies and evaluated their findings. A summary of the study results is presented here, and readers who wish to obtain a more detailed description of the studies are encouraged to read not only the review articles but also the original articles.

1. Study areas

Comstock (14, 15) tabulated the studies primarily by the size of geographical area considered. Country-wide studies of water hardness and mortality were conducted in the United States, Canada, United Kingdom, Ireland, Sweden, Netherlands, Finland, Italy, Rumania, and the Czech Republic. Studies in the United States considered mortality statistics for the periods 1949-1951 and 1951-1961 in standard metropolitan statistical areas and large municipalities or counties (14, 15). Masironi (16) studied mortality after 1961 in 42 of the states. In England and Wales, studies considered county boroughs and mortality statistics for the periods 1948-1954, 1958-1964, 1950-1965, and 1958-1967 (14, 15). In Canada, mortality during 1960-62 was evaluated in 516 municipalities and nine provinces (10, 11). Studies were also conducted in 33 large Swedish towns for 1951-60; 23 cities in the Netherlands for 1958-1962; 21 cities in Finland for 1967; 68 towns in Italy for 1955-1964; 10 localities in Rumania, and 53 districts of Bohemia and Moravia (14, 15). Studies in smaller regions (e.g., counties within a state, a province, or selected cities and localities) were also conducted in the United States, Wales, Scotland, Canada, Germany, Japan, Australia, Hungary, the Czechoslovakia, and Italy. International comparisons were conducted among populations in three Latin American cities, five European and 14 other cities (14, 15).

2. Consistency of Study Results

An inverse or protective association of water hardness with cardiovascular mortality was reported in most, but not all, studies. In studies involving very large geographical areas, there was a strong tendency to observe lower cardiovascular mortality with increasing hardness of drinking water sources. Inverse associations were frequently not found in studies of small regions or when companion communities or counties were compared. For example, in Canada when the country was looked at as a whole, an inverse association was found for cardiovascular mortality and municipal water hardness levels, but when the same data were analyzed for individual provinces, inverse associations were found only in Quebec and Ontario Provinces (10, 11, 14, 15). Correlations found in the remaining three provinces suggested increased rather than decreased mortality associated with increased hardness. Associations were usually found for both men and women but were often statistically significant for only one gender. Few studies considered different ethnic groups. When nonwhites were studied in the United States, investigators did not find significant inverse associations.

Sharrett (13) felt that the observed associations were suspect because they often contradicted each other and cautioned that "Specious correlations should be expected in geographic studies because the assumption of statistical independence is not met. Cities are not independent sampling units. They are clustered into geographic units with similar characteristics and mortality rates." Comstock (14, 15) noted that the lack of consistency in observing an inverse association might be due to inadequate analysis, the limited range of water hardness values, and random or systematic error. However, he believed that these deficiencies did not account for all the failures to observe the inverse association. Instead, he felt that the causality of the association might be indirect rather than direct or direct only under certain conditions.

3. Possible Random and Systematic Error

Since the studies are ecological, it is important to evaluate chance, confounding, and misclassification bias. This evaluation will affect how the association should be interpreted. In addition, water quality was determined for various time periods, and water exposures were reported in various ways. Many studies assessed water exposure in terms of hardness units rather than as concentrations of individual elements. Although calcium and magnesium ions are the two major contributors, all polyvalent cations contribute to what is known as water hardness. A further complication is that the water hardness units are defined differently in several countries.

4. Random error

Too many studies reported statistically significant correlations to make chance a likely explanation for the observed associations. However, the studies conducted before 1980 might be due to systematic error. Limited information is available to adequately interpret the results in this regard.

5. Ecological bias

Health, exposure, and demographic statistics in ecological studies characterize population groups, and the observed associations may not reflect a casual relationship (i.e., the ecological fallacy). The study of group attributes may lead to the observation of a relationship that is merely coincidental, and the magnitude and direction of an association at the group level may be quite different than the association observed when individuals are studied. The geographical area selected for study can also be a source of misclassification bias. When the group is not homogeneous with respect to the exposure, the average group exposures will not likely reflect individual exposures. The same caution applies for the outcome measures that are studied. However, if information is available to adequately characterize population exposures and health

outcomes, the ecological study, because of its statistical power, is valuable for assessing the health effects that may be associated with environmental exposures such as water hardness or other water quality parameters.

The success of cardiovascular disease studies in avoiding the ecological fallacy depends largely upon selecting areas that are relatively homogeneous in terms of population exposures to water hardness, calcium, or magnesium levels. The larger the geographical area, the more broadly representative its population and the more stable its death rates, but water supply sources may be more heterogeneous (13). Trace element exposure from water can vary considerably among individuals within a locality, the exposure assessment may be subject to sampling error (e.g., few samples collected for the relevant time period), and laboratory analyses may imprecise. All of these factors may contribute to exposure misclassification that can reduce the chance of detecting associations or increase the error in the assessment of their importance (13). Few investigators addressed the issue of heterogeneity for water exposures, and almost all of the studies classified areas by the hardness of finished water at the treatment plant rather than at the tap, and little regard was given to the use of home softeners in hard water areas. Not considering the use of home softeners might cause misclassification of exposure, since it was estimated in 1970 that the market saturation in the United States was 60-70 percent (14, 15). Another potential source of misclassification bias is the lack of consideration about water intake. Average daily water consumption may vary from area to area, and individuals may consume water not only from the home tap but also from other sources including bottled water.

6. Confounding factors

Many human characteristics (e.g., demographic, socio-economic, and cultural) vary with geography, and the hardness of water also varies with geography. Thus, the correlation of hardness with cardiovascular disease might represent the correlation of some other geographically-related characteristic with cardiovascular disease. Water hardness and cardiovascular disease each might be associated with another variable or variables that may confound the observed association. Few studies considered potential confounders, and it is difficult to determine whether the observed associations are due to minerals that make up water hardness, other water quality parameters associated with hardness, or other exposures, risk factors, and characteristics that are associated with hardness.

For example, climatic factors are related to geography. Two studies considered temperature in their analysis (14, 15). In the United Kingdom, temperature was found to be more closely related to cardiovascular mortality than hardness. In the United States, the most important correlate, after adjustment for age and indicators of socioeconomic status, was the comfort index, which is based on relative humidity and air temperature; water factors were second in importance. In the United Kingdom, two studies found that rainfall was closely related to cardiovascular mortality, more so than water hardness. In Canada, a study in Ontario found that latitude and mean temperature were more important than water hardness, but a study in Nova Scotia found latitude and temperature to be less important.

Some studies failed to make adjustments for age, race, and gender; others used broad age groups (14, 15). In failing to adjust for age or using broad age groups, the investigator assumes there are no important differences within the age range studied, and this assumption may not be valid. Few studies considered the possibility that smoking patterns or serum cholesterol may differ in hard and soft water areas (14, 15). Smoking patterns did not differ in a study in the United States but did in a study in the United Kingdom. In one study, higher serum cholesterol levels were found in the soft water area, and in another study, mean cholesterol levels were slightly lower in two soft water cities. In a third study, no differences were found among populations in hard and soft water areas.

Confounding factors cannot be ruled out as a cause of the associations. Relatively few studies considered confounding, and those that did, provided inadequate information to evaluate possible confounding. Major confounders can be controlled or assessed in analytical studies, and better information about confounding effects should be available from more recently conducted studies.

7. Water constituents associated with hardness or mortality

If the observed water hardness-cardiovascular associations are not confounded and not due to systematic bias, the question remains as to the water constituent that may be responsible. Constituents closely associated with hardness could be the explanation, or other water constituents may have their own direct correlation with the mortality rates. Sharrett (13) evaluated the composition of hard and soft water in terms of several biologically important elements, including calcium, magnesium, chromium, copper, zinc, cadmium, and lead. Voors (17) evaluated cadmium and lead as possibly increasing cardiovascular risks and selenium, zinc, and silicon as possibly being protective. Both investigators found that the available data were inconsistent and evidence inconclusive in regard to identifying any of these water constituents that might be associated with either hard water or independently associated with cardiovascular disease.

In the United States the hardness of water is just as closely associated with magnesium as with calcium levels, and the high correlation of both elements with each other and with hardness makes it difficult to attribute the association between hardness and mortality to either calcium or magnesium (13). In England and Wales, calcium was highly correlated with hardness but magnesium was not. These findings emphasize the importance of measuring specific constituents rather than water hardness.

IV. STRENGTH OF ASSOCIATION

The majority of studies considered a correlation coefficient (r) rather than a regression coefficient to measure the association. The correlation coefficient is affected much more by chance and provides no indication of the magnitude of effect; the regression coefficient is primarily affected by variation in the independent variable (10, 14, 15). It is possible to obtain a good correlation (i.e., high r value) between cardiovascular mortality and water hardness even though the dependent variable (e.g., mortality rate) may change little with change in the independent variable (e.g., water hardness).

For studies that provided sufficient data, Comstock (14, 15) calculated the relative risk (RR) for cardiovascular disease mortality associated with soft water (Table 1). Using information from studies in the United States (18), England and Wales (19), Canada (10) and Colorado (20), Comstock reported the RR associated with soft water (defined as 0 mg/l hardness) compared to hard water (defined as 200 mg/l hardness). The RRs ranged from 1.07 to 1.42 depending upon the geographic location. In Colorado, the RRs differed when the geographic areas were grouped by altitude or river basin; the larger RR is reported in Table 1. Anderson *et al.* (21) and Comstock (14, 15, 22) reported RRs for studies in Ontario and Maryland. The RRs reported in Table 1 suggest a weak association (23).

Morris *et al.* (24) found that the mortality rate for all cardiovascular disease in 83 county boroughs of England and Wales was 1.20 higher in boroughs where the total hardness of drinking water was less than 100 mg/l compared to boroughs where the hardness was 200 mg/l or greater. In 53 county boroughs where calcium levels were also reported, increased cardiovascular disease mortality (RR=1.30) was found in boroughs where water contained less than 10 mg/l calcium compared to boroughs with 100 mg/l or greater calcium (19). Anderson *et al.* (21) reported an

increased mortality risk ($RR=1.14$) for ischemic heart disease in areas of Ontario with water hardness of less than 100 mg/l (expressed in terms of calcium carbonate) compared to areas where the hardness was greater than 200 mg/l (Table 1). When these hardness values are expressed in terms of calcium levels, the increased risk ($RR=1.14$) is associated with water calcium levels of 40 mg/l compared to greater than 80 mg/l. When cities of more than 100,000 people were excluded from the analysis, the mortality associated with soft water increased ($RR=1.17$). In Washington County, Maryland, Comstock (14, 15, 22) found that risks differed for men and women. In white men, no increased risk of arteriosclerotic heart disease was associated with drinking water less than 150 mg/l, but in white women, an increased relative risk was associated with water hardness of less than 100 mg/l (Table 1).

V. EXPOSURE-RESPONSE RELATIONSHIP

Comstock (14, 15) concluded that the studies provided no information about either the exposure-response relationship or a threshold effect. Since the correlations tended to suggest a weak association, an exposure-response effect for water hardness might be difficult to detect in the studies.

VI. SPECIFICITY OF THE ASSOCIATION

Most studies reported inverse associations for mortality from arteriosclerotic and degenerative heart disease, hypertensive disease, and strokes. However, the results were inconsistent as to the disease that was most strongly associated with water hardness. Other causes of death, including all causes, were found to be inversely associated with water hardness and about as strongly as cardiovascular causes. The other causes of death included cancer, cirrhosis, peptic ulcer, infant mortality, and congenital malformations (14, 15). A lack of specificity suggests that the association might not be causal, and this concern was best described by Winton and McCabe (25): "Dissolved solids [in drinking water] may be important to man but one would not expect them to be this important."

VII. REVERSIBILITY

If the association is causal, the modification or elimination of the suspected cause should affect the frequency of the disease in question, and community-intervention studies should be able to demonstrate this change. Several studies in the United States and United Kingdom evaluated changes in mortality following changes made in water hardness either due to softening or replacing a soft surface water source with hard groundwater source (Comstock 1979a, b; Crawford *et al.* 1971). Comstock (1979a, b) found data analysis errors in several studies that had reported favourable changes in mortality rates associated with increased water hardness. When the errors were corrected, the mortality either remained high or did not decrease among populations when the soft water source was replaced with a hard water source. In the United Kingdom, Crawford *et al.* (26) studied mortality in towns where the water became softer (6 towns), harder (5 towns), or did not change (72 towns). After standardizing for socioeconomic status, death rate changes consistent with the hypothesis that hard water is beneficial were observed in 9 of the 11 towns with water hardness changes. There was a large variability in the mortality rates with considerable overlap between the towns where water became softer, harder, or did not change. Except for women aged 65-74, the cardiovascular mortality increased least or decreased most in the towns where water hardness increased.

VIII. BIOLOGICAL PLAUSIBILITY

If the association between water hardness and cardiovascular disease were causal, what constituent in hard water might be beneficial or what constituent in soft water might be harmful? Scientists who reviewed the studies thought the presumed benefit might be due to the presence of supplemental quantities of an important nutritional component or presence of a harmful water constituent in soft water. Soft waters are corrosive and may contain toxic metals, such as cadmium and lead leached from plumbing materials. In addition, some artificially softened water may contain high levels of sodium. These were considered as possible harmful constituents.

Although in some studies calcium was found to be associated with cardiovascular disease, the WHO Working group (8) concluded that this association lacked biological plausibility. However, some scientists felt that certain types of cardiac disease might be aggravated by the lack of calcium because calcium is required for muscle contractions and had been shown to decrease serum lipid levels (7). Little evidence for a protective effect of calcium was available from animal and laboratory experiments.

The supporting epidemiological evidence available in 1980 for magnesium was weak (7), but the role of magnesium was considered biologically plausible and was substantiated by animal and laboratory experiments (8). A plausible explanation might focus on a magnesium deficiency. Enough magnesium could be present in some hard waters to prevent borderline magnesium deficiencies in some persons, thereby reducing their liability to sudden cardiac death.

IX. CONCLUSIONS

The primary value of the studies reported during 1957-1979 was to call attention to the possible public health benefits of water hardness and need for additional research. Many, but not all, of the epidemiological studies published during 1957 to 1979 reported an inverse association between cardiovascular mortality and water hardness. Lower cardiovascular death rates were found in populations where the water supply contained relatively high levels of water hardness or calcium and magnesium compared to populations in areas with low levels. This protective effect was found for populations throughout the world, especially when country-wide studies were conducted. Limited information was available about the magnitude of the association or causality. Several reviewers estimated that populations who live in soft water areas may have, at best, a 25% percent excess cardiovascular disease mortality risk than populations in hard water areas.

In 1979 and 1980, scientists generally agreed that the strength of the association was relatively weak, the existence of a specific water factor was far from certain, and sufficient evidence was lacking to support a causal association. It was also agreed that because the absolute effect of hard water or a constituent of hard water in reducing mortality could be substantial, studies should be conducted to provide better information about the exposure-response relationship, biological plausibility, and causality.

References

1. Kobayashi J. On geographical relationship between the chemical nature of river water and death-rate from apoplexy. *Berichte des ohara institutes fur landwirtschaftliche biologie* 1957; **11**:12-21.
2. Schroeder H. Relations between hardness of water and death rates from certain chronic and degenerative diseases in the United States. *J Chronic Dis* 1960; **12**:586-591.
3. Schroeder H. Relationship between mortality from cardiovascular disease and treated water supplies. Variations in states and 163 largest municipalities of the United States. *J Amer Med Assoc* 1960; **172**:1902-1908.
4. Schroeder H. The water factor. *N Engl J Med* 1969; **280**:836-838.
5. NAS-NRC Subcommittee on the Geochemical Environment in Relation to Health and Disease. *Geochemistry and the Environment (Volume 3): Distribution of Trace Elements Related to the Occurrence of Certain Cancers, Cardiovascular Diseases, and Urolithiasis*. Washington, DC: National Academy of Sciences, 1978.
6. NAS-NRC Panel on Geochemistry of Water in Relation to Cardiovascular Disease. *Geochemistry of Water in Relation to Cardiovascular Disease*. Washington, DC: National Academy of Sciences, 1979: 1-98.
7. NAS-NRC Safe Drinking Water Committee. *Drinking Water and Health*, Volume 3. Washington, DC: National Academy Press, 1980: 1-2.
8. World Health Organization. Report of a Working Group: Health Effects of the Removal of Substances Occurring Naturally in Drinking-water, with Special Reference to Demineralized and Desalinated Water. (EURO Reports and Studies 16) Copenhagen: WHO Regional Office for Europe, 1979: 1-24.
9. Punsar S. Cardiovascular mortality and quality of drinking water. *Work Environ Health* 1973; **10**:107-125.
10. Neri LC, Mandel JS, Hewitt D. Relation between mortality and water hardness in Canada. *Lancet* 1972; **1**:931-934.
11. Neri LC, Hewitt D, Schreiber GB. Can epidemiology elucidate the water story? *Amer J Epidemiol* 1974; **99**(2):75-88.
12. Sharrett AR, Feinleib M. Water constituents and trace elements in relation to cardiovascular disease. *Preventive Med* 1975; **4**: 20-36.
13. Sharrett AR. The role of chemical constituents of drinking water in cardiovascular diseases. In: *Geochemistry of Water in Relation to Cardiovascular Disease*. Washington, DC: National Academy of Sciences, 1979: 69-81.
14. Comstock G. Water hardness and cardiovascular diseases. *Amer J Epidemiol* 1979; **110**(4):375-400.
15. Comstock G. The association of water hardness and cardiovascular diseases: An epidemiological review and critique. In: *Geochemistry of Water in Relation to Cardiovascular Disease*. Washington, DC: National Academy of Sciences, 1979: 48-68.
16. Masironi R. Cardiovascular mortality in relation to radioactivity and hardness of local water supplies in the USA. *Bull WHO* 1970; **43**:687-697.

17. Voors AW. The association of trace elements and cardiovascular diseases: A selected review of positive findings. In: *Geochemistry of Water in Relation to Cardiovascular Disease*. Washington, DC: National Academy of Sciences, 1979: 82-90.
18. Muss DL. Relationship between water quality and deaths from cardiovascular disease. *J Amer Water Works Assoc* 1962; **54**:1371-1378
19. Morris JN, Crawford MD, Heady JA. Hardness of local water supplies and mortality from cardiovascular disease in the county boroughs of England and Wales. *Lancet* 1961; **1**:860-862.
20. Morton WE. Hypertension and drinking water constituents in Colorado. *Amer J Public Health* 1971; **61**:1371-1378.
21. Anderson TW, LeRiche WH, MacKay JS. Sudden death and ischemic heart diseases. Correlation with hardness of local water supply. *New Engl J Med* 1969; **280**:805-807.
22. Comstock GW. Fatal arteriosclerotic heart disease, water hardness at home, and socio-economic characteristics. *Amer J Epidemiol* 1971; **94**:1-10.
23. Monson R. *Occupational Epidemiology*, 2nd edition, Boca Raton, Florida: CRC Press Inc., 1990.
24. Morris JN, Crawford MD, Heady JA. Hardness of local water supplies and mortality from cardiovascular disease. *Lancet* 1962; **2**:506-507.
25. Winton E, McCabe L. Studies relating to water mineralization and health. *J Amer Water Works Assoc* 1970; **62**:26-30.
26. Crawford MD, Gardner MJ, Morris JN. Changes in water hardness and local death rates. *Lancet* 1971; **2**:327-329.

Table 1. Relative risks of dying from specified causes associated with soft water compared to hard water (adapted from Comstock 1979 b)

Study area	Cause of death	Race, gender	Age	Hardness (mg/l CaCO ³)	Relative risk (RR)
USA	All CVD	WM	45-64	0 vs. 200**	1.25
England, Wales	All CVD	WM	45-64	0 vs. 200**	1.19
Canada	Stroke	M	35-64	0 vs. 200**	1.15
	Arteriosclerotic heart disease	M	35-64	0 vs. 200**	1.07
	Other circulatory	M	35-64	0 vs. 200**	1.10
Colorado (data grouped by river basin)	Hypertensive disease	M	*	0 vs. 200**	1.30
	Arteriosclerotic heart disease	M	*	0 vs. 200**	1.19
	Stroke	M	*	0 vs. 200**	1.11
	Other circulatory	M	*	0 vs. 200**	1.42
Ontario, Canada	Ischemic heart disease	MF	35-74	<100 vs. >200	1.14
Washington County, MD	Arteriosclerotic heart disease	WF	45-64	<100 vs. >150	1.47
	Arteriosclerotic heart disease	WM	45-64	<150 vs. >150	0.75

CVD= cardiovascular disease; M=male; F=female; W=white

*age-adjusted

**hardness units as reported by Comstock (1979 b) in his calculation of RR

11. DRINKING WATER HARDNESS AND CARDIOVASCULAR DISEASES: A REVIEW OF THE EPIDEMIOLOGICAL STUDIES 1979-2004

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I. INTRODUCTION

Cardiovascular diseases (CVDs) are among the main causes of mortality and morbidity in the industrialised countries and their main risk factors are hypertension, dyslipidemia, smoking, alcohol abuse, dietary habits and physical inactivity (1, 2). However, these classic factors do not entirely explain the variability of CVD mortality in different countries. In order to better understand the determinants of CVD, particular attention has been paid to environmental factors, such as weather, air pollution or the mineral content of drinking water (DW). Since the 1950s a causal relation between DW hardness and some CVDs has been hypothesized. The relationship between cardiovascular mortality and the mineral content of DW was first described by Kobayashi (3) in Japan and by Schroeder (4) in the United States. Since then, many epidemiological studies have been conducted worldwide, most of them describing a protective relationship between CVD mortality rates and DW hardness. The first series of studies were performed in the 1960s and 1970s. As noted in the previous chapter by Calderon and Craun, most studies had an ecological design and used mortality data from national registers; geographical areas were defined on the basis of administrative boundaries as units of analysis.

Critical reviews of these early studies emphasized that these studies had a major weakness. Because they considered average values of DW parameters, such as total hardness, calcium (Ca), or magnesium (Mg), exposures were likely subject to non-differential misclassification bias. Moreover, the temporal sequence of exposure and supposed effect (i.e., exposure to the DW risk factor precedes CVD mortality) was not always verified. In fact, the mineral content of DW was often determined at the time of the study and thus, may not represent the quality of the water the subjects had ingested during their lives. However, it should be pointed out that DW hardness is usually quite stable in time and that the health effects related to Ca and Mg concentrations may be both long- and short-term. Moreover, the main risk factors for CVD, which may confound the relationship between DW hardness and CVD mortality, had often not been taken into account in the analysis. More recently, several ecological studies were performed with more attention paid to exposure assessment and confounding factors. Epidemiological studies performed with a cohort design or with a case-control design were also carried out, but these studies are less numerous than the ecological studies even though they offer a greater potential for understanding the relationship between DW hardness and CVD mortality.

The hypothesized beneficial effect of DW hardness on CVD mortality may be due to: (1)

present in hard water (e.g., selenium, lithium, silicon, zinc, vanadium); (3) the reduced adverse effect of toxics such as lead, which may be present at a higher concentration in soft, low pH corrosive water (5-7). In fact, the presence of lead, even at low blood levels, has long been associated with hypertension and also with stroke (8, 9). In this review, we evaluated epidemiological studies on this issue published since 1979.

II. METHODS

In order to evaluate the cardiovascular effects of Ca and Mg, the principal minerals responsible for the hardness of DW, we collected articles published from 1979 through 2003. First we retrieved from the Medline database all articles using the keywords (Mesh terms) “hardness” or “calcium” or “magnesium” or “drinking water” and “human health”. Secondly, we selected articles of interest from the first list by examining the abstracts. Thirdly, we checked the references of the articles retrieved to find other papers of interest. We did not attempt to retrieve unpublished research. An additional paper available on-line in February 2004 (10) was retrieved when preparing the final version of this chapter.

Since studies published before 1979 have already been evaluated (11, 12), we excluded them from our review. Other exclusion criteria were: articles written in languages other than English; experimental studies on animals; studies on dietary intake of Ca or Mg; studies not reporting quantitative measures of associations between water hardness (or Ca/Mg concentration in DW) and human diseases. The articles were divided into the following categories: geographic correlation (ecological), case-control and cohort studies. After a critical review of these studies, we reached conclusions about the possible beneficial effects of water hardness, Ca, and Mg on the basis of the overall findings. We did not, however, perform a formal meta-analysis due to the heterogeneity of measures of effect and of exposure levels (Ca and Mg concentration in DW) in the studies reviewed. Although we did not include physiological, pathophysiological or experimental in-vitro or in-vivo studies, we considered this research in interpreting the results of the epidemiological studies.

III. RESULTS

1. Geographic Correlation Studies

Nineteen correlation studies were reviewed (Table 1). Some of them took into account potential confounders such as socio-economic status, income or climate (13-17), but only two of the 19 studies considered some of the major CVD risk factors in the populations that were compared (18, 19). Significant inverse correlations between water hardness and CVD mortality were found in 10 studies (10, 13, 15, 20-26). Lacey and Shaper (21) reported in males a 7.5% reduction of CVD mortality for 100 mg/L increased water hardness (as CaCO_3), and Yang et al. (15) reported a 10% increase in the risk of ischemic heart disease (IHD) mortality in persons with <75 mg/L hardness compared to persons with >150 mg/L hardness (as CaCO_3). Kousa et al. (10) reported that one unit in German degrees of water hardness decreased the risk of acute myocardial infarction (AMI) by 1%. The remaining eight studies reported a correlation coefficient (r). In the studies where Ca and Mg were evaluated separately, similar associations with CVD mortality were found for each of these minerals.

Although positive correlations were found between Mg concentration and both IHD and stroke mortality rates in the study by Flaten and Bolviken (27) in Norway, virtually all the municipalities investigated have soft water, and the findings may not have relevance to hard water. Six studies found either a very small or no association (14, 16, 17, 28-30). The study by

Zielhuis and Haring (30) considered various data sets; the most recent data were collected in 30 municipalities with >40,000 inhabitants and where there was no change in water hardness over the previous 20-30 years. Although an inverse correlation was found for stroke and IHD mortality rates in 1977 and Ca and Mg in water, the reported correlation coefficient was very small and not statistically significant.

The most informative of the correlation studies were carried out by Nerbrand et al. (18, 19) in Sweden. In the first study Nerbrand et al. found significant inverse associations for both IHD and stroke mortality. However, they further investigated 14,675 randomly selected subjects in the study areas using a postal questionnaire, and they found that water hardness and Ca were significantly associated with non-fatal IHD when the effects of the traditional risk factors were taken with account by multiple logistic regression analysis. Nerbrand et al. (19) conducted an additional investigation comparing a sample of 207 subjects from two municipalities, one with hard DW (Ca=66 mg/L and Mg=4.1 mg/L) and the other with soft DW (Ca=8.8 mg/L and Mg=0.74 mg/L). Although this study found increased mortality for CVD, and IHD in the soft water municipality, the study found no difference between the two populations in Ca and Mg level in the subjects' serum and urine, and no correlation between Ca or Mg concentrations in household water samples and the corresponding serum and urine levels in the subjects investigated. These findings suggest a lack of association between Ca or Mg in DW and CVD and IHD mortality when using individual- rather than population-based data, and their significance will be discussed later.

2. Case-control Studies

Seven case-control studies were included in our review. These studies investigated the association of Ca and Mg concentration with CVD mortality in Sweden, Taiwan, and Finland (Table 2). All found an inverse association between Mg levels in DW and mortality risks for AMI, stroke, or hypertension (HT); only one study found an inverse association with Ca (31-36).

In areas with DW Mg levels greater than 6.8 mg/L, Rubenowitz et al. (32) reported a statistically significant decreased risk of death due to AMI among men. Luoma et al. (31) observed that the AMI mortality risk increased among men as DW Mg levels decreased from greater than 3 mg/L to less than 1.2 mg/L, however, the increased risks were not statistically significant. Yang (33), Yang and Chiu (34) reported a statistically significant decreased risk of death due to stroke among men and women that was associated with Mg levels greater than 7.3 mg/L and a large, but statistically non-significant, decreased risk of death due to hypertension that was associated with increasing Mg levels greater than 3.8 mg/L. Rubenowitz et al. (35) found a statistically significant decreased risk of death due to AMI among women in areas with Mg levels greater than 9.8 mg/L, and in areas with Ca levels greater than 70 mg/L.

In only one of the seven studies did the investigators adjust the estimates of association for the major CVD risk factors measured at the individual level (36). In this study, a relatively large, but statistically non-significant, decreased risk for death due to AMI was found for both men and women aged 50-74 in areas with the highest quartile of Mg in DW. The same study also investigated the risk of AMI among subjects who were still alive (AMI survivors) by collecting individual data on exposure (Ca and Mg concentration in household water) and on major risk factors for the disease. No association was found between Ca or Mg levels and the prevalence of AMI among the AMI survivors.

Rosenlund et al. (37) studied the association between AMI risk and the average daily intake of drinking water constituents in a sub-set from a large Swedish population-based case-control study in the period 1992-1994. After adjustment for the matching variables and confounders, the odds ratio for AMI was 0.88 among those with a Mg intake from their drinking water above 1.86

mg per day. Although this odds ratio suggested a protective effect, analyses using multiple categories of exposure showed no exposure-response relationship. The odds ratios for hardness, sodium and Ca were also slightly less than one, but as was found for Mg, the odds ratios were not statistically significant and there was no exposure-response relationship.

3. Cohort Studies

We identified two cohort studies. One of them, conducted in two rural areas in Finland (38), found that populations residing in the area with lower Mg levels in DW (3.1 mg/L vs. 13.1 mg/L) had a proportionally higher mortality from CVD (14.7% vs. 8.7%). The other study, performed in the Washington County, Maryland, found no association between water hardness and CVD mortality (39). Neither study took into account measures of common CVD risk factors.

IV. DISCUSSION

Many, but not all, of the geographic correlation studies showed an inverse association between water hardness and mortality from CVD. Most case-control studies and one cohort study showed a statistically significant inverse relation between mortality from CVD and water levels of Mg, but not Ca levels. The two elements act differently in human cells and may play different roles in CVD development and evolution. The roles of Ca and Mg in DW as they may affect CVD will, therefore, be discussed separately.

1. Total hardness, calcium concentrations and CVD

Since Ca is the main element responsible for total water hardness, the results of studies that considered water hardness may be interpreted as concerning Ca as well. The majority of epidemiological studies on water hardness and CVD carried out so far have provided somewhat controversial results. Of the 19 geographical studies published since 1979 and included in the present review, 10 found a significant association, but the only two geographical studies which took into account the distribution of the main CVD risk factors (18, 19), both from Sweden, reported no association when individuals were considered. Of the 6 case-control studies that specifically considered Ca, only one (35) found a statistically significant protective effect of high Ca levels (>70 mg/L) in DW, but no exposure-response relationship was observed. An alternative explanation for the inverse association found between water hardness and CVD may be that hard water protects against the toxic effects of lead. Soft water is more aggressive and, therefore, richer in lead which may be present in plumbing materials.

One question is the possible role of Ca in the development and control of primary “essential” hypertension in humans (40). Some animal data and observational studies in humans support the hypothesis that Ca supplementation can reduce blood pressure. However, a recent meta-analysis of 42 randomised controlled trials on the influence of dietary and non-dietary Ca supplementation on blood pressure shows only a small, clinically modest, reduction in both systolic (mean reduction: - 1.44 mm Hg) and diastolic (mean reduction: - 0.84 mm Hg) blood pressure (41). These findings support present recommendations of an adequate dietary intake of Ca. The use of Ca supplements to prevent or treat hypertension is not, however, supported by current evidence.

2. Magnesium concentrations and CVD

Mg participates in many different biological functions, ranging from structural roles by complexing negatively charged groups, i.e. phosphates in nucleic acids, catalytic roles in enzyme activation or inhibition, and regulatory roles by modulating cell proliferation, to cell cycle progression and differentiation (42). Mg deficiency accelerates the development of atherosclerosis

and the induction of thrombocyte aggregation, therefore, it is described as a risk factor for AMI and for cerebrovascular disease (43, 44). Mg is known to be a protective agent against soft tissue calcification (particularly for myocytes), and its role in AMI has been well documented (5, 45).

The results of epidemiological studies on the possible association between Mg in DW and CVD are persuasive, although some discrepancies have been noted. Many, but not all, of the geographical correlation, cohort and case-control studies show that a high Mg water concentration protects against CVD and stroke mortality. Some studies found an exposure-response relationship. However, the only study investigating both CVD incidence and mortality (36) found that a high Mg concentration in DW reduced the risk of dying from, but not of developing, CVD, when taking the main CHD risk factors into account. These findings suggest that Mg may reduce the fatality from CHD among those who develop the disease (secondary prevention) rather than prevent the onset of the disease (primary prevention). Accordingly, a cohort study showed that serum Mg concentration was inversely associated with CHD mortality but not with incidence (46), and clinical data show that Mg is useful in treating patients with myocardial infarction and other acute CVDs (47). Furthermore, oral Mg therapy in CHD patients has been shown to have beneficial effects on the outcome (48, 49).

The role of minerals such as sodium, Ca and Mg in the development of human hypertension has been investigated widely since the first geographical studies showing a lower incidence of the disease in populations with a diet poor in sodium yet rich in Ca and Mg. Physiological and pathophysiological studies support the role of Mg in hypertension development (50). The protective role of Mg in reducing the incidence of hypertension has been reported in many observational studies (50). A recent prospective cohort study found a lower risk of hypertension in subjects with high Mg serum concentration among people free of the diseases at baseline (51). Interestingly, well-designed randomized controlled trials have shown that a diet rich in vegetables, fruit and whole grains, therefore, richer in Mg than common western diets, reduced blood pressure significantly (52, 53). However, taking Ca or Mg supplements did not reduce blood pressure in either normotensive or hypertensive subjects (54-56). In fact, the current recommendations of the US Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (57) are in favour of a regular dietary intake of Ca and Mg, but against taking more than the recommended dose of these mineral supplements.

Indirect evidence of the protective effects of Mg against CVD comes from several dietary preventive trials showing that a diet rich in vegetables, fruit and whole grains ("Oriental" diet) significantly reduces CVD incidence compared to the usual US diet ("American" diet) (58, 59). The Oriental diet is richer in Ca and Mg compared to western diets. However, it is also rich in many other putative factors protecting against CVD, such as vitamins, cofactors, anti-oxidants, polyunsaturated fats and selenium. Despite suggesting an association, these trials provide no conclusive evidence that Ca or Mg intake reduces the risk of CVD.

Various experimental studies carried out on animals support the hypothesis of a cause-effect relationship between Mg content in drinking water and ischemic heart disease. Experimentally-induced Mg deficiency changes the blood lipid composition in a more atherogenic direction (60, 61). It has recently been observed that Mg-fortified water reduced atherogenesis in low-density lipoprotein (LDL) receptor-deficient mice with respect to those receiving distilled water, with and without a high-cholesterol diet (62-64). Likewise, Mg supplementation in DW inhibited atherogenesis in apolipoprotein-E-deficient mice not receiving a high-fat diet; Mg supplementation in DW significantly inhibited atherogenesis in female but not in male mice (65).

Another issue of interest is the relationship between biological measures of Ca and Mg concentration in extracellular and intracellular body compartments and CVD development. Some recent cross-sectional (66, 67), case-control (68) and cohort studies (46, 69) showed that subjects

with low Mg serum levels have an increased risk of CHD compared to people with high levels, when also considering all the major risk factors for the disease as possible confounders.

A controversial point is the relevance of Mg intake by water compared to diet. Although food is usually the main source of Mg, modern western diets often contain very little of this mineral. Marx and Neutra (7) pointed out the apparent paradox that waterborne Mg, which contributes less than dietary Mg to total intake, may have as great an effect (relative risks of 1.5-2.0) on CVD mortality as that observed in some studies of other risk factors. Marx and Neutra criticised the methods of previous studies and noted that the studies are not supported by pharmacokinetic data. They also emphasized that confounding by other waterborne or dietary factors associated with Mg is the most serious concern and argued that further, more valid studies using personal data would be needed to clarify the issue once and for all. Nevertheless, it has been shown that the daily intake of Mg in industrialized countries does not reach the current recommended daily allowance in many subjects and therefore marginal Mg deficiencies are common. An extensive national sample survey among US adults showed that about 23% have Mg serum concentrations <0.80 mmol/L, a level considered as hypomagnesemia (46). Mg intake through DW may be important in these populations because of the higher bioavailability of the mineral in DW than in food. It has been pointed out that 2 litres of water rich in Mg (40 mg/L) will provide 80 mg of Mg, which is about 25% of an adult's total requirement (18).

3. Interpreting the epidemiological evidence

The strengths and limitations of epidemiology for investigating the causes of human diseases are well known. Weak associations, especially those regarding environmental factors, are difficult to interpret and require a number of well-designed investigations, with precise measures of both the factor under study and the possible confounders and effect modifiers at an individual level. There is as yet no conclusive evidence of the relationship between DW hardness and CVD, mainly because the numerous epidemiological studies carried out thus far do not satisfy the criteria for establishing causality. The main drawbacks of these studies are the lack of exposure data at an individual level, with the risk of exposure misclassification, and the lack of control of confounders, including the recognized risk factors for CVD. Although the epidemiological study results may be confounded, it should be remembered that a risk factor for a disease is a confounder if it is associated with exposure under investigation (70). Major CVD risk factors such as serum cholesterol, hypertension, diabetes mellitus, cigarette smoking, obesity and physical exercise may confound the relationship between water hardness and CVD mortality only if they are associated with soft DW. However, there is no reason to believe that major CVD risk factors are usually associated with low Ca or Mg concentration in DW. It, therefore, seems unlikely that confounding alone can explain the associations found in several geographical and case-control studies carried out in different populations and at different times. The role of chance in finding an association should be excluded as well, since numerous studies reported an association, whereas only 5% would expect to find a significant association by chance alone.

A study performed in two areas at substantially different levels of DW hardness provides a good example of how a geographical correlation study can produce invalid results (19). The study investigated two communities, one in the west and the other in the east of Sweden, with substantial differences in both DW hardness concentration and CVD mortality rates: the population with the lower DW hardness (west) had about double the mortality rate of the other population (east). However, the authors also collected individual data from 207 subjects, randomly sampled from the two populations (approximately 100 from each), including the following: Ca and Mg measurement in a sample of tap water from the subject's household; total dietary intake of Ca and Mg, determined by means of a questionnaire; serum and urine Ca concentration, and serum, urine and muscle Mg concentration; serum levels of LDL and HDL cholesterol, triglycerides and other risk factors for

CVD. Total Ca and Mg intakes were found to be higher in the population drinking softer water due to a higher intake of food rich in these minerals. However, there was no difference between the two populations in mean serum or urine levels of Ca and Mg. No correlation was found between Ca and Mg levels in DW and the mean values in serum or urine. Of the investigated risk factors for CVD, the LDL:HDL cholesterol ratio was higher in the west than in the east population, possibly explaining the higher mortality rates for CVD in the former. The research by Nerbrand et al. does not show a direct correlation between Ca and Mg in DW and CVD and IHD mortality at an individual level, in spite of an apparent geographical correlation. These findings are consistent with those from another study showing that a large part of the geographical variation observed in CHD incidence in British towns was reduced after adjustment for the main risk factors (71). At least 80% of major CHD events in middle-aged men can be attributed to the three highest risk factors, i.e. serum total cholesterol, cigarette smoking and blood pressure, as recently estimated (72). It follows that the contribution of other risk factors, including environmental ones, in CHD incidence or mortality is necessarily modest.

Should the association between DW Ca or Mg concentration and CVD be true, why have some studies not found an association. The possible reasons include:

- 1.) the relatively small differences between the areas compared. For instance, only one of the 5 rate-based studies considered in the review by Marx and Neutra (7) compared populations with substantial differences in Mg concentration in DW (Figure 2 in reference 7);
- 2.) the dilution of the effect due to heterogeneity of exposure among individuals in the same population, caused by substantial differences in water and food consumption;
- 3.) the relatively weak strength of the association.

V. CONCLUSIONS

There is little evidence that supports an association between water hardness or Ca concentration in DW and CVD. However, the available information from experimental, clinical and epidemiological studies supports the hypothesis that a lower than recommended intake of Mg is a condition that increases the risk of dying from, and possibly developing, CVD, stroke or hypertension. Similar conclusions about the benefits of Mg in water have been reached by others (43, 44, 73, 74). Although some scientists may argue that additional information is needed to establish causality, the following information strongly supports the conclusions reached :

- In-vitro studies show that exposure of endothelial cells to low Mg causes some of the events involved in the pathogenesis of atherosclerosis;
- Animal studies show that a low-Mg diet causes inflammation and high serum cholesterol levels, particularly LDL cholesterol, thus favouring atherosclerosis development, and conversely that high Mg intake protects against the atherosclerotic effects of oxidative stress and hypercholesterolemia-inducing diets;
- In patients with CHD, Mg in pharmacological doses has been shown to reduce endothelial lesions and is a useful anti-ischemic and anti-arrhythmic agent;
- Most correlation studies show a high mortality for CVD and stroke in populations with low Mg concentration in DW, and vice-versa;
- Some cross-sectional and cohort studies show that people with low serum Mg levels are at a higher risk of hypertension, CHD and stroke;
- Dietary trials show that a diet rich in vegetables and fruit, i.e. rich in Mg, reduces the risk of CVD.

References

1. Hornstra G, Barth CA, Galli C, et al. Functional food science and the cardiovascular system. *Br J Nutr* 1998;80(suppl):113-146.
2. Wilson PW. Metabolic risk factors for coronary heart disease: current and future prospects. *Curr Opin Cardiol* 1999;14:176-185.
3. Kobayashi J. Geographical relationship between chemical nature of river water and death rate from apoplexy. *Ber Ohara Inst Landwirtsch Biol Okayama Univ* 1957;11:12-21.
4. Schroeder HA. Relation between mortality from cardiovascular disease and treated water supplies Variations in states and 163 largest municipalities of the United States. *J Am Med Assoc* 1960;172:1902- 1908.
5. Eisenberg MJ. Magnesium deficiency and sudden death. *Am Heart J* 1992;124:544-549.
6. Rylander R. Environmental magnesium deficiency as a cardiovascular risk factor. *J Cardiovasc Risk* 1996;3:4-10.
7. Marx A, Neutra RR. Magnesium in drinking water and ischemic heart disease. *Epidemiol Rev* 1997;19:258-272.
8. Pirkle JL, Schwartz J, Landis JR, Harlan WR. The relationship between blood lead levels and blood pressure and its cardiovascular risk implications. *Am J Epidemiol* 1985;121:246-258.
9. Perry HM, Roccella EJ. Conference report on stroke mortality in the Southeastern United States. *Hypertension* 1998;31:1206-1215.
10. Kousa A, Moltchanova E, Viik-Kajander M, et al. Geochemistry of ground water and the incidence of acute myocardial infarction in Finland. *J Epidemiol Community Health* 2004;58:136-139.
11. Comstock GW. The epidemiologic perspective: water hardness and cardiovascular disease. *J Environ Pathol Toxicol* 1980;4:9-25.
12. Sharrett AR. Water hardness and cardiovascular disease. *Circulation* 1981;63:247A-250A.
13. Pocock SJ, Shaper AG, Cook DG, et al. British Regional Heart Study: geographic variation in cardiovascular mortality, and the role of water quality. *Br Med J* 1980;280:1243-1249.
14. Gyllerup S, Lanke J, Lindholm H, Schersten B. Water hardness does not contribute substantially to the high coronary mortality in cold region of Sweden. *J Intern Med* 1991;230:487-492.
15. Yang CY, Chiu JF, Chiu HF, et al. Relationship between water hardness and coronary mortality in Taiwan. *J Toxicol Environ Health* 1996;49:1-9.
16. Miyake Y, Iki M. Ecological study of water and cerebrovascular mortality in Japan. *Arch Environ Health* 2003;58:163-166.
17. Maheswaran R, Morris S, Falconer S, et al. Magnesium in drinking water supplies and mortality from acute myocardial infarction in north west England. *Heart* 1999;82:455-460.
18. Nerbrand C, Svardsudd K, Ek J, Tibblin G. Cardiovascular mortality and morbidity in seven counties in Sweden in relation to water hardness and geological settings. *Eur Heart J* 1992;13:721-727.

19. Nerbrand C, Agreus L, Lenner RA, et al. The influence of calcium and magnesium in drinking water and diet on cardiovascular risk factors in individuals living in hard and soft water areas with differences in cardiovascular mortality. *BMC Public Health* 2003;3:21-29.
20. Masironi R, Pisa Z, Clayton D. Myocardial infarction and water hardness in the WHO myocardial infarction registry network. *Bull WHO* 1979;57:291-299.
21. Lacey RF, Shaper AG. Changes in water hardness and cardiovascular death rates. *Int J Epidemiol* 1984;13:18-24.
22. Leoni V, Fabiani L, Ticchiarelli L. Water hardness and cardiovascular mortality rate in Abruzzo, Italy. *Arch Environ Health* 1985;40:274-278.
23. Leary WP, Reyes AJ, Lockett CJ, et al. Magnesium and deaths ascribed to ischaemic heart disease in South Africa. A preliminary report. *S Afr Med J* 1983;64:775-776.
24. Rylander R, Bonevik H, Rubenowitz E. Magnesium and calcium in drinking water and cardiovascular mortality. *Scand J Work Environ Health* 1991;17:91-94.
25. Sauvant MP, Pepin D. Geographic variation of the mortality from cardiovascular disease and drinking water in a French small area (Puy de Dome). *Environ Res* 2000;84:219-227.
26. Marque S, Jacqmin-Gadda H, Dartigues JF, Commenges D. Cardiovascular mortality and calcium and magnesium in drinking water: an ecological study in elderly people. *Eur J Epidemiol* 2003;18:305-309.
27. Flaten TP, Bolviken B. Geographical associations between drinking water chemistry and the mortality and morbidity of cancer and some other diseases in Norway. *Sci Total Environ* 1991;102:75-100.
28. Scassellati-Sforzolini G, Damiani P, Romoli R, et al. Correlazione epidemiologica tra qualità delle acque potabili e mortalità per malattie del sistema circolatorio. *L' Igiene Moderna* 1979;4:3-35 [In Italian].
29. Smith WC, Crombie IK. Coronary heart disease and water hardness in Scotland. Is there a relationship? *J Epidemiol Community Health* 1987;41:227-228.
30. Zielhuis RL, Haring BJ. Water hardness and mortality in The Netherlands. *Sci Total Environ* 1981;18:35-45.
31. Luoma H, Aromaa A, Helminen S, et al. Risk of myocardial infarction in Finnish men in relation to fluoride, magnesium and calcium concentration in drinking water. *Acta Med Scand* 1983;213:171-176.
32. Rubenowitz E, Axelsson G, Rylander R. Magnesium in drinking water and death from acute myocardial infarction. *Am J Epidemiol* 1996;143:456-462.
33. Yang CY. Calcium and magnesium in drinking water and risk of death from cerebrovascular disease. *Stroke* 1998;29:411-414.
34. Yang CY, Chiu HF. Calcium and magnesium in drinking water and the risk of death from hypertension. *Am J Hypertens* 1999;12:894-899.
35. Rubenowitz E, Axelsson G, Rylander R. Magnesium and calcium in drinking water and death from acute myocardial infarction in women. *Epidemiology* 1999;10:31-36.
36. Rubenowitz E, Molin I, Axelsson G, Rylander R. Magnesium in drinking water in relation to morbidity and mortality from acute myocardial infarction. *Epidemiology* 2000;11:416-421.

37. Rosenlund M, Berglind N, Hallqvist J, Bluhm G. Drinking water hardness and myocardial infarction in the Stockholm heart epidemiology program (SHEEP)[abstract]. *Epidemiology* 2002;13(suppl):192.
38. Punsar S, Karvonen MJ. Drinking water quality and sudden death: observations from West and East Finland. *Cardiology* 1979;64:24-34.
39. Comstock GW, Cauthen GM, Helsing KJ. Water hardness at home and deaths from arteriosclerotic heart disease in Washington County, Maryland. *Am J Epidemiol* 1980;112:209-216.
40. Resnik LM. The role of dietary calcium in hypertension. *Am J Hypertens* 1999;12:99-112.
41. Griffith LE, Guyatt GH, Cook RJ, Bucher HC, Cook DJ. The influence of dietary and nondietary calcium supplementation on blood pressure: an update meta-analysis of randomized controlled trials. *Am J Hypertens* 1999;12:84-92.
42. Hartwig A. Role of magnesium in genomic stability. *Mutat Res* 2001;475:113-121.
43. Altura BM, Altura BT. Magnesium and cardiovascular biology: an important link between cardiovascular risk factors and atherogenesis. *Cel Mol Biol Res* 1995;41:347-359.
44. Saris NE, Mervaala E, Karppanen H, et al. Magnesium. An update on physiological, clinical and analytical aspects. *Clin Chim Acta* 2000;294:1-26.
45. Durlach J, Bara M, Guet-Bara A. Magnesium level in drinking water and cardiovascular risk factor: a hypothesis. *Magnesium* 1985;4:5-15.
46. Ford ES. Serum magnesium and ischaemic heart disease: findings from a national sample of US adults. *Int J Epidemiol* 1999;28:645-651.
47. Reinhart RA. Clinical correlates of the molecular and cellular actions of magnesium on the cardiovascular system. *Am Heart J* 1991;121:1513-1521.
48. Shechter M, Sharis M, Labrador MJ, et al. Oral magnesium therapy improves endothelial function in patients with coronary artery disease. *Circulation* 2000;102:2353-2358.
49. Shechter M, Merz CN, Rude RK, et al. Low intracellular magnesium levels promote platelet-dependent thrombosis in patients with coronary artery disease. *Am Heart J* 2000;140:212-218.
50. Laurant P, Touyz RM. Physiological and pathophysiological role of magnesium in the cardiovascular system: implication in hypertension. *J Hypertens* 2000;18:1177-1191.
51. Peacock JM, Folsom AR, Arnett DK, et al. Relationship of serum and dietary magnesium to incident hypertension: the atherosclerosis risk in communities (ARIC) study. *Ann Epidemiol* 1999;9:159-165.
52. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med* 1997;336:1117-1124.
53. Conlin PR, Chow D, Miller ER, et al. The effect of dietary patterns on blood pressure control in hypertensive patients: results from the dietary approaches to stop hypertension (DASH) Trial. *Am J Hypertens* 2000;13:949-955.
54. Sacks FM, Brown LE, Appel LJ, et al. Combinations of potassium, calcium, and magnesium supplements in hypertension. *Hypertension* 1995;26:950-956.
55. Sacks MF, Willet WC, Smith A, et al. Effect on blood pressure of potassium, calcium, and magnesium in women with low habitual intake. *Hypertension* 1998;31:131-138.

56. Yamamoto ME, Applegate WB, Klag MJ, et al. Lack of blood pressure effect with calcium and magnesium supplementation in adults with high-normal blood pressure. Results from Phase 1 of the Trial of Hypertension Prevention (TOHP). *Ann Epidemiol* 1995;5:96-107.
57. Joint National Committee. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 1997;157:2413-2446.
58. Singh RB. Effect of dietary magnesium supplementation in the prevention of coronary heart disease and sudden cardiac death. *Magnes Trace Elem* 1990;9:143-151.
59. Singh RB, Rastogi SS, Verma R, et al. Randomised controlled trial of cardioprotective diet in patients with recent acute myocardial infarction: result of one year follow up. *Br Med J* 1992;304:1689-1690.
60. Altura BT, Brust M, Bloom S, et al. Magnesium dietary intake modulates blood lipid levels and atherogenesis. *Proc Natl Acad Sci USA* 1990;87:1840-1844.
61. Yamaguchi Y, Kitagawa S, Kunitomo M, Fujiwara M. Preventive effects of magnesium on raised serum lipid peroxide level and aortic cholesterol deposition in mice fed an atherogenic diet. *Magnes Res* 1994; 7:31-37.
62. Sherer Y, Shaish A, Levkovitz H, et al. Magnesium fortification of drinking water suppresses atherogenesis in male LDL-receptor-deficient mice. *Pathobiology* 1999;67:207-213.
63. Sherer Y, Shoenfeld Y, Shaish A, et al. Suppression of atherogenesis in female low-density lipoprotein receptor knockout mice following magnesium fortification of drinking water: the importance of diet. *Pathobiology* 2000;68:93-98.
64. Cohen H, Sherer Y, Shaish A, et al. Atherogenesis inhibition induced by magnesium-chloride fortification of drinking water. *Biol Trace Elem Res* 2002;90:251-259.
65. Ravn HB, Korsholm TL, Falk E. Oral magnesium supplementation induces favourable antiatherogenic ApoE-deficient mice. *Arterioscler Thromb Vasc Biol* 2001;21:858-862.
66. Ma J, Folsom AR, Melnick SL, et al. Associations of serum and dietary magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid arterial wall thickness: the ARIC study. *J Clin Epidemiol* 1995;48:927-940.
67. Singh RB, Niaz MA, Moshiri M, et al. Magnesium status and risk of coronary artery disease in rural and urban populations with variable magnesium consumption. *Magnes Res* 1997;10:205-213.
68. Singh RB, Gupta UC, Mittal N, et al. Epidemiologic study of trace elements and magnesium on risk of coronary artery disease in rural and urban Indian population. *J Am Coll Nutr* 1997;16:62-67.
69. Liao F, Folsom AR, Brancati FL. Is low magnesium concentration a risk factor for coronary heart disease? The atherosclerosis risk in communities (ARIC) study. *Am Heart J* 1998;136:480-490.
70. Gordis L. *Epidemiology*. 2nd ed. Philadelphia: W.B. Saunders Co., 2000.
71. Morris RW, Wincup PH, Lampe FC, et al. Geographic variation in incidence of coronary heart disease in Britain: the contribution of established risk factors. *Heart* 2001;86:277-283.

72. Emberson JR, Whincup PH, Morris RW, Walker M. Re-assessing the contribution of serum total cholesterol, blood pressure and cigarette smoking to the aetiology of coronary heart disease: impact of regression dilution bias. *Eur Heart J* 2003;24:1719-1726.
73. Maier JA. Low magnesium and atherosclerosis: an evidence-based link. *Mol Aspects Med* 2003;24:137-146.
74. Sauvant MP, Pepin D. Drinking water and cardiovascular disease. *Food Chem Toxicol* 2002;40:1311-1325.

Table 1. Geographic correlation studies on the relationship between cardiovascular diseases or stroke and hardness and/or calcium/magnesium concentration of drinking water.

Authors, year of publication	Country, area and population	Period	Drinking water parameters	CVD or stroke mortality	Results
Scassellati-Sforzolini et al., 1979 (28)	Italy, Umbria Region, 12 municipalities,	1967-1976	Total hardness	Mortality for: - IHD - Stroke	M & F: $r = +0.28$ M & F: $r = -0.07$
			Ca concentration	Mortality for: - IHD - Stroke	M & F: $r = +0.37$ M & F: $r = -0.05$
			Mg concentration	Mortality for: - IHD - Stroke	M & F: $r = -0.26$ M & F: $r = -0.28$
Masironi et al., 1979 (20)	Europe, 17 towns, 45-64 years	1974	Total hardness	AMI incidence	M & F: $r = -0.46$
Pocock et al., 1980 (13)	Great Britain, 253 municipalities, 35-74 years	1969-1973	Total hardness	Mortality for CVD	M & F: $r = -0.67$
Zielhuis and Haring, 1981(30)	The Netherlands, 30 communities	1977	Ca concentration	Mortality for: - IHD - Stroke	M: $r = -0.01$ F: $r = -0.11$ M: $r = -0.14$ F: $r = -0.12$
			Mg concentration	Mortality for: - IHD - Stroke	M: $r = -0.19$ F: $r = -0.10$ M: $r = -0.02$ F: $r = -0.07$
Leary et al., 1983 (23)	South Africa, 12 districts	1978-1982	Mg concentration	Mortality for IHD	M: $r = -0.68$

Lacey and Shaper, 1984 (21)	England and Wales, 14 areas, 45-74 years	1968-1972	Total hardness	Mortality for CVD	Males: 7.5% reduction of mortality for 100 mg/L increase of hardness*
Leoni et al., 1985 (22)	Italy, Abruzzo Region	1969-1978	Total hardness	Mortality for: - CVD - IHD - Stroke	M & F: r= - 0.55** M & F: r= - 0.59* M & F: r= - 0.24
Smith and Crombie, 1987 (29)	Scotland, 56 districts	1979-1983	Total hardness	Mortality for IHD	M: r= -0.17
Rylander et al., 1991 (6)	Sweden, 27 municipalities	1969-1978	Total hardness	Mortality for: - IHD - Stroke	M: r= - 0.60 F: r= - 0.37 M: r= - 0.48 F: r= - 0.45
			Ca concentration	Mortality for: - IHD - Stroke	M: r= - 0.47 F: r= - 0.41 M: r= - 0.52 F: r= - 0.32
			Mg concentration	Mortality for: - IHD - Stroke	M: r= - 0.62 F: r= - 0.45 M: r= - 0.16 F: r= - 0.49
Gyllerup et al., 1991 (14)	Sweden, 259 municipalities, (males only) 40-64 years	1975-1984	Total hardness	Mortality for AMI	Inverse association, with lower relevance after adjusting for cold climate
			Mg concentration	Mortality for AMI	
Flaten and Bolviken, 1991 (27)	Norway, 97 municipalities	1974-1983	Ca concentration	Mortality for: - IHD - Stroke	NR NR
			Mg concentration	Mortality for: - IHD - Stroke	M: r= +0.33*** F: r= +0.23* M: r= +0.22** F: r= +0.35**
	Country, area and	Period	Drinking water	CVD or stroke mortality	Results

Authors, year of publication	population		parameters			
Nerbrand et al., 1992 (19)	Sweden, 76 municipalities, males and females	1969-1983	Total hardness	Mortality for: - IHD - Stroke	M*** M***	F* F***
			Ca concentration	Mortality for: - IHD - Stroke	M** M	F*** F***
			Mg concentration	Mortality for: - IHD - Stroke	M M	F F
Yang et al., 1996 (15)	Taiwan, 227 municipalities	1981-1990	Total hardness ^a	Mortality for IHD	RR (95% CI)	
			<75 mg/L		1.096 (1.084-1.108)*	
			75-150 mg/L		1.045 (1.032-1.058)*	
			>150 mg/L		Reference	
Maheswaran et al., 1999 (17)	England, 305 areas, (>45 years)	1990-1992		Mortality for AMI	RR (95% CI) for 4-fold increase of Ca and Mg concentration in drinking water:	
			Ca concentration		Ca: 0.99 (0.94-1.05)	
			Mg concentration		Mg: 1.01 (0.96-1.06)	
Sauvant and Pepin, 2000 (25)	France, Puy de Dôme Department, 52 districts	1988-1992	Total hardness	Mortality for: - IHD - Stroke -CVD	M: r = -0.33 M: r = -0.32 M: r = -0.34	F: r = -0.18 F: r = -0.34 F: r = -0.37

Marque et al., 2003 (26)	France South-West, 69 areas (>65 years)	1990-1996	Ca concentration	Mortality for:	RR (95% CI) for highest vs lowest tertile:
				- CVD - IHD - Stroke	0.90 (0.84-0.96)** 0.90 (0.84-0.97)** 0.86 (0.77-0.96)*
			Mg concentration	Mortality for:	RR (95% CI) for highest vs lowest tertile:
				- CVD - IHD - Stroke	0.93 (0.86-1.01) 0.96 (0.87-1.05) 0.92 (0.80-1.06)
Nerbrand et al., 2003 (18)	Sweden, 2 municipalities in the West and East	1989-1998	West (Ca : 8.8 mg/L, Mg: 0.74 mg/L)	Mortality for [§] :	Mortality rates:
				- IHD - CVD	M: 21/1000 F: 5/1000 M: 31/1000 F: 11/1000
			East (Ca : 66 mg/L, Mg: 4.1 mg/L)	Mortality for [§] :	Mortality rates:
				- IHD - CVD	M: 10/1000 F: 2/1000 M: 20/1000 F: 6/1000
					RR (West /East) for: IHD=M: 2.03 F: 2.56 CVD=M: 1.56 F: 1.71
Miyake and Iki, 2003 (16)	Japan, 44 municipalities	1995	Total hardness ^a <46.5 mg/L 46.5-51.9 mg/L >51.9 mg/L	Mortality for Stroke	RR (95% CI) Reference 0.97 (0.91-1.03) 0.93 (0.84-1.02)
	Country, area and	Period	Drinking water	CVD or stroke mortality	Results

Authors, year of publication	population		parameters		
Kousa et al., 2004 (10)	Finland, whole country (males, 35-74 years)	1983, 1988 and 1993	Total hardness ^a	Incidence of AMI	Rates per 100,000:
			<30.6 mg/L		562.1
			30.6-93.08 mg/L		469.5
			>93.08 mg/L		437.6

^aTotal hardness in mg/L of CaCO₃.

IHD = ischaemic heart diseases; AMI = acute myocardial infarction; CVD = cardiovascular diseases; NR = not reported; RR = relative risk; CI = confidence interval; M = males; F = females; r = correlation coefficient.

* p<0.05; ** p< 0.01; *** p<0.001; if no * shown, p>0.05.

§ Study of 207 inhabitants found positive association for Ca and systolic blood pressure; inverse association for Ca in DW and LDL and total cholesterol; no association for Mg and major CVD risk factors.

Table 2. Case-control studies on the relationship between cardiovascular diseases (CVD) and hardness and/or calcium/magnesium concentrations of drinking water.

Authors, years of publication	Country and area	Population	Age (years)	Drinking water parameters	Odds ratio (OR) (95% CI)	
Luoma et al., 1983 (31)	Finland	58 males with AMI, alive or dead (cases)	37-64		Hospital controls	Population controls
		58 males (hospital controls)		Ca concentration		
				<16 mg/L	0.73 (0.22-1.99)	0.56 (0.25-1.28)
				16-18 mg/L	0.77 (0.30-1.91)	1.07 (0.48- 2.42)
		50 males (population controls)		19-20 mg/L	0.91 (0.35-2.36)	1.64 (0.73-3.85)
				>20 mg/L	Reference	Reference
				Mg concentration		
				<1.2 mg/L	2.00 (0.69-6.52)	4.67 (1.30-25.32)*
				1.2-1.5 mg/L	1.11 (0.41-3.10)	2.29 (0.88-6.58)
				1.6-3.0 mg/L	1.00 (0.36-3.08)	1.63 (0.62-4.52)
				>3.0 mg/L	Reference	Reference
Rubenowitz et al., 1996 (32)	Southern Sweden, 17 municipalities	854 males dead for AMI (cases)	50-69	Ca concentration	OR age-adjusted:	
				<34 mg/L	Reference	
		989 males dead for cancer (controls)		34-45 mg/L	0.88 (0.65-1.19)	
				46-81 mg/L	0.84 (0.64-1.10)	
				≥82 mg/L	1.06 (0.82-1.38)	
				Mg concentration	OR age-adjusted:	

				<3.6 mg/L	Reference
				3.6-6.8 mg/L	0.88 (0.66-1.16)
				6.9-9.7 mg/L	0.70 (0.53-0.93)*
				≥9.8 mg/L	0.65 (0.50-0.84)*
Yang, 1998 (33)	Taiwan, 252 municipalities	17,133 males and females dead for stroke (cases)	50-69	Ca concentration	OR adjusted for age and sex:
				<24.4 mg/L	Reference
		17,133 males and females dead for other causes, excluding CVD (controls)		24.4-42.3 mg/L	1.5 (0.99-1.11)
				42.4-81.0 mg/L	0.95 (0.88-1.01)
				Mg concentration	OR adjusted for age and sex:
				<7.3 mg/L	Reference
				7.4-13.4 mg/L	0.75 (0.65-0.85)*
				13.5-41.3 mg/L	0.60 (0.52-0.70)*

Authors, years of publication	Country and area	Population	Age (years)	Drinking water parameters	Odds ratio (OR) (95% CI)
Yang and Chiu, 1999 (34)	Taiwan, 252 municipalities	2336 males and females dead for HT (cases)	50-69	Ca concentration	OR adjusted for age, sex, urbanization and Mg:
				4.0-11.3 mg/L	Reference
		2336 males and females dead for other causes, excluding CVD (controls)		11.4-30.0 mg/L	1.23 (0.94-1.62)
				30.1-37.7 mg/L	1.32 (0.98-1.78)
				37.8-53.4 mg/L	1.12 (0.83-1.51)
				53.5-81.0 mg/L	1.26 (0.92-2.02)
				Mg concentration	OR adjusted for age, sex, urbanization and Ca:
				1.5-3.8 mg/L	Reference
				3.9-8.2 mg/L	0.73 (0.57-0.93)***
				8.3-11.1 mg/L	0.66 (0.50-0.87)***
		11.2-16.3 mg/L		0.67 (0.50-0.89)***	
		16.4-41.3 mg/L		0.63 (0.47-0.84)***	
Rubenowitz et al., 1999 (35)	Southern Sweden, 16 municipalities	378 females dead for AMI (cases)	50-69	Ca concentration	OR adjusted for age and Mg :
		1368 females dead for cancer (controls)		≤31 mg/L	Reference
				32-45 mg/L	0.61 (0.39-0.94)*
				46-69 mg/L	0.71 (0.49-1.02)
				≥70 mg/L	0.66 (0.47-0.94)*
		Mg concentration		OR adjusted for age and Ca:	
		≤3.4 mg/L		Reference	

				3.5-6.7 mg/L	1.08 (0.78-1.49)
				6.8-9.8 mg/L	0.93 (0.64-1.34)
				≥9.9 mg/L	0.70 (0.50-0.99)*
Rubenowitz et al., 2000 (36)	Southern Sweden, 18 municipalities	263 males and females dead for AMI (cases)	50-74	OR adjusted for age and Mg (highest/lowest quartiles) Ca concentration M: 1.01 (0.64-1.59) F: 0.68 (0.29-1.59)	
		258 males and females dead for other causes (controls)		OR adjusted for age and Ca (highest/lowest quartiles) Mg concentration M: 0.69 (0.43-1.09) F: 0.51 (0.21-1.22)	
		823 males and females surviving after an AMI (cases)	50-74	OR adjusted for age and Mg (highest/lowest quartiles) Ca concentration M: 0.97 (0.75-1.26) F: 0.90 (0.59-1.38)	
		853 males and females without AMI (controls)		OR adjusted for age and Ca (highest/lowest quartiles) Mg concentration M: 1.19 (0.91-1.54) F: 1.09 (0.70-1.70)	
Rosenlund et al., 2002 (37)	Sweden	570 males and females with AMI (cases)	45-70	Mg intake in drinking water	OR (95% CI) 0.88 (0.67-1.15)
		753 males and females without AMI (controls)		>1.86 mg per day	

AMI = acute myocardial infarction; CVD = cardiovascular diseases; HT = hypertension; M = males; F = females.

95% CI = confidence interval.

* p<0.05; *** p< 0.001; all others not statistically significant.

12. HEALTH RISKS FROM DRINKING DEMINERALISED WATER

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I. INTRODUCTION

The composition of water varies widely with local geological conditions. Neither groundwater nor surface water has ever been chemically pure H_2O , since water contains small amounts of gases, minerals and organic matter of natural origin. The total concentrations of substances dissolved in fresh water considered to be of good quality can be hundreds of mg/L. Thanks to epidemiology and advances in microbiology and chemistry since the 19th century, numerous waterborne disease causative agents have been identified. The knowledge that water may contain some constituents that are undesirable is the point of departure for establishing guidelines and regulations for drinking water quality. Maximum acceptable concentrations of inorganic and organic substances and microorganisms have been established internationally and in many countries to assure the safety of drinking water. The potential effects of totally unmineralised water had not generally been considered, since this water is not found in nature except possibly for rainwater and naturally formed ice. Although rainwater and ice are not used as community drinking water sources in industrialized countries where drinking water regulations were developed, they are used by individuals in some locations. In addition, many natural waters are low in many minerals or soft (low in divalent ions), and hard waters are often artificially softened.

Awareness of the importance of minerals and other beneficial constituents in drinking water has existed for thousands years, being mentioned in the Vedas of ancient India. In the book Rig Veda, the properties of good drinking water were described as follows: “Sheetham (cold to touch), Sushihi (clean), Sivam (should have nutritive value, requisite minerals and trace elements), Isthām (transparent), Vimalam lahu Shadgunam (its acid base balance should be within normal limits)” (1). That water may contain desirable substances has received less attention in guidelines and regulations, but an increased awareness of the biological value of water has occurred in the past several decades.

Artificially-produced demineralised waters, first distilled water and later also deionized or reverse osmosis-treated water, had been used mainly for industrial, technical and laboratory purposes. These technologies became more extensively applied in drinking water treatment in the 1960's as limited drinking water sources in some coastal and inland arid areas could not meet the increasing water demands resulting from increasing populations, higher living standards, development of industry, and mass tourism. Demineralisation of water was needed where the primary or the only abundant water source available was highly mineralized brackish water or sea water. Drinking water supply was also of concern to ocean-going ships, and spaceships as well. Initially, these water treatment methods were not used elsewhere since they were technically exacting and costly.

In this chapter, demineralised water is defined as water almost or completely free of dissolved minerals as a result of distillation, deionization, membrane filtration (reverse osmosis or nanofiltration), electrodialysis or other technology. The total dissolved solids (TDS) in such water can vary but TDS could be as low as 1 mg/L. The electrical conductivity is generally less than 2 mS/m and may even be lower (<0.1 mS/m). Although the technology had its beginnings in the 1960's, demineralization was not widely used at that time. However, some countries focused on public health research in this field, mainly the former USSR where desalination was introduced to produce drinking water in some Central Asian cities. It was clear from the very beginning that desalinated or demineralised water without further enrichment with some minerals might not be fully appropriate for consumption. There were three reasons for this:

- Demineralised water is highly aggressive and if untreated, its distribution through pipes and storage tanks would not be possible. The aggressive water attacks the water distribution piping and leaches metals and other materials from the pipes and associated plumbing materials.
- Distilled water has poor taste characteristics.
- Preliminary evidence was available that some substances present in water could have beneficial effects on human health as well as adverse effects. For example, experience with artificially fluoridated water showed a decrease in the incidence of tooth caries, and some epidemiological studies in the 1960's reported lower morbidity and mortality from some cardiovascular diseases in areas with hard water.

Therefore, researchers focused on two issues: 1.) what are the possible adverse health effects of demineralised water, and 2.) what are the minimum and the desirable or optimum contents of the relevant substances (e.g., minerals) in drinking water needed to meet both technical and health considerations. The traditional regulatory approach, which was previously based on limiting the health risks from excessive concentrations of toxic substances in water, now took into account possible adverse effects due to the deficiency of certain constituents.

At one of the working meetings for preparation of guidelines for drinking water quality, the World Health Organization (WHO) considered the issue of the desired or optimum mineral composition of desalinated drinking water by focusing on the possible adverse health effects of removing some substances that are naturally present in drinking water (2). In the late 1970's, the WHO also commissioned a study to provide background information for issuing guidelines for desalinated water. That study was conducted by a team of researchers of the A.N. Sysin Institute of General and Public Hygiene and USSR Academy of Medical Sciences under the direction of Professor Sidorenko and Dr. Rakhmanin. The final report, published in 1980 as an internal working document (3), concluded that "not only does completely demineralised water (distillate) have unsatisfactory organoleptic properties, but it also has a definite adverse influence on the animal and human organism". After evaluating the available health, organoleptic, and other information, the team recommended that demineralised water contain 1.) a minimum level for dissolved salts (100 mg/L), bicarbonate ion (30 mg/L), and calcium (30 mg/L); 2.) an optimum level for total dissolved salts (250-500 mg/L for chloride-sulfate water and 250-500 mg/L for bicarbonate water); 3.) a maximum level for alkalinity (6.5 meq/l), sodium (200 mg/L), boron (0.5 mg/L), and bromine (0.01 mg/L). Some of these recommendations are discussed in greater detail in this chapter.

During the last three decades, desalination has become a widely practiced technique in providing new fresh water supplies. There are more than 11 thousand desalination plants all over the world with an overall production of more than 6 billion gallons of desalinated water per day (Cotruvo, in this book). In some regions such as the Middle East and Western Asia more than half

of the drinking water is produced in this way. Desalinated waters are commonly further treated by adding chemical constituents such as calcium carbonate or limestone, or blended with small volumes of more mineral-rich waters to improve their taste and reduce their aggressiveness to the distribution network as well as plumbing materials. However, desalinated waters may vary widely in composition, especially in terms of the minimum TDS content. Numerous facilities were developed without compliance with any uniform guidelines regarding minimum mineral content for final product quality.

The potential for adverse health effects from long term consumption of demineralised water is of interest not only in countries lacking adequate fresh water, but also in countries where some types of home water treatment systems are widely used or where some types of bottled water are consumed. Some natural mineral waters, in particular glacial mineral waters, are low in TDS (less than 50 mg/l) and in some countries, even distilled bottled water has been supplied for drinking purposes. Other brands of bottled water are produced by demineralising fresh water and then adding minerals for desirable taste. Persons consuming certain types of water may not be receiving the additional minerals that would be present in more highly mineralized waters. Consequently, the exposures and risks should be considered not only at the community level, but also at the individual or family level.

II. HEALTH RISKS FROM CONSUMPTION OF DEMINERALISED OR LOW-MINERAL WATER

Knowledge of some effects of consumption of demineralised water is based on experimental and observational data. Experiments have been conducted in laboratory animals and human volunteers, and observational data have been obtained from populations supplied with desalinated water, individuals drinking reverse osmosis-treated demineralised water, and infants given beverages prepared with distilled water. Because limited information is available from these studies, we should also consider the results of epidemiological studies where health effects were compared for populations using low-mineral (soft) water and more mineral-rich waters. Demineralised water that has not been remineralised is considered an extreme case of low-mineral or soft water because it contains only small amounts of dissolved minerals such as calcium and magnesium that are the major contributors to hardness.

The possible adverse consequences of low mineral content water consumption are discussed in the following categories:

- Direct effects on the intestinal mucous membrane, metabolism and mineral homeostasis or other body functions.
- Little or no intake of calcium and magnesium from low-mineral water.
- Low intake of other essential elements and microelements.
- Loss of calcium, magnesium and other essential elements in prepared food.
- Possible increased dietary intake of toxic metals.

1. Direct effects of low mineral content water on the intestinal mucous membrane, metabolism and mineral homeostasis or other body functions

Distilled and low mineral content water (TDS < 50 mg/L) can have negative taste characteristics to which the consumer may adapt with time. This water is also reported to be less thirst quenching (3). Although these are not considered to be health effects, they should be taken into account when considering the suitability of low mineral content water for human

consumption. Poor organoleptic and thirst-quenching characteristics may affect the amount of water consumed or cause persons to seek other, possibly less satisfactory water sources.

Williams (4) reported that distilled water introduced into the intestine caused abnormal changes in epithelial cells of rats, possibly due to osmotic shock. However, the same conclusions were not reached by Schumann *et al.* (5) in a more recent study based on 14-day experiments in rats. Histology did not reveal any signs of erosion, ulceration or inflammation in the oesophagus, stomach and jejunum. Altered secretory function in animals (i.e., increased secretion and acidity of gastric juice) and altered stomach muscle tone were reported in studies for WHO (3), but currently available data have not unambiguously demonstrated a direct negative effect of low mineral content water on the gastrointestinal mucous membrane.

It has been adequately demonstrated that consuming water of low mineral content has a negative effect on homeostasis mechanisms, compromising the mineral and water metabolism in the body. An increase in urine output (i.e., increased diuresis) is associated with an increase in excretion of major intra- and extracellular ions from the body fluids, their negative balance, and changes in body water levels and functional activity of some body water management-dependent hormones. Experiments in animals, primarily rats, for up to one-year periods have repeatedly shown that the intake of distilled water or water with TDS ≤ 75 mg/L leads to: 1.) increased water intake, diuresis, extracellular fluid volume, and serum concentrations of sodium (Na) and chloride (Cl) ions and their increased elimination from the body, resulting in an overall negative balance., and 2.) lower volumes of red cells and some other hematocrit changes (3). Although Rakhmanin *et al.* (6) did not find mutagenic or gonadotoxic effects of distilled water, they did report decreased secretion of tri-iodothyronine and aldosterone, increased secretion of cortisol, morphological changes in the kidneys including a more pronounced atrophy of glomeruli, and swollen vascular endothelium limiting the blood flow. Reduced skeletal ossification was also found in rat fetuses whose dams were given distilled water in a one-year study. Apparently the reduced mineral intake from water was not compensated by their diets, even if the animals were kept on standardized diet that was physiologically adequate in caloric value, nutrients and salt composition.

Results of experiments in human volunteers evaluated by researchers for the WHO report (3) are in agreement with those in animal experiments and suggest the basic mechanism of the effects of water low in TDS (e.g. < 100 mg/L) on water and mineral homeostasis. Low-mineral water markedly: 1.) increased diuresis (almost by 20%, on average), body water volume, and serum sodium concentrations, 2.) decreased serum potassium concentration, and 3.) increased the elimination of sodium, potassium, chloride, calcium and magnesium ions from the body. It was thought that low-mineral water acts on osmoreceptors of the gastrointestinal tract, causing an increased flow of sodium ions into the intestinal lumen and slight reduction in osmotic pressure in the portal venous system with subsequent enhanced release of sodium into the blood as an adaptation response. This osmotic change in the blood plasma results in the redistribution of body water; that is, there is an increase in the total extracellular fluid volume and the transfer of water from erythrocytes and interstitial fluid into the plasma and between intracellular and interstitial fluids. In response to the changed plasma volume, baroreceptors and volume receptors in the bloodstream are activated, inducing a decrease in aldosterone release and thus an increase in sodium elimination. Reactivity of the volume receptors in the vessels may result in a decrease in ADH release and an enhanced diuresis. The German Society for Nutrition reached similar conclusions about the effects of distilled water and warned the public against drinking it (7). The warning was published in response to the German edition of *The Shocking Truth About Water* (8), whose authors recommended drinking distilled water instead of "ordinary" drinking water. The Society in its position paper (7) explains that water in the human body always contains

electrolytes (e.g. potassium and sodium) at certain concentrations controlled by the body. Water resorption by the intestinal epithelium is also enabled by sodium transport. If distilled water is ingested, the intestine has to add electrolytes to this water first, taking them from the body reserves. Since the body never eliminates fluid in form of "pure" water but always together with salts, adequate intake of electrolytes must be ensured. Ingestion of distilled water leads to the dilution of the electrolytes dissolved in the body water. Inadequate body water redistribution between compartments may compromise the function of vital organs. Symptoms at the very beginning of this condition include tiredness, weakness and headache; more severe symptoms are muscular cramps and impaired heart rate.

Additional evidence comes from animal experiments and clinical observations in several countries. Animals given zinc or magnesium dosed in their drinking water had a significantly higher concentration of these elements in the serum than animals given the same elements in much higher amounts with food and provided with low-mineral water to drink. Based on the results of experiments and clinical observations of mineral deficiency in patients whose intestinal absorption did not need to be taken into account and who received balanced intravenous nutrition diluted with distilled water, Robbins and Sly (9) presumed that intake of low-mineral water was responsible for an increased elimination of minerals from the body.

Regular intake of low-mineral content water could be associated with the progressive evolution of the changes discussed above, possibly without manifestation of symptoms or causal symptoms over the years. Nevertheless, severe acute damage, such as hyponatremic shock or delirium, may occur following intense physical efforts and ingestion of several litres of low-mineral water (10). The so-called "water intoxication" (hyponatremic shock) may also occur with rapid ingestion of excessive amounts not only of low-mineral water but also tap water. The "intoxication" risk increases with decreasing levels of TDS. In the past, acute health problems were reported in mountain climbers who had prepared their beverages with melted snow that was not supplemented with necessary ions. A more severe course of such a condition coupled with brain oedema, convulsions and metabolic acidosis was reported in infants whose drinks had been prepared with distilled or low-mineral bottled water (11).

2. Little or no intake of calcium and magnesium from low-mineral water

Calcium and magnesium are both essential elements. Calcium is a substantial component of bones and teeth. In addition, it plays a role in neuromuscular excitability (i.e., decreases it), the proper function of the conducting myocardial system, heart and muscle contractility, intracellular information transmission and the coagulability of blood. Magnesium plays an important role as a cofactor and activator of more than 300 enzymatic reactions including glycolysis, ATP metabolism, transport of elements such as sodium, potassium, and calcium through membranes, synthesis of proteins and nucleic acids, neuromuscular excitability and muscle contraction.

Although drinking water is not the major source of our calcium and magnesium intake, the health significance of supplemental intake of these elements from drinking water may outweigh its nutritional contribution expressed as the proportion of the total daily intake of these elements. Even in industrialized countries, diets deficient in terms of the quantity of calcium and magnesium, may not be able to fully compensate for the absence of calcium and, in particular, magnesium, in drinking water.

For about 50 years, epidemiological studies in many countries all over the world have reported that soft water (i.e., water low in calcium and magnesium) and water low in magnesium is associated with increased morbidity and mortality from cardiovascular disease (CVD) compared to hard water and water high in magnesium. An overview of epidemiological evidence

is provided by recent review articles (12-15) and summarized in other chapters of this monograph (Calderon and Craun, Monarca *et al.*). Recent studies also suggest that the intake of soft water, i.e. water low in calcium, may be associated with higher risk of fracture in children (16), certain neurodegenerative diseases (17), pre-term birth and low weight at birth (18) and some types of cancer (19, 20). In addition to an increased risk of sudden death (21-23), the intake of water low in magnesium seems to be associated with a higher risk of motor neuronal disease (24), pregnancy disorders (so-called preeclampsia) (25), and some cancers (26-29).

Specific knowledge about changes in calcium metabolism in a population supplied with desalinated water (i.e., distilled water filtered through limestone) low in TDS and calcium, was obtained from studies carried out in the Soviet city of Shevchenko (3, 30, 31). The local population showed decreased activity of alkaline phosphatase, reduced plasma concentrations of calcium and phosphorus and enhanced decalcification of bone tissue. The changes were most marked in women, especially pregnant women and were dependent on the duration of residence in Shevchenko. The importance of water calcium was also confirmed in a one-year study of rats on a fully adequate diet in terms of nutrients and salts and given desalinated water with added dissolved solids of 400 mg/L and either 5 mg/L, 25 mg/L, or 50 mg/L of calcium (3, 32). The animals given water dosed with 5 mg/L of calcium exhibited a reduction in thyroidal and other associated functions compared to the animals given the two higher doses of calcium.

While the effects of most chemicals commonly found in drinking water manifest themselves after long exposure, the effects of calcium and, in particular, those of magnesium on the cardiovascular system are believed to reflect recent exposures. Only a few months exposure may be sufficient consumption time effects from water that is low in magnesium and/or calcium (33). Illustrative of such short-term exposures are cases in the Czech and Slovak populations who began using reverse osmosis-based systems for final treatment of drinking water at their home taps in 2000-2002. Within several weeks or months various complaints suggestive of acute magnesium (and possibly calcium) deficiency were reported (34). The complaints included cardiovascular disorders, tiredness, weakness or muscular cramps and were essentially the same symptoms listed in the warning of the German Society for Nutrition (7).

3. Low intake of some essential elements and microelements from low-mineral water

Although drinking water, with some rare exceptions, is not the major source of essential elements for humans, its contribution may be important for several reasons. The modern diet of many people may not be an adequate source of minerals and microelements. In the case of borderline deficiency of a given element, even the relatively low intake of the element with drinking water may play a relevant protective role. This is because the elements are usually present in water as free ions and therefore, are more readily absorbed from water compared to food where they are mostly bound to other substances.

Animal studies are also illustrative of the significance of microquantities of some elements present in water. For instance, Kondratyuk (35) reported that a variation in the intake of microelements was associated with up to six-fold differences in their content in muscular tissue. These results were found in a 6-month experiment in which rats were randomized into 4 groups and given: a.) tap water, b.) low-mineral water, c.) low-mineral water supplemented with iodide, cobalt, copper, manganese, molybdenum, zinc and fluoride in tap water, d.) low-mineral water supplemented with the same elements but at ten times higher concentrations. Furthermore, a negative effect on the blood formation process was found to be associated with non-supplemented demineralised water. The mean hemoglobin content of red blood cells was as much as 19% lower in the animals that received non-supplemented demineralised water compared to that in animals

given tap water. The haemoglobin differences were even greater when compared with the animals given the mineral supplemented waters.

Recent epidemiological studies of an ecologic design among Russian populations supplied with water varying in TDS suggest that low-mineral drinking water may be a risk factor for hypertension and coronary heart disease, gastric and duodenal ulcers, chronic gastritis, goitre, pregnancy complications and several complications in newborns and infants, including jaundice, anemia, fractures and growth disorders (36). However, it is not clear whether the effects observed in these studies are due to the low content of calcium and magnesium or other essential elements, or due to other factors.

Lutai (37) conducted a large cohort epidemiological study in the Ust-Ilim region of Russia. The study focused on morbidity and physical development in 7658 adults, 562 children and 1582 pregnant women and their newborns in two areas supplied with water different in TDS. One of these areas was supplied with water lower in minerals (mean values: TDS 134 mg/L, calcium 18.7 mg/L, magnesium 4.9 mg/L, bicarbonates 86.4 mg/L) and the other was supplied with water higher in minerals (mean values: TDS 385 mg/L, calcium 29.5 mg/L, magnesium 8.3 mg/L, bicarbonates 243.7 mg/L). Water levels of sulfate, chloride, sodium, potassium, copper, zinc, manganese and molybdenum were also determined. The populations of the two areas did not differ from each other in eating habits, air quality, social conditions and time of residence in the respective areas. The population of the area supplied with water lower in minerals showed higher incidence rates of goiter, hypertension, ischemic heart disease, gastric and duodenal ulcers, chronic gastritis, cholecystitis and nephritis. Children living in this area exhibited slower physical development and more growth abnormalities, pregnant women suffered more frequently from edema and anemia. Newborns of this area showed higher morbidity. The lowest morbidity was associated with water having calcium levels of 30-90 mg/L, magnesium levels of 17-35 mg/L, and TDS of about 400 mg/L (for bicarbonate containing waters). The author concluded that such water could be considered as physiologically optimum.

4. High loss of calcium, magnesium and other essential elements in food prepared in low-mineral water

When used for cooking, soft water was found to cause substantial losses of all essential elements from food (vegetables, meat, cereals). Such losses may reach up to 60 % for magnesium and calcium or even more for some other microelements (e.g., copper 66 %, manganese 70 %, cobalt 86 %). In contrast, when hard water is used for cooking, the loss of these elements is much lower, and in some cases, an even higher calcium content was reported in food as a result of cooking (38-41).

Since most nutrients are ingested with food, the use of low-mineral water for cooking and processing food may cause a marked deficiency in total intake of some essential elements that was much higher than expected with the use of such water for drinking only. The current diet of many persons usually does not provide all necessary elements in sufficient quantities, and therefore, any factor that results in the loss of essential elements and nutrients during the processing and preparation of food could be detrimental for them.

5. Possible increased dietary intake of toxic metals

Increased risk from toxic metals may be posed by low-mineral water in two ways: 1.) higher leaching of metals from materials in contact with water resulting in an increased metal content in drinking water, and 2.) lower protective (antitoxic) capacity of water low in calcium and magnesium.

Low-mineralized water is unstable and therefore, highly aggressive to materials with which it comes into contact. Such water more readily dissolves metals and some organic substances from pipes, coatings, storage tanks and containers, hose lines and fittings, being incapable of forming low-absorbable complexes with some toxic substances and thus reducing their negative effects.

Among eight outbreaks of chemical poisoning from drinking water reported in the USA in 1993-1994, there were three cases of lead poisoning in infants who had blood-lead levels of 15 µg/dL, 37 µg/dL, and 42 µg/dL. The level of concern is 10 µg/dL. For all three cases, lead had leached from brass fittings and lead-soldered seams in drinking water storage tanks. The three water systems used low mineral drinking water that had intensified the leaching process (42). First-draw water samples at the kitchen tap had lead levels of 495 to 1050 µg/L for the two infants with the highest blood lead; 66 µg/L was found in water samples collected at the kitchen tap of the third infant (43).

Calcium and, to a lesser extent, magnesium in water and food are known to have antitoxic activity. They can help prevent the absorption of some toxic elements such as lead and cadmium from the intestine into the blood, either via direct reaction leading to formation of an unabsorbable compound or via competition for binding sites (44-50). Although this protective effect is limited, it should not be dismissed. Populations supplied with low-mineral water may be at a higher risk in terms of adverse effects from exposure to toxic substances compared to populations supplied with water of average mineralization and hardness.

6. Possible bacterial contamination of low-mineral water

All water is prone to bacterial contamination in the absence of a disinfectant residual either at source or as a result of microbial re-growth in the pipe system after treatment. Re-growth may also occur in desalinated water. Bacterial re-growth within the pipe system is encouraged by higher initial temperatures, higher temperatures of water in the distribution system due to hot climates, lack of a residual disinfectant, and possibly greater availability of some nutrients due to the aggressive nature of the water to materials in contact with it. Although an intact desalination membrane should remove all bacteria, it may not be 100 % effective (perhaps due to leaks) as can be documented by an outbreak of typhoid fever caused by reverse osmosis-treated water in Saudi Arabia in 1992 (51). Thus, virtually all waters including desalinated waters are disinfected after treatment. Non pathogenic bacterial re-growth in water treated with different types of home water treatment devices was reported by Geldreich *et al.* (52) and Payment *et al.* (53, 54) and many others. The Czech National Institute of Public Health (34) in Prague has tested products intended for contact with drinking water and found, for example, that the pressure tanks of reverse osmosis units are prone to bacterial regrowth, primarily do to removal of residual disinfectant by the treatment. They also contain a rubber bag whose surface appears to be favourable for bacterial growth.

III. DESIRABLE MINERAL CONTENT OF DEMINERALISED DRINKING WATER

The corrosive nature of demineralised water and potential health risks related to the distribution and consumption of low TDS water has led to recommendations of the minimum and optimum mineral content in drinking water and then, in some countries, to the establishment of obligatory values in the respective legislative or technical regulations for drinking water quality. Organoleptic characteristics and thirst-quenching capacity were also considered in the recommendations. For example, human volunteer studies (3) showed that the water temperatures of 15-35°C best satisfied physiological needs. Water temperatures above 35°C or below 15°C

resulted in a reduction in water consumption. Water with a TDS of 25-50 mg/L was described tasteless (3).

1. The 1980 WHO report

Salts are leached from the body under the influence of drinking water with a low TDS. Because adverse effects such as altered water-salt balance were observed not only in completely desalinated water but also in water with TDS between 50 and 75 mg/L, the team that prepared the 1980 WHO report (3) recommended that the minimum TDS in drinking water should be 100 mg/L. The team also recommended that the optimum TDS should be about 200-400 mg/L for chloride-sulphate waters and 250-500 mg/L for bicarbonate waters (WHO 1980). The recommendations were based on extensive experimental studies conducted in rats, dogs and human volunteers. Water exposures included Moscow tap water, desalinated water of approximately 10 mg/L TDS, and laboratory-prepared water of 50, 100, 250, 300, 500, 750, 1000, and 1500 mg/L TDS using the following constituents and proportions: Cl^- (40%), HCO_3^- (32%), SO_4 (28%) / Na (50%), Ca (38%), Mg (12%). A number of health outcomes were investigated including: dynamics of body weight, basal and nitrogen metabolism, enzyme activity, water-salt homeostasis and its regulatory system, mineral content of body tissues and fluids, hematocrit, and ADH activity. The optimal TDS was associated with the lowest incidence of adverse effect, negative changes to the human, dog, or rat, good organoleptic characteristics and thirst-quenching properties, and reduced corrosivity of water.

In addition to the TDS levels, the report (3) recommended that the minimum calcium content of desalinated drinking water should be 30 mg/L. These levels were based on health concerns with the most critical effects being hormonal changes in calcium and phosphorus metabolism and reduced mineral saturation of bone tissue. Also, when calcium is increased to 30 mg/L, the corrosive activity of desalinated water would be appreciably reduced and the water would be more stable (3). The report (3) also recommended a bicarbonate ion content of 30 mg/L as a minimum essential level needed to achieve acceptable organoleptic characteristics, reduced corrosivity, and an equilibrium concentration for the recommended minimum level of calcium.

2. Recent recommendations

More recent studies have provided additional information about minimum and optimum levels of minerals that should be in demineralised water. For example, the effect of drinking water of different hardness on the health status of women aged from 20 to 49 years was the subject of two cohort epidemiological studies (460 and 511 women) in four South Siberian cities (55, 56). The water in city A had the lowest levels of calcium and magnesium (3.0 mg/L calcium and 2.4 mg/L magnesium). The water in city B had slightly higher levels (18.0 mg/L calcium and 5.0 mg/L magnesium). The highest levels were in city C (22.0 mg/L calcium and 11.3 mg/L magnesium) and city D (45.0 mg/L calcium and 26.2 mg/L magnesium). Women living in cities A and B more frequently showed cardiovascular changes (as measured by ECG), higher blood pressure, somatoform autonomic dysfunctions, headache, dizziness, and osteoporosis (as measured by X-ray absorptiometry) compared to those of cities C and D. These results suggest that the minimum magnesium content of drinking water should be 10 mg/L and the minimum calcium content should be 20 mg/L rather than 30 mg/L as recommended in the 1980 WHO report (3).

Based on the currently available data, various researchers have recommended that the following levels of calcium, magnesium, and water hardness should be in drinking water:

- For magnesium, a minimum of 10 mg/L (33, 56) and an optimum of about 20-30 mg/L (49, 57);

- For calcium, a minimum of 20 mg/L (56) and an optimum of about 50 (40-80) mg/L (57, 58);
- For total water hardness, the sum of calcium and magnesium should be 2 to 4 mmol/L (37, 50, 59, 60).

At these concentrations, minimum or no adverse health effects were observed. The maximum protective or beneficial health effects of drinking water appeared to occur at the estimated desirable or optimum concentrations. The recommended magnesium levels were based on cardiovascular system effects, while changes in calcium metabolism and ossification were used as a basis for the recommended calcium levels. The upper limit of the hardness optimal range was derived from data that showed a higher risk of gall stones, kidney stones, urinary stones, arthrosis and arthropathies in populations supplied with water of hardness higher than 5 mmol/L.

Long-term intake of drinking water was taken into account in estimating these concentrations. For short-term therapeutic indications of some waters, higher concentrations of these elements may be considered.

IV. GUIDELINES AND DIRECTIVES FOR CALCIUM, MAGNESIUM, AND HARDNESS LEVELS IN DRINKING WATER

The WHO in the 2nd edition of *Guidelines for Drinking-water Quality* (61) evaluated calcium and magnesium in terms of water hardness but did not recommend either minimum levels or maximum limits for calcium, magnesium, or hardness. The first European Directive (62) established a requirement for minimum hardness for softened or desalinated water (≥ 60 mg/L as calcium or equivalent cations). This requirement appeared obligatorily in the national legislations of all EEC members, but this Directive expired in December 2003 when a new Directive (63) became effective. The new Directive does not contain a requirement for calcium, magnesium, or water hardness levels. On the other hand, it does not prevent member states from implementing such a requirement into their national legislation. Only a few EU Member States (e.g. the Netherlands) have included calcium, magnesium, or water hardness into their national regulations as a binding requirement. Some EU Member States (e.g. Austria, Germany) included these parameters at lower levels as unbinding regulations, such as technical standards (e.g., different measures for reduction of water corrosivity). All four Central European countries that became part of the EU in May 2004 have included the following requirements in their respective regulations but varying in binding power;

- Czech Republic (2004): for softened water ≥ 30 mg/L calcium and ≥ 10 mg/L magnesium; guideline levels of 40-80 mg/L calcium and 20-30 mg/L magnesium (hardness as $\Sigma \text{Ca} + \text{Mg} = 2.0 - 3.5$ mmol/L).
- Hungary (2001): hardness 50 – 350 mg/L (as CaO); minimum required concentration of 50 mg/L must be met in bottled drinking water, new water sources, and softened and desalinated water.
- Poland (2000): hardness 60-500 mg/L (as CaCO_3).
- Slovakia (2002): guideline levels > 30 mg/L calcium and 10 – 30 mg/L magnesium.

The Russian technical standard Astronaut environment in piloted spaceships – general medical and technical requirements (64) defines qualitative requirements for recycled water intended for drinking in spaceships. Among other requirements, the TDS should range between 100 and 1000 mg/L with minimum levels of fluoride, calcium and magnesium being specified by

a special commission separately for each cosmic flight. The focus is on how to supplement recycled water with a mineral concentrate to make it “physiologically valuable” (65).

V. CONCLUSIONS

Drinking water should contain minimum levels of certain essential minerals (and other components such as carbonates). Unfortunately, over the two past decades, little research attention has been given to the beneficial or protective effects of drinking water substances. The main focus has been on the toxicological properties of contaminants. Nevertheless, some studies have attempted to define the minimum content of essential elements or TDS in drinking water, and some countries have included requirements or guidelines for selected substances in their drinking water regulations. The issue is relevant not only where drinking water is obtained by desalination (if not adequately re-mineralised) but also where home treatment or central water treatment reduces the content of important minerals and low-mineral bottled water is consumed.

Drinking water manufactured by desalination is stabilized with some minerals, but this is usually not the case for water demineralised as a result of household treatment. Even when stabilized, the final composition of some waters may not be adequate in terms of providing health benefits. Although desalinated waters are supplemented mainly with calcium (lime) or other carbonates, they may be deficient in magnesium and other microelements such as fluorides and potassium. Furthermore, the quantity of calcium that is supplemented is based on technical considerations (i.e., reducing the aggressiveness) rather than on health concerns. Possibly none of the commonly used ways of re-mineralization could be considered optimum, since the water does not contain all of its beneficial components. Current methods of stabilization are primarily intended to decrease the corrosive effects of demineralised water.

Demineralised water that has not been remineralized, or low-mineral content water – in the light of the absence or substantial lack of essential minerals in it – is not considered ideal drinking water, and therefore, its regular consumption may not be providing adequate levels of some beneficial nutrients. This chapter provides a rationale for this conclusion. The evidence in terms of experimental effects and findings in human volunteers related to highly demineralised water is mostly found in older studies, some of which may not meet current methodological criteria. However, these findings and conclusions should not be dismissed. Some of these studies were unique, and the intervention studies, although undirected, would hardly be scientifically, financially, or ethically feasible to the same extent today. The methods, however, are not so questionable as to necessarily invalidate their results. The older animal and clinical studies on health risks from drinking demineralised or low-mineral water yielded consistent results both with each other, and recent research has tended to be supportive.

Sufficient evidence is now available to confirm the health consequences from drinking water deficient in calcium or magnesium. Many studies show that higher water magnesium is related to decreased risks for CVD and especially for sudden death from CVD. This relationship has been independently described in epidemiological studies with different study designs, performed in different areas, different populations, and at different times. The consistent epidemiological observations are supported by the data from autopsy, clinical, and animal studies. Biological plausibility for a protective effect of magnesium is substantial, but the specificity is less evident due to the multifactorial aetiology of CVD. In addition to an increased risk of sudden death, it has been suggested that intake of water low in magnesium may be associated with a higher risk of motor neuronal disease, pregnancy disorders (so-called preeclampsia), sudden death in infants, and some types of cancer. Recent studies suggest that the intake of soft water, i.e. water low in calcium, is associated with a higher risk of fracture in children, certain neurodegenerative

diseases, pre-term birth and low weight at birth and some types of cancer. Furthermore, the possible role of water calcium in the development of CVD cannot be excluded.

International and national authorities responsible for drinking water quality should consider guidelines for desalination water treatment, specifying the minimum content of the relevant elements such as calcium and magnesium and TDS. If additional research is required to establish guidelines, authorities should promote targeted research in this field to elaborate the health benefits. If guidelines are established for substances that should be in demineralised water, authorities should ensure that the guidelines also apply to uses of certain home treatment devices and bottled waters.

References

1. Sadgir P, Vamanrao A. Water in Vedic Literature. In: Abstract Proceedings of the 3rd international Water History Association Conference (http://www.iwha.net/a_abstract.htm), Alexandria: 2003.
2. Working group report (Brussels, 20-23 March 1978). Health effects of the removal of substances occurring naturally in drinking water, with special reference to demineralized and desalinated water. EURO Reports and Studies 16. Copenhagen: World Health Organization, 1979.
3. Guidelines on health aspects of water desalination. ETS/80.4. Geneva: World Health Organization, 1980.
4. Williams AW. Electron microscopic changes associated with water absorption in the jejunum. *Gut* 1963; 4: 1-7.
5. Schumann K, Elsenhans B, Reichl FX, et al. Does intake of highly demineralized water damage the rat gastrointestinal tract? *Vet Hum Toxicol* 1993; 35: 28-31.
6. Rakhmanin YuA, Mikhailova RI, Filippova AV, et al. On some aspects of biological effects of distilled water. (In Russian.) *Gig Sanit* 1989; 3: 92-93.
7. Deutsche Gesellschaft für Ernährung. Drink distilled water? (In German.) *Med Mo Pharm* 1993; 16: 146.
8. Bragg PC, Bragg P. The Shocking Truth about Water. 27th ed. Santa Barbara, CA, Health Science, 1993.
9. Robbins DJ, Sly MR. Serum zinc and demineralized water. *Am J Clin Nutr* 1981; 34: 962-963.
10. Basnyat B, Sleggs J, Springer M. Seizures and delirium in a trekker: the consequences of excessive water drinking? *Wilderness Environ Med* 2000; 11: 69-70.
11. Anonymous. Hyponatremic seizures among infants fed with commercial bottled drinking water – Wisconsin, 1993. *MMWR* 1994; 43: 641-643.
12. Sauvant M-P, Pepin D. Drinking water and cardiovascular disease. *Food Chem Toxicol* 2002; 40: 1311-1325.
13. Donato F, Monarca S, Premi S, Gelatti U. Drinking water hardness and chronic degenerative diseases. Part III. Tumors, urolithiasis, fetal malformations, deterioration of the cognitive function in the aged and atopic eczema. (In Italian.) *Ann Ig* 2003; 15: 57-70.
14. Monarca S, Zerbini I, Simonati C, Gelatti U. Drinking water hardness and chronic degenerative diseases. Part II. Cardiovascular diseases. (In Italian.) *Ann Ig* 2003; 15: 41-56.
15. Nardi G, Donato F, Monarca S, Gelatti U. Drinking water hardness and chronic degenerative diseases. Part I. Analysis of epidemiological research. (In Italian.) *Annali di igiene - medicina preventiva e di comunita* 2003; 15: 35-40.
16. Verd Vallespir S, Domingues Sanches J, Gonzales Quintial M, et al. Association between calcium content of drinking water and fractures in children. (In Spanish.) *An Esp Pediatr* 1992; 37: 461-465.
17. Jacqmin H, Commenges D, Letenneur L, et al. Components of drinking water and risk of cognitive impairment in the elderly. *Am J Epidemiol* 1994; 139: 48-57.

18. Yang CY, Chiu HF, Chang C, et al. Association of very low birth weight with calcium levels in drinking water. *Environ Research* 2002; Section A, 89: 189-194.
19. Yang CY, Chiu HF, Chiu JF, et al. Calcium and magnesium in drinking water and risk of death from colon cancer. *Jpn J Cancer Res* 1997; 88: 928-933.
20. Yang CY, Cheng MF, Tsai SS, et al. Calcium, magnesium, and nitrate in drinking water and gastric cancer mortality. *Jpn J Cancer Res* 1998; 89: 124-130.
21. Eisenberg MJ. Magnesium deficiency and sudden death. *Am Heart J* 1992; 124: 544-549.
22. Bernardi D, Dini FL, Azzarelli A, et al. Sudden cardiac death rate in an area characterized by high incidence of coronary artery disease and low hardness of drinking water. *Angiology* 1995; 46: 145-149.
23. Garzon P, Eisenberg MJ. Variation in the mineral content of commercially available bottled waters: implication for health and disease. *Am J Med* 1998; 105: 125-130.
24. Iwami O, Watanabe T, Moon CS, et al. Motor neuron disease on the Kii Peninsula of Japan: excess manganese intake from food coupled with low magnesium in drinking water as a risk factor. *Sci Total Environ* 1994; 149: 121-135.
25. Melles Z, Kiss SA. Influence of the magnesium content of drinking water and of magnesium therapy on the occurrence of desalinized water. *Magnes Res* 1992; 5: 277-279.
26. Yang CY, Chiu HF, Cheng MF, et al. Esophageal cancer mortality and total hardness levels in Taiwan's drinking water. *Environ Research* 1999; 81: 302-308.
27. Yang CY, Chiu HF, Cheng MF, et al. Pancreatic cancer mortality and total hardness levels in Taiwan's drinking water. *J Toxicol Environ Health* 1999; 56: 361-369.
28. Yang CY, Tsai SS, Lai TC, et al. Rectal cancer mortality and total hardness levels in Taiwan's drinking water. *Environ Research* 1999; 80: 311-316.
29. Yang CY, Chiu HF, Cheng MF, et al. Calcium and magnesium in drinking water and the risk of death from breast cancer. *J Toxicol Environ Health* 2000; 60: 231-241.
30. Pribytkov YuN. Status of phosphate-calcium metabolism (turnover) at inhabitants of town Shevchenko using desalinated drinking water. (In Russian.) *Gig Sanit* 1972; 1: 103-105.
31. Rakhmanin YA, Lyncnikova TD, Michailova RI. Water Hygiene and the Public Health Protection of Water Bodies. (In Russian.). Moscow: Acad. Med. Sci. USSR, 1973: 44-51.
32. Rakhmanin YA, Bonasevskaya TI, Lestrovoy AP, et al. Public Health Aspects of Environmental Protection. (In Russian.). Moscow: Acad. Med. Sci. USSR, 1976: (fasc 3) 68-71.
33. Rubenowitz E, Molin I, Axelsson G, Rylander R. Magnesium in drinking water in relation to morbidity and mortality from acute myocardial infarction. *Epidemiology* 2000; 11: 416-421.
34. National Institute of Public Health. Internal data. Prague: 2003.
35. Kondratyuk VA. On the health significance of microelements in low-mineral water. (In Russian.) *Gig Sanit* 1989; 2: 81-82.
36. Mudryi IV. Effects of the mineral composition of drinking water on the population's health (review). (In Russian.) *Gig Sanit* 1999; 1: 15-18.
37. Lutai GF. Chemical composition of drinking water and the health of population. (In Russian.) *Gig Sanit* 1992; 1: 13-15.

38. Anonymous. How trace elements in water contribute to health. WHO Chronicle 1978; 32: 382-385.
39. Haring BSA, Van Delft W. Changes in the mineral composition of food as a result of cooking in "hard" and "soft" waters. Arch Environ Health 1981; 36: 33-35.
40. Oh CK, Lücker PW, Wetzelsberger N, et al. The determination of magnesium, calcium, sodium and potassium in assorted foods with special attention to the loss of electrolytes after various forms of food preparations. Mag Bull 1986; 8: 297-302.
41. Durlach J. (1988) The importance of magnesium in water. In Magnesium in Clinical Practice Durlach J, ed. London: John Libbey & Co Ltd, 1988:221-222.
42. Kramer MH, Herwaldt BL, Craun GF, et al.. Surveillance for Waterborne-Disease Outbreaks—United States, 1993-1994. MMWR 1996; 45 (No. SS-1): 1-33.
43. Anonymous. Epidemiologic notes and reports lead-contaminated drinking water in bulk-storage tanks – Arizona and California, 1993. MMWR 1994; 43(41): 751; 757-758.
44. Thompson DJ. Trace element in animal nutrition. 3rd ed. Illinois: Int. Minerals and Chem. Corp., 1970.
45. Levander OA. Nutritional factors in relation to heavy metal toxicants. Fed Proc 1977; 36: 1683-1687.
46. Oehme FW, ed. Toxicity of heavy metals in the environment. Part 1. New York: M.Dekker, 1979.
47. Hopps HC, Feder GL. Chemical qualities of water that contribute to human health in a positive way. Sci Total Environ 1986; 54: 207-216.
48. Nadeenko VG, Lenchenko VG, Krasovskii GN. Combined effect of metals during their intake with drinking water. (In Russian.) Gig Sanit 1987; 12: 9-12.
49. Durlach J, Bara M, Guet-Bara A. Magnesium level in drinking water: its importance in cardiovascular risk. In: Itokawa Y, Durlach J. eds. Magnesium in Health and Disease. London: J.Libbey & Co Ltd, 1989: 173-182.
50. Plitman SI, Novikov YV, Tulakina NV, et al. On the issue of correction of esalini standards with account of drinking water hardness. (In Russian.) Gig Sanit 1989; 7: 7-10.
51. al-Qarawi SN, el Bushra HE, Fontaine RE. Et al. Typhoid fever from water esalinized using reverse osmosis. Epidemiol Infect 1995; 114: 41-50.
52. Geldreich EE, Taylor RH, Blannon JC, et al. Bacterial colonization of point-of-use water treatment devices. J Amer Water Works Assoc 1985; 77: 72-80.
53. Payment P. Bacterial colonization of reverse-osmosis water filtration units. Can J Microbiol 1989; 35: 1065-1067.
54. Payment P, Franco E, Richardson L, et al. Gastrointestinal health effects associated with the consumption of drinking water produced by point-of-use domestic reverse-osmosis filtration units. Appl Environ Microbiol 1991; 57: 945-948.
55. Levin AI, Novikov JV, Plitman SI, et al. Effect of water of varying degrees of hardness on the cardiovascular system. (In Russian.) Gig Sanit 1981; 10: 16-19.
56. Novikov JV, Plitman SI, Levin AI, et al. Hygienic regulation for the minimum magnesium level in drinking water. (In Russian.) Gig Sanit 1983; 9: 7-11.

57. Kozisek F. Biogenic value of drinking water. (In Czech.) PhD thesis. Praha: National Institute of Public Health, 1992.
58. Rachmanin YA, Filippova AV, Michailova RI. Hygienic assessment of mineralizing lime materials used for the correction of mineral composition of low-mineralized water. (In Russian.) Gig Sanit 1990; 8: 4-8.
59. Muzalevskaya LS, Lobkovskii AG, Kukarina NI. Incidence of chole- and nephrolithiasis, osteoarthritis, and salt arthropathies and drinking water hardness. (In Russian.) Gig Sanit 1993; 12: 17-20.
60. Golubev IM, Zimin VP. On the standard of total hardness in drinking water. (In Russian.) Gig Sanit 1994; 3: 22-23.
61. Guidelines for Drinking-water Quality. 2nd edn, vol. 2, Health Criteria and Other Supporting Information. Geneva: World Health Organization, 1996: 237-240.
62. European Union Council Directive 80/778/EEC of 15 July 1980 relating to the quality of water intended for human consumption. Off J Eur Commun 1980; L229: 11-29.
63. European Union Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption. Off J Eur Commun 1998; L330: 32-54.
64. Anonymous. GOST R 50804-95 Astronaut environment in piloted spaceships – general medical and technical requirements. (In Russian.) Moscow: Gosstandard Rossii, 1995.
65. Sklyar EF, Amiragov MS, Berezkin SV, Kurochkin MG, Skuratov VM. Recovered water mineralization technique. (In Russian.) Aviakosm Ekolog Med 2001; 35(5): 55-59.

13.

NUTRIENT MINERALS IN DRINKING WATER: IMPLICATIONS FOR THE NUTRITION OF INFANTS AND YOUNG CHILDREN

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I. INTRODUCTION

The WHO Global Strategy on Infant and Young Child Feeding emphasizes the importance of infant feeding and promotes exclusive breastfeeding in the first six months of life. In infants who cannot be breast-fed or should not receive breast milk, substitutes are required. These should be a formula that complies with the appropriate Codex Alimentarius Standards or, alternatively, a home-prepared formula with micronutrient supplements (1). Drinking water is indispensable for the reconstitution of powdered infant formulae and needed for the preparation of other breast-milk substitutes. As a result of the long-term intake of a considerable volume in relation to body weight, the concentrations of nutrient minerals in drinking water may contribute significantly to the total trace element and mineral intake of infants and young children. This is especially applicable to formula-fed infants during the first months of life, who may be the most vulnerable group affected by excessive concentrations of nutrients or contaminants in drinking water.

Defining essential requirements of the composition of infant formulae, the importance of the quality of the water used for their reconstitution has been acknowledged by the Scientific Committee on Food, SCF, of the European Commission (2). Although it was noted that the mineral content of water may vary widely depending upon its source, the optimal composition remained undefined. Recommendations for the composition of infant formulae refer to total nutrient content as prepared ready for consumption according to manufacturer's instructions. However, these usually inform the consumer about the quantity of powder and drinking water required as well as other technical advice for the reconstitution of the formula, but do not refer to the mineral concentration in drinking water itself.

The use of desalination to provide drinking water may continue to increase all over the world. Remineralization of mineral content in waters that have been treated by demineralization may provide an opportunity to improve compositional choices. Specific aspects of vulnerable groups have to be considered, but the needs of infants and young children, especially if nourished with infant formula instead of human milk, may be of special concern. The question arises whether special nutrient mineral properties of these waters should be considered for use for infants and young children.

II. ASSESSMENT OF MINERAL INTAKE IN INFANT NUTRITION

Public health decisions about the composition of infant foods and the use of drinking water in infancy require awareness of the approaches used in the study methodology applied to nutrition trials in infancy and early childhood. These approaches may be of crucial importance in the interpretation of the results and potential limitations of their significance for the issues raised.

Analytical results of infant formulae may only refer to analyses of the powder itself or formulae prepared under standardized laboratory conditions with defined water (3). Metabolic studies investigating mineral bioavailability have attempted to exclude or minimize the potential influences of different water supplies, e.g. (4). They therefore have been performed either in the clinic, on metabolic wards, or at home using a standardized water supply or ready-to-feed liquid infant formula. On the other hand, recently published epidemiological trials concerning mineral supplementation in infancy neither assess representative mineral concentrations in the drinking water at a household level or the quantitative water intake (5-7). For example, investigations concerning the effects of copper concentrations in drinking water, analyzed neither the respective nutrition nor representative specimens (8). Finally, studies addressing both drinking water and powdered infant formula referred to the concentrations given by the manufacturer, but analysed the reconstituted formula, too (9).

III. THE QUANTITATIVE INTAKE OF DRINKING WATER IN INFANCY AND EARLY CHILDHOOD

Health and well-being in early childhood are dependent on an optimal supply of essential nutrients. Nutrient requirements for growth necessitate intake and positive retention of essential trace elements and minerals. The immaturity of homeostatic mechanisms in gastrointestinal and renal functions of resorption and excretion also raises a concern over the susceptibility to an excess or a deficiency of nutrients as well as to toxic substances during this crucial period for mental and motor development. A major factor in the nutrient mineral intake from drinking water is the quantity of water consumed.

1. The Choice of Nutrition – a significant Factor of Drinking Water Intake in Infancy

In considering the consumption of drinking water by vulnerable populations, a figure of 0.75 litres per day has been used for a 5kg child and a figure of one litre per day for a 10kg child (10). Although these figures may be applicable for standard calculations, the range of quantitative water intake observed in populations at that age might be considerable according to the Food and Nutrition Board of the Institute of Medicine (11). The choices made in terms of how an infant is fed, especially in the first six months of life, are significant factors in determining the level of nutrient mineral intake from drinking water:

- *Healthy, exclusively breast-fed infants* nourished according to present recommendations (1) will not directly consume drinking water in the first six months of life. They might eventually be indirectly affected by a potential passage of (trace) minerals into human milk. Unfortunately, sometimes the early introduction of supplementary feedings of water, tea or other nutrients is practised. After six months, the introduction of complementary foods and breastfeeding for up to two years of age or beyond is recommended. During this period, household drinking water intake will depend on the extent of breastfeeding and on whether complementary foods are prepared at home or bought commercially.
- *Healthy infants fed powdered infant formula* consume drinking water from the day they are born owing to the fact that it is used to reconstitute the product. Both may contribute to the mineral intake up until complementary foods are introduced. Different sources of water may be used, including tap water, well water, and natural bottled mineral water labelled as suitable for infant nutrition. Specific compositional characteristics of water used in a household or the use of stagnant water are very likely to have an effect throughout the entire formula feeding period if parents are not aware of the potential consequences. Infants are likely to be fed formula prepared at home, while older children or adults may consume considerable amounts

of drinking water from sources outside the household. Powdered formulae do not necessarily originate from the region in which they are consumed and may be subject to specific directives established by the place of origin. Therefore, different ecological and legal factors may independently affect the two components making up the nutrient mineral composition of infant formula.

- *Home-prepared formulas* are more likely to be based on local produce and are affected by local factors such as soil composition, the use of fertilizers or pollution. These may influence, too, the composition of the drinking water in the area. Home-prepared formulae may be prepared with a 1:1 dilution of cow's milk to drinking water with the addition of other components (12). Other concepts are based on a 2:1 dilution of cow's milk (13), with a resulting lower quantitative intake of drinking water. After the age of six months, drinking water intake will also be dependent on the choice of complementary foods and beverages and how they are prepared.
- *The choice of complementary food introduced after six months* may vary widely and it influences the evaluation of the nutrient mineral content in drinking water considerably. Inappropriate increases of the mineral intake may be of concern. Use of foods that are naturally rich in trace elements like zinc and iron (e.g. meat) or minerals like calcium (e.g. dairy products) is recommended, but may not be practised because these foods are not available, affordable or acceptable for the family. This may lead to reliance on predominantly plant-based or vegetarian diets of poor nutritional quality (12, 14). In these situations, and depending on its composition, drinking water may contribute a considerable part of the dietary mineral intake.

Assumptions about the mineral intake in infants may be influenced by factors not directly linked to the actual product composition. The “standard intake” of drinking water calculated by WHO in early infancy is 750 ml (10); the same figure is given by the SCF (2) for infant formula. Most standard instructions for infant formulae require 90g water to 100g formula. Therefore, the basic intake assumptions for the quantitative intake of drinking water in formula-fed infants could differ by approximately 10%. Recent recommendations supported a reduction of the upper margins for caloric density in infant formulae and follow-on formulae. As nutrient requirements for powdered infant formulae are given per 100 kcal intake (e.g. (2)), this results in a reduction of the recommended upper levels of mineral concentrations (-7% or -12%). These examples may only refer to differences of approximately 10%, but they emphasize the need for transparency regarding the factors that influence the final composition of infant formulae.

2. Specific aspects of quantitative intake of drinking water in infancy and childhood

In exclusively breast-fed infants, the mean intake increases from 699g up to 854g at the age of six months (15). The quantitative milk consumption of formula-fed infants exceeds the intake of breast-fed infants at the age of 2-4 months (16). The potential implications for the quantitative intake of household drinking water (Figure 1) have been calculated by re-evaluating data assessed in a longitudinal trial on nutrient mineral supply in breast-fed and formula-fed infants (17, 18):

Exclusive breast-feeding had been recommended for a minimum of four months in infants receiving human milk, the other families were provided with liquid infant-milk formulae. For infants from the age of five months, powdered follow-on formulae, age-specific complementary feeds, powdered cereals and a standard mineral water suitable for infant feeding were supplied. Weighing each meal over a period of 72 hours enabled its nutrient intake to be assessed. Liquid infant formulae were recalculated based on the assumption that the powdered formula and drinking water used corresponded to an equivalent product marketed in Germany. This precept

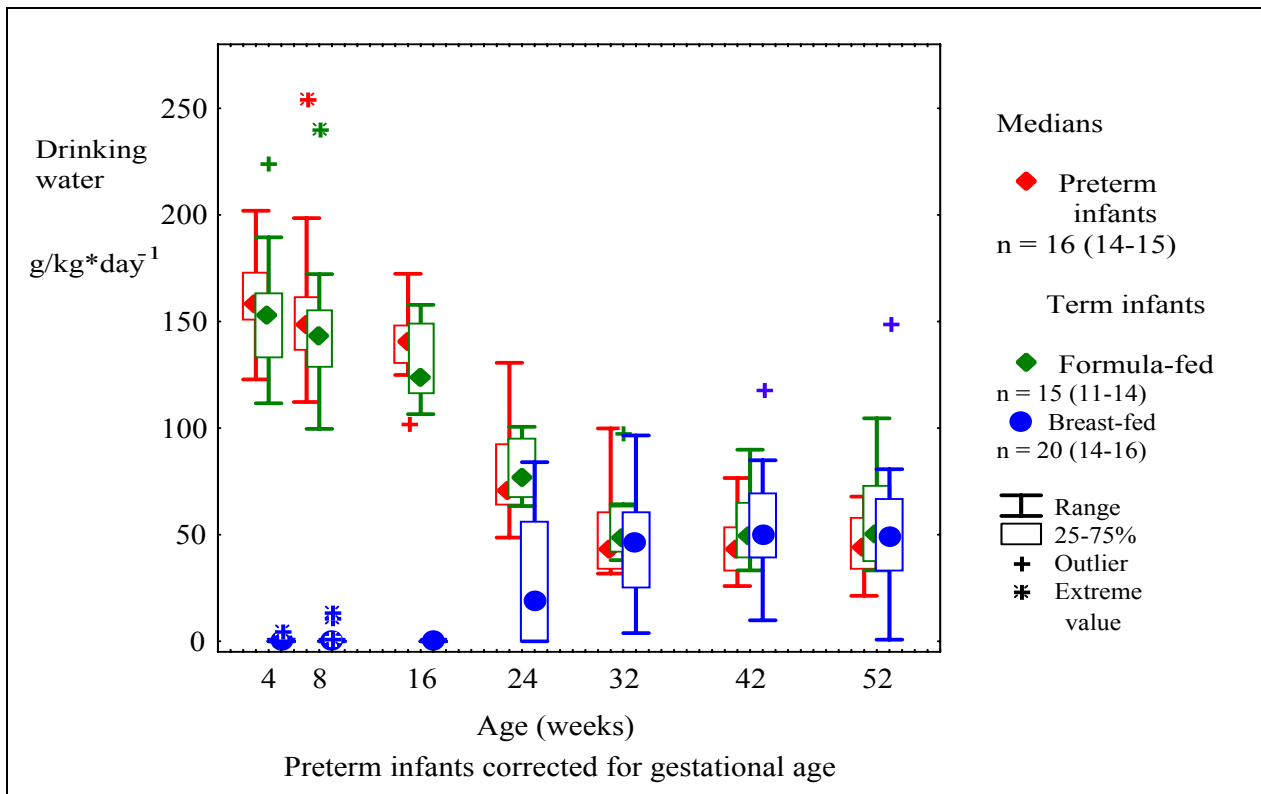
enabled the differences in drinking-water intake between full-term, breast-fed infants and premature or full-term formula-fed infants to be assessed (Figure 1, Table 1). Up until the age of four months, only two breast-fed infants consumed small amounts of drinking water. At the same time, the daily drinking water intake needed for the re-constitution of powdered infant formula decreased from 158 to 140g/kg in premature infants and from 153 to 122.9g/kg in full-term infants. With all families in the study being provided with standardized complementary feeds, it was not until infants reached the age of 32 weeks that comparable intakes of drinking water in all groups (57% of total water intake, Table 1) were attained.

Table 1. Drinking water intake in infancy (median, range)

Age \pm 2 weeks	4	8	16	24	32	42	52
Infants studied	Total water intake, g x kg ⁻¹ x d ⁻¹						
FF-Pt	158.3 (128.1-201.9)	148.0 (123.2-254.2)	140.1 (102.2-172.4)	90.2 (52.9-130.6)	78.5 (58.0-116.2)	77.9 (65.1-110.9)	81.3 (56.9-116.6)
FF-T	152.7 (111.8-224.1)	142.6 (99.6-240.0)	122.9 (106.5-157.8)	94.5 (81.9-117.8)	87.9 (69.3-139.6)	83.7 (53.8-135.3)	77.7 (63.4-149.9)
BF-T	132.7 (81.7-147.7)	111.4 (75.6-153.0)	97.8 (50.1-144.2)	98.8 (66.9-132.2)	84.9 (71.4-140.3)	82.9 (60.0-165.3)	93.7 (49.2-192.2)
	Drinking water intake, g x kg ⁻¹ x d ⁻¹						
FF-PT	158.3 (122.8-201.9)	148.0 (112.3-254.2)	140.1 (102.2-172.4)	70.3 (48.6-130.6)	43.1 (31.7-99.9)	42.9 (25.9-76.6)	43.9 (21.3-67.9)
FF-T	152.7 (111.8-224.1)	142.6 (99.6-240.0)	122.9 (106.5-157.8)	76.5 (63.4-100.6)	47.8 (38.0-97.8)	48.7 (33.3-89.9)	50.0 (33.2-104.6)
BF-T	0.0 (0.0-4.7)	0.0 (0.0-14.0)	0.0	18.6 (0.0-83.9)	46.6 (3.8-96.5)	49.5 (9.8-118.1)	48.9 (0.8-148.8)
	Drinking water intake, % of total water intake						
FF-PT	100.0 (95.8-100.0)	100.0 (91.1-100.0)	100.0 (98.9-100.0)	88.2 (65.4-100.0)	57.7 (41.4-85.9)	53.3 (39.6-73.5)	55.2 (37.4-71.9)
FF-T	100.0	100.0 (99.9-100.2)	100.0	81.7 (67.8-100.0)	57.7 (48.1-70.1)	58.2 (54.8-75.1)	58.9 (44.8-70.4)
BF-T	0.0 (0.0. to 3.6)	0.0 (0.0-11.4)	-	16.8 (0.0-84.3)	57.0 (4.6-71.6)	63.8 (12.2-77.3)	66.3 (0.9-81.3)

FF-PT: Premature, formula-fed infants, investigated in parallel with term infant groups, gestational age at birth 29 (25 – 32) weeks; fed cow's-milk-protein-based infant formula at least up until the age of 16 weeks, corrected for gestational age; n= 16 (14-15) infants. FF-T: Term, formula-fed infants, fed cow's-milk-protein-based infant formula at least up until the age of 16 weeks; n=15 (11-14) Infants. BF-T: Term, exclusively or predominantly breast-fed infants up until the age of 16 weeks; n = 20 (14-16) infants.

Figure 1. Household drinking water intake of breast-fed term infants and formula-fed term and preterm infants (based on mineral nutrition studies: 17, 18).



These drinking water intakes exceed those assessed in the DONALD (Dortmund Nutritional and Anthropometrical Longitudinally Designed) Study (19). The authors reported that in formula-fed infants, the daily intake decreased longitudinally from 107 ± 28 g/kg at three months to 33 ± 25 g/kg at twelve months of age. Comparing specifically the tap-water intake of formula- and breast-fed infants, the mean total daily tap-water intake in breast-fed infants observed throughout the first year was 15 ± 23 g/kg and, of formula-fed infants, 49 ± 33 g/kg. Between the ages of one and three years, tap-water intake averaged 15 ± 20 g/kg. The differences may be explained by several factors: the DONALD study omitted early infancy up until 3 months of age, where higher intakes are observed. Lower intakes of tap drinking water may be indicative of a higher proportion of home-prepared meals. The DONALD study also reported on water intake in school children (20) and assessed the hydration status of children aged 4 to 10.9 years through the analysis of water intake, urine volume and urine osmolality. Based on their estimates of adequate daily total water intake, the authors confirmed the total water intake of 1.0 ml/kcal in children that was recommended earlier (21). The mean intake volumes reported for the age groups 4.0-6.9 and 7.0-10.9 were 1495 g and 1834 g for boys, and 1318 g and 1545 g for girls. The trends over the 15-year period of the study revealed an increase in total water intake in 2-13-year-old children irrespective of sex, attributable to increased beverage consumption on the one hand, and decreased milk, coffee/tea and soft-drink consumption on the other (22). The results may be influenced by regional aspects and the high interest in nutrition documented by the longitudinal participation in the trial. Other authors have been rather concerned about consumption of large quantities of squash on the one hand and the low consumption of plain water on the other (23).

IV. THE CONTRIBUTION OF DRINKING WATER TO NUTRIENT MINERAL INTAKE IN INFANCY AND EARLY CHILDHOOD

The potential significance of mineral nutrients in infant nutrition, but especially in human milk, has attracted a great deal of attention over the last few decades (2, 14, 15). The upperbound acceptable mineral concentrations in WHO Drinking Water Guidelines, mature human milk, and the recent recommendations on the composition of infant formulae and follow-on formulae are compared in Table 2. Age-specific nutrient recommendations from different authorities have been compiled by Olivares (24). In view of the specific needs of this age group and recent modifications in the assumptions of adequate intakes in infancy, some aspects of current guidelines or directives for drinking water may be reconsidered. The evaluation of adequacy or optimization potential in terms of feeding infants and young children have preferably to be based at household level to enable the assessment of leaching from water pipes or contamination by other sources.

Public health recommendations should take into account that both desalinated water (25) and infant formula (26) are manufactured products and offer the potential of influencing the final nutrient mineral supply to the infant. Remineralization of processed waters should aim to achieve concentrations that are acceptable when combined with infant formulae but which are potentially useful in early childhood thereafter. However, the assessment may differ for each mineral under consideration.

1. Manganese and Molybdenum.

Manganese and molybdenum concentrations set out in the WHO drinking water guidelines (10, 27) are much higher than those observed in human milk and in the recommendations regarding their respective daily adequate intake (28), Table 2.

Manganese is an essential nutrient in the formation of bone, amino acids, cholesterol and carbohydrate metabolism and present in the metalloenzymes arginase, glutamine synthetase, and manganese superoxide dismutase. The recommended adequate intake (AI) is based on the intake from human milk and set at 0.003mg/day in the first six months (preceding recommendation: 0.3-0.6 mg (21)). Thereafter, an increased intake of 0.6mg/day (7-12 months) and 1.2mg/day for children aged 1-3 years (28) has been recommended. During the last decade other recommendations and directives have also decreased considerably: In Germany, infant formulae for special medical purposes had to provide 0.5 to 2mg manganese per day, equivalent to 0.66 to 2.67mg/L (29), but actual requirements are set at 0.325 to 1.3 mg/L (30). Analytical results of formulae ranged from 0.0 to 7.8mg Mn/L (3), with high concentrations observed in soy-protein-based formulae and formulae for special medical purposes. Subsequently considerably lower results were assessed (0.44 and 0.53mg Mn/L, (31)). Recommendations for infant milk formulae yielded a range of 1-100µg/100kcal (2), equivalent to 0.007 to 0.65mg Mn/L. Therefore, regardless of any change in drinking water composition or respective regulations, the potential significance of the contribution of drinking water supply to infant nutrition has increased considerably.

Table 2. Trace minerals in human milk and in drinking water guidelines

Mineral	Mature human milk (Lawrence and Lawrence 1999, (54))	Drinking water guidelines (WHO 1996 (27))	EC, SCF 2003 (2) (Recommended energy content: 60-70kcal/dl; based on 65kcal/dl, cow's-milk- protein- based formula)
	mg/L	mg/L	mg/L
Calcium (mg/L)	280	n.g.	325-910 (Ca:P=1-2)
Iron (mg/L)	0.40	0.3 ^b	1.95-8.45
Zinc (mg/L)	1.2	3.0 ^b	3.25-9.75
Copper (mg/L)	0.25	1.0 ^b ; 2.0 ^a (P)	0.228-0.65
Selenium (µg/L)	20	10 ^a	20-59
Fluoride (mg/L)	0.016	1.5 (P)	≤ 0.65
Magnesium (mg/L)	30	n.g.	33-98
Sodium (mg/L)	180	200 ^a	130-390
Sulphate (mg/L)	140 (sulphur)	250 ^a	n.g.
Chloride (mg/L)	420 (chlorine)	250 ^a	325-1040
Manganese (µg/L)	6	100 ^b ; 500 ^a (P)	6.5-650
Molybdenum (µg/L)	2µg/d ^c	70 ^a	n.g.

^a Health-based guideline value, (P): provisional; ^b Parameters in drinking water that may give rise to complaints from consumers, ^c FNB (28)

A WHO guideline value has been set at 0.5mg/L based upon aesthetics for manganese in drinking water (27). Powdered infant formula with the mean recommended manganese concentration (0.325mg/L) would exceed the maximum suggested by the SFC (2) if prepared with drinking water in the upper range of WHO guideline values. Animal studies (32, 33) indicate that neonatal manganese metabolism may be of special concern. Balance studies in infants confirmed substantial quantitative manganese retention in infants fed special diets as a result of metabolic disease or in premature infants fed routine mineral supplements and containing manganese by contamination (34, 35). Recommendations concerning drinking water for the reconstitution of infant formulae should take into consideration the low concentration in human milk and concerns about the safety of high manganese intakes. In situations where high manganese concentrations in drinking water cannot be avoided, the potential combination with formulae of high manganese content with high manganese water should be discouraged.

Molybdenum is a co-factor in the enzymes sulphite oxidase, xanthine oxidase and aldehyde oxidase (36). The adequate intake in infants and young children has been set for the age of 0-6 months at 2µg/day, derived from the intake by human milk (preceding recommendation: 15-30µg/day; (21)). In contrast to manganese, however, the AI for the age 7-12 months has been derived from the likely intake with human milk as a sole source (3µg/day) and not from the estimated intake with a mixed diet (28). This value will be greatly exceeded by formula-fed infants and by infants nourished with the recommended complementary feeds (37). The

uncertainty over molybdenum requirements is also reflected in the tolerable upper intake (UL) level defined for adults with 0.01mg/kg body weight (38) or, alternatively, 0.03mg/kg body weight (28). Both were based on the same trial (39), but differed in the assessment of the uncertainty factors. Despite concern about the infant's capacity to deal with excess amounts of Mo, no UL has been set for infancy.

The upper level of Mo intake has been set at 10µg/100kcal for nutrients for special dietary purposes in infancy (30). An infant formula prepared in accordance with this directive may result in a daily Mo uptake > 10µg/kg. In addition, an upper guideline value of 70µg/L has been set for drinking water (10). The maximum Mo intake by water used for powdered formula preparation exceeds 10µg/kg at an intake of 150ml/kg or more. This volume, however, is quite common in premature and young full-term infants (Figure 1) and unsupplemented infant formulae repeatedly contained > 100µg/L (40). The threshold for long-term safe molybdenum intake in infancy may need to be reconsidered and re-evaluated by studies in areas with naturally longterm high molybdenum intakes by drinking water before present WHO guidelines are extended on other processed waters.

2. Copper

Both copper deficiency and excess are of clinical importance: copper deficiency has been described in premature infants and is characterized by oedema, anaemia, leucopenia, neutropenia and osteoporosis (41). On the other hand, concerns have been raised after the description of Non-Indian Childhood Cirrhosis associated with excessive copper concentrations in well waters with a low pH and copper pipes (42). Examinations in a subgroup of infants from households with copper concentrations exceeding 0.8mg/L yielded no indication of a hazard resulting from copper pipes connected to public water supplies (8). The safety of the WHO guideline value (2mg/L) for copper in drinking water during infancy has been supported (43). Leaching from copper pipes and other potential problems of infant formula preparation have raised concern and have been addressed in respective recommendations (44).

Differences in the quality of water available from the tap or directly drawn at the water plant may be important in terms of its suitability in infancy and early childhood. The problems of the use of well water have to be considered in both developed and developing countries, though the proportion of public water supply and the use of home wells may vary considerably. In Germany, in 1998, only 2.5% of the drinking water supply was derived from well supplies. However, more than 58% of the [adult] study population consumed first-draw drinking water for their personal consumption (45). Concerns arise that common awareness of problems caused by the application of this practice to formula preparation cannot be assumed.

The FNB (28) recommendations in the first year for adequate copper intake, based on intake by human milk and adequate complementary feeds thereafter, were set for the first 6 months at 200µg/day and, in the 7-12 months thereafter, at 220µg/day. For young children of 1-3 years, the intake was set at 340µg/day. Regulations for both components of infant formulae - the powdered formula and the water - have declined considerably during the last few years: In the past, national directives for copper intake by foods for medical purposes in infancy were set at 0.5 to 2mg Cu per day, equivalent to 0.670 to 2.7mg/L formula (29). This has been reduced to 0.130 to 0.780mg Cu/L formula (30), slightly lower values are recommended in infant formulae (2). At the same time, the WHO Guideline value of 2mg/L (27) has been transferred into present regulations on drinking water, which formerly set a cut-off value of 3mg/L (46, 47). These changes result in a reduction of the upper margin of daily copper intake from > 4 mg/d to 2 mg/d at an intake of 750 ml/d.

3. Iron and zinc

Iron and zinc drinking guideline values are only set at levels that may give rise to complaints from consumers (27). Recommendations for both elements in infant food other than human milk have to take into consideration the importance of bioavailability (14). Other than for manganese, molybdenum and copper, these are within the concentrations observed in mature (iron) human milk or colostrum and transitional human milk (zinc), Table 2.

The low iron intake recommended in the first six months of life by the FNB (28), 0.27mg Fe/d, is based on the highly bioavailable intake with human milk. Thereafter, however, increased intakes are needed to cover the demands of growth, especially the increase in blood volume (7-12 months: 11mg/d; 1-3 years: 7mg/d). The American Academy of Pediatrics (48) advocated an iron supplementation of 4-12mg/L of infant formulae. The SCF (2) of the European Commission regarded 2-8mg/L as suitable for cow's-milk-based infant formula and 6-15mg/L for soy-based follow-on formula. 2mg/L in drinking water were not considered to present a hazard to health, but it has been assumed that acceptability would usually be affected above 0.3mg Fe/L because of the staining of laundry and plumbing fixtures (27). Therefore, in infants fed iron supplemented formulae, the contribution of drinking water to the iron intake may be of minor importance.

This assessment may be different in infants fed home-prepared, non-supplemented formulae or complementary feeds. In Bangladesh, children drinking water containing > 1mg Fe/L were significantly taller than those drinking < 1mg Fe/L (49). The higher iron concentrations were caused by soil characteristics and high concentrations occurred in clusters of tube wells. However, other minerals present in the soil along with iron may have promoted linear growth too. The effects of other trace elements (e.g. zinc, copper) have not been reported in a trial investigating the fortification of drinking water with iron for pre-school children attending day-care community institutions in Brazil. A reduction of anaemia in preschool children in a day care centre and in families with a low socio-economic status (50, 51) was assessed.

Zinc in colostrum may exceed 10mg/L, declining continuously down to a level of about 1.2mg/L at 4 months (52). Despite the high bioavailability of zinc in human milk, it may be difficult to satisfy needs adequately after a period of four to six months (15). In view of different bioavailability depending on the nutritional source, intake recommendations range from 1.1 to 6.6mg/day during the first six months of life, and 2.5 to 6.4mg/day thereafter (14). The FNB (28) recommended 2 and 3mg respectively, based on the zinc concentration in human milk as the basic source. Recommendations for infant and follow-on formulae (2) in accordance with the current infant formulae EC directive, yield 3.3–10mg/L or, if based on soy protein, 4.9–15.6mg/L. The upper level of tolerable zinc intake for children aged 1-3 years (53) has been set at 7mg/day. Water yielding a zinc concentration within the upper range of WHO guideline values (3mg/L, Table 2) might contribute considerably to the zinc intake in infancy.

4. Calcium and Magnesium

The calcium and magnesium concentrations in cow's milk far exceed those present in human milk (54) and have to be modified e.g. during the manufacturing of infant formulae based on cow's milk protein. The adequate intake (AI) for calcium has been set at 210mg (formula-fed infants: 315mg/d), 270mg and 500mg, respectively, for ages 0-6 and 7-12 months and 1-3 years. The AI for magnesium was set at 30mg (formula-fed infants: 35mg) and 75mg (0-6 and 7-12 months) and for ages 1-3 years the RDA was set at 80mg (11). The ranges recommended for infant formulae by the SCF (2) were 325-910mg/L Ca and 33-88mg/L Mg, respectively. Lesser absorption from infant milk formula compared to human milk has been considered, therefore the minimum requirements are set above that found in human milk.

High mineral concentrations in water increase the renal solute load and, therefore, are of concern in infancy. For natural mineral water labelled as “suitable for the feeding of infants”, the Committee on Nutrition of the German Society of Paediatrics (55) advocated, amongst others, concentrations of < 20mg Na/L and < 200mg/L sulphate. The Committee assessed that, at that time, the cut-off value for sulphate (200mg/L) in mineral waters with a sodium concentration < 20mg/L led to a natural limitation of the calcium and magnesium concentration. In view of this finding, no cut-off value for calcium and magnesium was set. In Switzerland, however, a cut-off value has been set for calcium < 200mg/L and magnesium < 40mg/L (56). Public drinking water in Germany yielded a mean concentration of 66.4 (0-555.9) mg/L calcium and 11.8 (0-555.9) mg/L magnesium (57). Transparency should be provided for the consumer with respect to Ca and Mg concentrations in public drinking water, this may not be achieved by referring to “water hardness”. Older infants fed mainly plant-based complementary foods and young children on vegetarian nutrition may benefit from drinking water contributing to calcium and / or magnesium intake.

5. Sodium

Children, the elderly, and persons with compromised renal systems are more susceptible than healthy adults to harmful effects of high sodium intake. The FNB (28) set the adequate intake (AI) at 120mg, derived from the intake of breast-fed infants. In accordance with respective regulations in the USA, the regulation for infant milk formulae in Europe supports an intake of 20-60mg/100kcal (58), equivalent to 127-292.5mg Na/d. Mineral quantities have been calculated and incorporated into baby formula by the manufacturers in accordance with current directives.

Actual data on sodium metabolism in infants fed modern infant milk formulae, however, are scarce and the interpretation has to take into account specific information: longitudinal sodium balance studies in infancy compared ready-to-feed liquid infant milk formula-fed (269mg Na/L) infants with breast-fed (138mg Na/L) infants (4). The daily retentions observed were 11.5mg/kg and 9.2mg/kg, respectively. The actual composition of this brand marketed as powdered infant formula has a sodium content of 120mg Na/100g powder. In Germany, a mean sodium drinking water concentration of 12.4 (<1.0-210) mg/L has been observed (59), concentrations exceeding 150mg/L are the rare exception. The upper level of the Drinking Water Ordinance is 200mg/L (47), equivalent to respective WHO guidelines. Prepared according to current recommendations for the preparation of infant feeds/formula in the first months of life (12, 44), these factors may theoretically result in a considerable range of sodium intake:

- Up to 186mg/L (formula + bottled mineral water labelled as suitable for the preparation of infant formula, containing \leq 20mg/L).
- Up to 366mg/L (formula + drinking water with the upper limit of 200mg/L).
- Up to 310 or 490mg/L, respectively, through the components drinking water (as used in 1) or 2) and cow’s milk (580mg/L,(54)) if parents insist on the use of home-prepared formula and prepare it according to Kersting (12).

These examples also highlight potential hazards; drinking water with high sodium concentrations may elevate the sodium concentration of infant formulae considerably. Cow’s-milk-based infant formulae with low sodium content may be either not available, not affordable or inadequately prepared owing to regional or social constraints. The home-prepared replacement formula recipe described by WHO/UNICEF/UNAIDS (13) comprises a 2:1 dilution of cow’s milk with drinking water and added sugar. Cow’s milk contains more sodium than human milk; the sodium concentrations to be expected will range from slightly less than 406mg/L up to 586mg/L

or above (based on the recommendation of $\leq 20\text{mg/L}$ for bottled drinking water for infant use to $\leq 200\text{mg/L}$ for drinking water). Other minerals may potentially increase the renal solute load, too, necessitating higher quantities of water available to form urine in view of the reduced ability of infants to concentrate urine. This may reduce the margin of safety, especially under conditions of stress, such as infections accompanied by fever.

Where definite problems exist with drinking water (e.g. excessive nitrate content), packaged mineral water should be considered as an alternative to drinking water from the public supply. The infant formula industry does try to lower the higher mineral concentration of cow's milk compared to human milk, but with the addition of mineral waters this content may be increased again. Considerable ranges for sodium in packaged mineral waters have been observed in Europe (26.6 (1.3-1723.0) Na, (60)). This necessitates transparency as to whether a product is suitable for the use in infant nutrition or not. Paediatric recommendations for the suitable composition of packaged waters for use in infant feeding were set at $<20\text{mg Na/L}$ (44, 55). A certain contradiction arises in view of the previously mentioned cut-off value for public drinking water (200mg/L). However, these differences may scarcely be of practical relevance for public drinking water in Germany. In other regions, where sodium concentrations exceeding 180mg/L have been repeatedly described in drinking water (9,61), the assessment may differ considerably and preferable choices should be considered if processed water yields options.

Concern has been raised due to higher blood pressure in infants fed infant formulas with a higher sodium content due to the concentration in the drinking water (9). In addition, an association between formula feeding and blood pressure later in life has been found and attributed in part to the difference in sodium content between human milk and infant formula (62). There is a need for epidemiological studies that focus on the potential health effects of different concentrations of sodium and other [trace] mineral supply by drinking water on infants and young children. These should be conducted in regions where "natural experiments" render exposures close to the upper margins of current recommendations and necessitate these evaluations in view of potential consequences for the use of drinking water.

Especially in infancy, fluid consumption may serve nutritional purposes including caloric requirements but it also plays an important role in hydration. This is obvious in cases of diarrhoea, where increased fluid intake is necessary for rehydration and ORS (oral rehydration solution) recommended. A reduction in morbidity has been achieved by lowering the sodium concentration of the former standard solution from 90 to 75 mmol/L (2070mg/L to 1725 mg/L) (63). Oral rehydration solutions containing 60mmol/L (1380 mg/L) have been recommended in Europe in view of the concern over hypernatraemia or the osmotically-driven increase in stool output, especially in infants and young children (64).

Other hazards concerning sodium in infancy may arise from inadequate feeding practices. Hyponatremic seizures resulting from water intoxication have been associated with bottled drinking water used as an inexpensive "supplement" to cow's-milk-based infant formula (65). The labelling had been misinterpreted to indicate that the product had been produced specifically for infants and contained nutrients adequate for use as a feeding supplement. Inadequate dilution of infant foods may result in nutritionally insufficient feeding. Misjudgement, inexperience or poverty may lead to the use of bottled water products marketed specifically for infants as an affordable and appropriate feeding supplement. These aspects underline the importance of adequate labelling and instructions for the parent or carer.

V. CONCLUSIONS

Public health recommendations on infant nutrition should consider the complete process that includes all the stages involved in the source of the nutrients. This refers to the choice of the base ingredients used for the production of manufactured or home-prepared products well as to the provision of adequate instructions for the reconstitution and the feeding to the infant. Water companies should comply with existing guidelines and legislation, however the quality of water available from the tap may differ from that at the water plant and additional water treatment is possible at household level. Transparency in terms of a water's suitability for infant and child nutrition is essential for the consumer to make an informed choice. Depending on region and social status, consumers may have a choice of water (tap, mineral, bottled water) or have to accept what is available. Social inequalities and lack of information may result in non-recommended practices of infant feeding that can cause inadequate mineral intake.

Guidelines that are to be effective in terms of trace element intake in infants and young children have to consider age-specific trace element requirements. It is essential that they take into account the combined effects of general recommendations on infant feeding on a comparable organizational level. For example:

- *The WHO global strategy on infant and young child feeding* and specific recommendations for trace mineral and mineral intakes in infancy;
- The Standards of the Codex Alimentarius for infant formulae;
- The WHO/UNAIDS/UNICEF recommended (and other) recipes for home-prepared replacement milks for infants of HIV-infected mothers, and
- The WHO Guidelines for Drinking Water Quality.

The awareness of potential variations and analysis of the water used by a population is important for epidemiological assessments of the trace element supply in infancy. Intervention studies in communities in the intention of changing water sources or treatment could facilitate the evaluations of the implications of different mineral intakes in infancy and early childhood. The natural occurrence of concentrations in drinking water within the upper range of WHO drinking water guidelines may support the assessment of the safety for some minerals (e.g. molybdenum). In view of the consequences for public health recommendations and potential consequences for infant morbidity on the one hand, and potential economic consequences for governments and households on the other, there is a need for further scientific evidence of the optimal mineral concentrations in drinking water in early childhood.

References

1. WHO, World Health Organization, and UNICEF. Global Strategy for Infant and Young Child Feeding. Geneva: World Health Organization, 2003.
2. SCF, Scientific Committee on Food. Report of the Scientific Committee on Food on the Revision of Essential Requirements of Infant Formulae and Follow-on Formulae. SCF/CS/NUT/IF/65, 2003.
3. Lönnerdal B, Keen CL, Ohtake M, Tamura T. Iron, zinc, copper, and manganese in infant formulas. *Am J Dis Child* 1983;137:433-437.
4. Schulz-Lell G, Dörner K, Oldigs H-D, et al. Sodium and potassium metabolism in infancy. *Monatsschr Kinderheilkd* 1992;40:117-121.
5. Dijkhuizen MA, Wieringa FT, West CE, et al. Effects of iron and zinc supplementation in Indonesian infants on micronutrient status and growth. *J Nutr* 2001;131:2860-2865.
6. Lind T, Lönnerdal B, Stenlund H, et al. A community-based randomized controlled trial of iron and zinc supplementation in Indonesian infants: interactions between iron and zinc. *Am J Clin Nutr* 2003;77:883-890.
7. Penny ME, Marin R, Duran A, et al. Randomized controlled trial of the effect of daily supplementation with zinc or multiple micronutrients on the morbidity, growth, and micronutrient status of young Peruvian children. *Am J Clin Nutr* 2004;79:457-465.
8. Zietz BP, Dieter HH, Lakomed M., et al. Epidemiological investigation on chronic copper toxicity to children exposed via the public drinking water supply. *Sci Total Environ* 2003;302:127-144.
9. Pomeranz A, Dolfen T, Korzets Z, et al. Increased sodium concentrations in drinking water increase blood pressure in neonates. *J Hypertension* 2002;20:203-207.
10. WHO. Guidelines for drinking-water quality. Recommendations, 2nd edition. Geneva: WHO, 1993.
11. FNB, Food Nutrition Board, Institute of Medicine. Dietary reference intakes for water, potassium, sodium, chloride, and sulphate. Washington, D.C.: The National Academies Press, 2003.
12. Kersting M. Ernährung des gesunden Säuglings: Lebensmittel- und mahlzeitenbezogene Empfehlungen. *Monatsschr Kinderheilkd* 2001;149:4-10.
13. WHO, UNAIDS, UNICEF. HIV and infant feeding counselling: A training course. Geneva: World Health Organization, 2000.
14. FAO, Food and Agriculture Organization and WHO, World Health Organization. Human vitamin and mineral requirements. Report of a Joint FAO/WHO Expert Consultation, Bangkok, Thailand. Rome: FAO/WHO, 2001.
15. Butte NF, Lopez-Alarcon MG, Garza C. Nutrient adequacy of exclusive breastfeeding for the term infant during the first six months of life. Geneva: World Health Organization, 2002.
16. Hofvander Y, Hagman U, Hillervik C, Sjölin S. The amount of milk consumed by 1-3 months old breast- or bottle-fed infants. *Acta Paediatr Scand* 1982;71:953-958.
17. Sievers E, Schleyerbach U, Garbe-Schönberg D, et al. Zinc intakes and plasma concentrations in infancy. *Adv Exp Med Biol* 2000;478:383-4.

18. Sievers E, Schleyerbach U, Arpe T et al. Molybdenum supply of very low-birth-weight premature infants during the first months of life. *Biol Trace Elem Res* 2001;80:97-106.
19. Hilbig A, Kersting M, Sichert-Hellert W. Measured consumption of tap water in German infants and young children as background for potential health risk assessments: data of the DONALD Study. *Food Addit Contam* 2002;19:829-836.
20. Manz F, Wentz A, Sichert-Hellert W. The most essential nutrient: Defining the adequate intake of water. *J Pediatr* 2002;141:587-592.
21. FNB, Food and Nutrition Board, Commission on Life Sciences, National Research Council. Recommended Dietary Allowances. 10th Edition. Washington D.C.: National Academy Press, 1989.
22. Sichert-Hellert W, Kersting M, Manz F. Fifteen year trends in water intake in German children and adolescents: Results of the DONALD Study. *Acta Paediatr* 2001; 90:732-737.
23. Petter LPM, Hourihane JO, Rolles CJ. Is water out of vogue? A survey of the drinking habits of 2-7 year olds. *Arch Dis Child* 1995;72:137-140.
24. Olivares M. Comprehensive Overview Paper: Essential Nutrients in Drinking Water . In: Present publication, in press.
25. Cotruvo J. Desalination Guidelines Development for Drinking Water: Background. In this publication.
26. Tomita M. New technologies and their application in the milk industry. *Asian-Aus. J. Anim. Sci., Animal Production for a Consuming World* 2000;13(suppl):376-382.
27. WHO and World Health Organization. Guidelines for drinking-water quality. Health criteria and other supporting information. Geneva: WHO, 1996.
28. FNB, Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes: Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zinc. Washington DC: National Academy Press, 2001.
29. BMJFFS, Bundesminister für Jugend Familie Frauen und Gesundheit. Verordnung zur Änderung der Nährwert-Kennzeichnungsverordnung und der Diätverordnung. *Bundesgesetzblatt*, 1988;Teil 1:677-693.
30. EC, European Commission. Commission Directive 1999/21/EC on dietary foods for special medical purposes. *Official Journal of the European Communities* 1999;L 91:29-36.
31. Krachler M, Rossipal E, Irgolic KJ. Trace elements in formulas based on cow and soy milk and in Austrian cow milk determined by inductively coupled plasma mass spectrometry. *Biol. Trace Elem. Res* 1998;65:53-73.
32. Keen CL, Bell JG, Lönnerdal B. The effect of age on manganese uptake and retention from milk and infant formulas in rats. *J Nutr* 1986;116:395-402.
33. Tran TT, Chowanadisai W, Lönnerdal B, et al. Effects of neonatal dietary manganese exposure on brain dopamine levels and neurocognitive functions. *Neurotoxicology* 2002;145:1-7.
34. Sievers E, Oldigs H-D, Dörner K, et al. Trace element excess in PKU diets ? *J. Inher Metab Dis* 1990;13:897-905.
35. Sievers E, Kollmann M, Oldigs H-D, et al. Manganese (Mn) balances in preterm infants. In: Momcilovic B, ed. Trace elements in man and animals 7; 7th International Congress on

Trace Elements in Man and Animals (TEMA 7) Dubrovnik (Yu) 1990, Nova Gradiska, GTP Gembarovski, 1990:11-14-11-16.

36. Turnlund JR. Molybdenum metabolism and requirements in humans. In: Sigel A et al. eds. Metal ions in biological systems. Molybdenum and tungsten: Their roles in biological processes, New York, Basel: Marcel Dekker, Inc. 2002;39:727-739.
37. Anke M, Lösch E, Glei M et al. Der Molybdängehalt der Lebensmittel und Getränke Deutschlands. In: Anke M ed. Mengen- und Spurenelemente, 13. Arbeitstagung. MTV Hammerschmidt GmbH, Gersdorf, 1993:537-553.
38. European Commission – Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Molybdenum. ACF/CS/NUT/UPPLE/22, 2000.
39. Fungwe TV, Buddingh F, Demick DS, et al. The role of dietary molybdenum on oestrous activity, fertility, reproduction and molybdenum and copper enzyme activities of female rats. Nutr Res 1990;10:515-524.
40. Sievers E. Nutrient requirements for preterm infant formulas - molybdenum. J Nutr 2003;133:236-237.
41. Sutton AM, Harvie A, Cockburn F, et al. Copper deficiency in the preterm infant of very low birthweight. Arch Dis Child 1985;60:644-651.
42. Dieter HH, Schimmelpfennig E, Meyer E, Tabert M. Early childhood cirrhosis (ECC) in Germany between 1982 and 1994 with special considerations of copper aetiology. Eur. J Med Res 1999;4:233-242.
43. Olivares M, Pizarro FSH, Lonnerdal B, Uauy R. Copper in infant nutrition: safety of World Health Organization provisional guideline value for copper content of drinking water. J Pediatr Gastroenterol Nutr 1998;26:251-257.
44. Committee on Nutrition, German Society of Pediatrics. Hinweise zur Zubereitung und Handhabung von Säuglingsnahrungen. Monatsschr Kinderheilkd 2004;152:318-320.
45. Becker K, Kaus S, Helm D, et al. Umwelt-Survey 1998, Band IV. Trinkwasser, Elementgehalte in Stagnationsproben des häuslichen Trinkwassers der Bevölkerung in Deutschland. Berlin: Fa. Werbung und Vertrieb, 2001.
46. BMJFG, Bundesminister für Jugend Familie Frauen und Gesundheit. Verordnung zur Änderung der Trinkwasser-Verordnung und der Mineral- und Tafelwasser-Verordnung. Bundesgesetzblatt 1990;I:2600-2629.
47. BMG, Bundesministerin für Gesundheit, and BMEVL, Bundesministerin für Ernährung Verbraucherschutz und Landwirtschaft. Verordnung zur Novellierung der Trinkwasserverordnung vom 21. Mai 2001. Bundesgesetzblatt 2001;24:959-981.
48. AAP, American Academy of Pediatrics, Committee on nutrition. Iron fortification of infant formulas. Pediatrics 1999;104:119-23.
49. Briend A, Hoque BA, Aziz KMA. Iron in tubewell water and linear growth in rural Bangladesh. Arch Dis Child 1990;65, 224-237.
50. Dutra-de-Oliveira JE, Ferreira JB, Vasconcellos VP, Marchini JS. Drinking water as an iron carrier to control anemia in preschool children in a day-care center. J Am Coll Nutr 1994;13:198-202.

51. Dutra-de-Oliveira JE and Nogueira de Almeida CA. Domestic drinking water - an effective way to prevent anaemia among low socioeconomic families in Brazil. *Food Nutr Bull* 2002;23:213-216.
52. Dorea JG. Zinc in human milk. *Nutr Res* 2000;20:1645-1687.
53. SCF, Scientific Committee on Food . Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Zinc. SCF/CS/NUT/UPPLEV/62, 2003.
54. Lawrence RA, Lawrence RM: Breastfeeding. A guide for the medical profession. St.Louis, Missouri: Mosby Inc., 1999.
55. Committee on Nutrition, German Society of Pediatrics. Zur Zubereitung von Säuglingsnahrung mit Mineralwasser. *Sozialpädiatrie* 1991;13:722-728.
56. Committee on Nutrition, Swiss Society of Pediatrics. Mineralwasser zur Herstellung von Säuglingsnahrung. *SÄZ* 1990;71:487-489.
57. Schimatschek HF. Vorkommen, Bedeutung und Analytik von Calcium und Magnesium. In: Grohmann A, Hässelbarth U, Schwerdtfeger W, ed. *Die Trinkwasserverordnung*, 4th edn., Berlin, Erich Schmidt Verlag, 2003:511-515.
58. EEC, European Commission. Commission Directive 91/321/EEC on infant formulae and follow-on formulae. *Official Journal of the European Communities*, 1991:35-49.
59. Wolter R . Erhebung BIBIDAT 1989, cited in: Großklaus R, Vorkommen, Bedeutung und Bestimmung von Natrium und Chlorid. In: Grohmann A, Hässelbarth U, Schwerdtfeger W, eds. *Die Trinkwasserverordnung* 4th edn. Berlin, Erich Schmidt Verlag 2003:547-555.
60. Misund A., Frengstad B, Siewers U, Reimann C (1999) Variation of 66 elements in European bottled mineral waters. *Sci Total Environ* 1999;243/244 :21-41.
61. Alam IA, Sadiq M. Metal contamination of drinking water from corrosion of distribution pipes. *Environ Pollut* 1989;57:167-178.
62. Martin RM, McCarthy A, Smith GD, et al. Infant nutrition and blood pressure in early adulthood: the Barry Caerphilly growth study. *Am J Clin Nutr* 2003;77:1489-1497.
63. WHO and UNICEF. Reduced osmolarity oral rehydration salts (ORS) formulation report from a meeting of experts. New York: WHO/FCH/CAH/01, 2001.
64. ESPGAN, European Society of Pediatric Gastroenterology and Nutrition. Recommendations for composition of oral rehydration solutions for the children of Europe. *J Ped Gastroenterol Nutr* 1992;14:113-115.
65. CDC, Centres for Disease Control and Prevention: Hyponatraemic seizures among infants fed with commercial bottled drinking water - Wisconsin, 1993. *MMWR* 1994;43:641-643.

14.

FLUORIDE

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I. INTRODUCTION

Fluoride has both beneficial and detrimental effects on human health. In terms of dental health, the prevalence of dental caries is inversely related to the concentration of fluoride in drinking water; while there is a dose-response relationship between the concentration of fluoride in drinking water and the prevalence of dental fluorosis (1). In terms of general health, in communities where drinking water and foodstuffs are excessively high in fluoride, skeletal fluorosis and bone fracture are the most relevant adverse effects. However, there are also other sources of fluoride. Processes such as desalination and some membrane and anion exchange water treatment processes will remove virtually all fluoride from water. In terms of using such sources for drinking water, the implications for public health will strongly depend on local circumstances. However, the public health requirement is to maximise the beneficial effects of fluoride in drinking water supplies for caries prevention, whilst minimising the unwanted dental and potential general health effects.

The aetiology of dental caries involves the interplay on the tooth surface between certain oral bacteria and simple sugars (e.g. sucrose) derived from the diet. In the absence of those sugars in foods and drinks dental caries will not be a public health problem. However where sugar consumption is high or is increasing, dental caries will be *or will become* a major public health problem unless there is appropriate intervention. Removing fluoride from a local drinking water supply could potentially exacerbate an existing or developing dental public health problem.

II. FLUORIDE INTAKE IN HUMANS

Fluoride is widely distributed in the lithosphere mainly as fluorspar, fluorapatite and cryolite, and is recognised as the thirteenth most common element in the earth's crust. It is found in seawater at a concentration of around 1.2 – 1.4 mg/litre, in ground waters at concentrations up to 67 mg/litre, and in most surface waters at concentrations less than 0.1 mg/litre (2). Fluoride is also found in foods particularly fish and tea (3).

Whilst almost all foodstuffs contain at least traces of fluoride, water and non-dairy beverages are the main sources of ingested fluoride, accounting for 66 to 80% of fluoride intake in US adults according to the concentration of fluoride in the public drinking water. Other significant sources of ingested fluoride are toothpaste in very young children (who tend to swallow most of their toothpaste), tea in tea-drinking communities, and inhaled fluoride in some communities in China where coal containing very high levels fluoride is burned indoors. Absorption of ingested fluoride is via the stomach and small intestine (3).

Most of the fluoride in water, either naturally occurring or added, will be in the form of the free fluoride ion (3). The effect of water hardness in the range 0 to 500 mg Ca Co₃ /litre has little effect on ionic dissociation, and therefore little effect on the bioavailability of fluoride (4). Absorption of a standard dose of fluoride will vary from 100% on a fasting stomach, to 60% when taken with a calcium-rich breakfast.

III. DENTAL EFFECTS OF INGESTED FLUORIDE

The dental effects of fluoride naturally present in public drinking water were established during the 1930s and 40s by Trendley Dean and his colleagues at the US Public Health Service. In a series of epidemiological studies across the United States they demonstrated that as the concentration of fluoride naturally present in drinking water increased, the prevalence and severity of dental fluorosis increased and, the prevalence and severity of dental caries (decay) decreased (5). Furthermore Dean's data suggested that at a natural fluoride concentration of around 1 mg/litre, the prevalence, severity and cosmetic impact of dental fluorosis was not of public health significance, and that the increased resistance to dental caries was of substantial public health importance.

Inevitably this led to the question as to whether artificially raising the fluoride level of public drinking water would have the same effects. The first intervention study was undertaken under the direction of USPHS in Grand Rapids in 1945. The results after 6 years of fluoridation were published in 1953. Additional studies were started in 1945/6 in New York State, in Illinois, and in Ontario Canada. Further intervention studies were established in the Netherlands (1953), New Zealand (1954), the UK (1955-6), and East Germany (1959). All of these intervention studies demonstrated clinically important reductions in the incidence of dental caries (5). Following the publication of the results of these intervention studies the application of water fluoridation as a public health measure became widespread. Some of the countries involved and the populations receiving artificially fluoridated water are listed in Table 1. The optimal concentration of fluoride varies according to climatic conditions with the range 0.5mg-1.0mg/litre being generally recommended (6). Worldwide around 355 million people are receiving artificially fluoridated water. In addition, around 50 million people receive water naturally fluoridated at a concentration of around 1 mg/litre. Table 2 lists countries where community drinking water supplies with a natural fluoride concentration of around 1 mg/litre serve populations of 1 million or more. In some countries, particularly parts of India, Africa and China, drinking water can contain very high concentrations of naturally occurring fluoride -well in excess of the WHO's recommended Guideline Value of 1.5 mg/litre.

Many countries that have introduced water fluoridation continue to monitor the effects on both dental caries and dental fluorosis using cross-sectional random samples of children aged 5 through 15 years. An excellent example of such monitoring is a recently published report of child dental health in the Republic of Ireland (mainly fluoridated) and the North of Ireland (not fluoridated)(7). (See Table 3).

IV. INGESTED FLUORIDE AND HEALTH

The health effects of ingested fluoride were reviewed by Moulton in 1942 (8) prior to the Grand Rapids intervention and regularly ever since by numerous organisations and individuals. More recently IPCS (3) have carried out a detailed review of fluoride and the potential for impacts on health. Studies and reviews have concentrated on bone fractures, skeletal fluorosis, cancers and birth defects but also cover many other disorders claimed to be caused, or aggravated, by fluoridation (1, 9, 10, 11, 12, 13, 14). There is no good evidence of any adverse medical effects associated with the consumption of water with fluoride naturally or artificially added at a concentration of 0.5 – 1.0mg/litre other than the increase in dental fluorosis described above. Furthermore, US studies in areas with natural fluoride levels of up to 8 mg/litre found no clinical evidence of harm. However there is clear evidence from India and China that skeletal fluorosis and an increased risk of bone fractures occur as a result of long-term excessive exposure to fluoride (total intakes of 14 mg fluoride per day), and evidence suggestive of an increased risk of bone effects at total intakes above about 6 mg fluoride per day (3).

The U.S. National Academy of Sciences Institute of Medicine (15) has recommended an Adequate Intake (AI) of fluoride from all sources as 0.05 mg F/kg body weight/day, defined as the estimated intake that has been shown to reduce the occurrence of dental caries maximally in a population without causing unwanted side effects including moderate dental fluorosis. The U.S. Environmental Protection Agency sets a maximum contaminant level of 4.0 mg/litre to protect against skeletal fluorosis, and a secondary (guidance) value of 2 mg/litre to protect against moderate to severe dental fluorosis. The WHO's drinking water quality Guideline Value for fluoride is 1.5 mg/litre (16). However, WHO emphasises that in setting *national* standards for fluoride it is particularly important to consider climatic conditions, volumes of water intake, and intake of fluoride from other sources (e.g. food and air). WHO (16) also noted that in areas with high natural fluoride levels the Guideline Value might be difficult to achieve in some circumstances with the limited technology available.

Fluoride is not irreversibly bound to bone. During the growth phase of the skeleton, a relatively high portion of an ingested fluoride dose will be deposited in the skeleton. The "balance" of fluoride in the body i.e. the difference between the amount of fluoride ingested and the amount of fluoride excreted in the urine and the faeces can be positive and negative. When the fluoride is derived from human milk or cow's milk, biological fluids with a low fluoride content (0.005 mg/L) urinary excretion generally exceeds intake i.e. there is a negative fluoride balance. In infants when fluoride intakes are extremely low sufficient fluoride is released from bone to extracellular fluid to result in urinary excretion higher than intake. This is in great contrast to the situation in an adult approximately one half of the daily fluoride intake by adults will be deposited in the skeleton and the rest excreted in the urine. Thus, fluoride will be mobilized slowly but continuously from the skeleton depending on present and past fluoride exposure. This relationship is largely due to the fact that bone is not static but, continuously undergoes a remodelling, whereby old bone is resorbed and new bone is formed (17, 18).

V. IMPLICATIONS OF DESALINATION

Desalination will remove virtually all fluoride from seawater thus the product water will be low in fluoride and other minerals unless it is reconstituted. Many natural drinking waters are also low in minerals, including fluoride. The public health implications of this will depend on the balance of benefits to risks locally.

There are substantial variations in the levels of dental decay both between and within the continents. WHO recommends the index DMFT at 12 years of age (mean number of decayed,

missing and filled teeth) as the most appropriate national indicator, and the WHO oral health database provides extensive information (19). The aetiological factors in dental caries involve the interplay on the tooth surface between certain oral bacteria and simple sugars (e.g. sucrose) derived from the diet. In the absence of those sugars in foods and drinks (an average national consumption of say less than 15 kg per person per year) dental caries will not be a public health problem. Under such circumstances, the public health concern will be to avoid the harmful effects of any excessive fluoride consumption from drinking water.

However, where caries risk is high (or increasing) the effects of a decision to remove fluoride from the public drinking water are more complex. In countries such as the Scandinavian countries, where public dental awareness is very high and alternative vehicles for fluoride (e.g. tooth paste) are widely available and widely used, a decision not to replace fluoride removed from the drinking water would be of no consequence. On the other hand in some developing countries, where public dental awareness might be much lower, water fluoridation at concentrations of 0.5-1.0 mg/litre would remain an important public health objective. In yet other countries (e.g. the UK) the situation is mixed. In parts, such as the South East of England, dental caries is mainly under control without water fluoridation; in other regions, such as the North West of England, the prevalence of dental caries is substantially higher and water fluoridation remains an important public health objective.

VI. CONCLUSION

The significance of a decision to use demineralized water as a drinking water source without addition of fluoride during remineralization will depend upon:

- the existing concentration of fluoride in the local supply;
- climatic conditions and the volume of water consumed;
- dental caries risk (i.e. sugar consumption);
- the level of public dental awareness and the general availability of alternative vehicles for fluoride available to the whole population.

However, total fluoride intake from other sources and the need to ensure an appropriate minimum intake of fluoride to prevent loss from bone also need to be considered.

References

1. McDonagh M, Whiting P, Bradley M, Cooper J, Sutton A, Chestnut I, Misso K, Wilson P, Treasure E, Kleijnen J. A systematic review of public water fluoridation. York: The University of York NHS Centre for Reviews and Dissemination, 2000.
2. Smith FA, Ekstrand J. The occurrence and the chemistry of fluoride. In: Fejerskov O, Ekstrand J, Burt BA, eds. Fluoride in dentistry, 2nd ed. Copenhagen: Munksgaard, 1996:20-21.
3. IPCS. Environmental Health Criteria 227 Fluorides. Geneva: World Health Organisation, 2002.
4. Jackson P, Harvey P, Young W. Chemistry and bioavailability aspects of fluoride in drinking water. Marlow, Buckinghamshire: WRC-NSF, 2002.
5. Murray JJ, Rugg-Gunn AJ, Jenkins GN. Fluorides in caries prevention. 3rd ed. Oxford: Wright, 1991:7-37.
6. World Health Organisation Expert Committee on Oral Health Status and Fluoride Use. Fluorides and oral health. WHO Technical Report Series No. 846. Geneva: World Health Organisation, 1994.
7. Whelton H, Crowley E, O'Mullane D, Cronin M, Kelleher V. Children's oral health in Ireland 2002: preliminary results. Dublin: Irish Government Department of Health and Children, 2003. <http://www.dohc.ie/publications/pdf/coral.pdf?direct=1>
8. Moulton F. Fluorine and dental health. Washington DC: American Association for the Advancement of Science, 1942.
9. Demos L, Kazda H, Cicuttini F, Sinclair M, Fairely C. Water fluoridation, osteoporosis, fractures - recent developments. Aust Dent J 2001;46:80-87.
10. Fottrell F (Chairman). Forum on fluoridation Ireland. Dublin: Stationery Office, 2002.
11. Knox EG. Fluoridation of water and cancer: a review of the epidemiological evidence. London: HMSO, 1985.
12. Medical Research Council. Working group report: Water fluoridation and health. London: MRC, 2002.
13. National Research Council National Academy of Sciences Committee on Toxicology. Health effects of ingested fluoride. Washington DC: National Academy Press, 1993.
14. Royal College of Physicians. Fluoride teeth and health. London: Pitman Medical, 1976.
15. Institute of Medicine. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D and fluoride. Washington DC: National Academy Press, 1997.
16. World Health Organisation. Guidelines for drinking-water quality. Vol 1 Recommendations. 2nd ed. Geneva: World Health Organization, 1993.
17. Ekstrand J. Fluoride metabolism. In: Fejerskov O, Ekstrand J, Burt B, eds. Fluoride in dentistry 2nd ed. Copenhagen: Munksgaard, 1996:55-68.
18. Ekstrand J, Ziegler EE, Nelson SE, Fomon SJ. Absorption and retention of dietary and supplemental fluoride by infants. Adv Dent Res 1994;8:175-180.
19. WHO Oral Health Database. Online at: <http://www.whocollab.od.mah.se/countriesalphab.html>

Table 1. Countries with water fluoridation schemes covering populations of 1 million or more

Country	Population (millions)	Adjusted fluoride	
		Population covered (millions)	Population covered (%)
Argentina	35.9	3.1	9.0
Australia	19.3	11.7	60.6
Brazil	172.5	65.6	38.0
Canada	31.0	13.3	42.9
Chile	15.4	5.4	35.1
Colombia	42.8	29.4	68.7
Guatemala	11.7	1.8	15.4
Hong Kong	6.7	6.7	100.0
Ireland	3.8	2.3	60.5
Israel	6.4	4.3	67.2
Korea	46.1	5.4	11.7
Malaysia	22.6	15.8	69.9
New Zealand	3.8	2.3	60.5
Philippines	77.1	5.0	6.5
Singapore	4.1	4.1	100.0
Spain	39.9	4.0	10.0
UK	59.5	5.4	9.1
USA	281.4	171.0	60.8
Vietnam	79.7	4.4	5.5

Table 2. Countries with drinking water supplies with a natural fluoride concentration of around 1 mg/litre covering populations of 1 million or more

Country	Population (Millions)	Natural fluoride at or around 1mg/litre	
		Population covered (millions)	Population covered (%)
Argentina	35.9	4.5	12.5
France	59.4	1.8	3.0
Gabon	1.3	1.3	100
Libya	5.4	1.0	18.5
Mexico	100.4	3.0	3.0
Senegal	9.7	1.0	10.3
Sri Lanka	19.1	2.8	14.7
Tanzania	35.0	12.2	34.9
USA	281.4	10.0	3.6
Zimbabwe	13.0	2.6	20.0

Table 3. Mean number of decayed, missing and filled teeth in children resident in fluoridated (f) and non-fluoridated (nf) parts of the Republic of Ireland (RoI) and in non-fluoridated (nf) Northern Ireland (NI)

Age	RoI (f)	RoI (nf)	NI (nf)
5 years	1.0	1.7	1.8
15 years	2.1	3.2	3.6

