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Editorial:

Everything under control

I am a convinced believer in the Russian saying that tells you to “trust, but confirm” (dowerjai, no prowerjai). So I am very glad that a team of dedicated specialists checks all the texts for Nutriview before they are published to ensure the information is accurate and reliable. Most of the time, the members of the Nutriview Editorial Board are lenient in their criticisms of my editing. However, they have also saved me several times from making unjustifiable statements.

In almost fifteen years of publication, Nutriview has been extremely fortunate to have people on its Editorial Board who command an extraordinary level of expertise, and are highly respected in the nutrition community. Mutations in membership have been rare. The longest serving member, Dr Alfred Sommer, has been on the Board since 1993; his fellow member in the early days of Nutriview was Dr Lawrence Machlin (a retired Roche scientist who passed away in 2000). In 1994, Dr Ricardo Uauy and Dr Aree Valyasevi joined the team. Dr Valyasevi was active until 2005. Dr Ratko Buzina was officially on the Board from 1999, following his retirement from the WHO, until the end of 2001.

It is therefore a sad moment for me to have

to inform you that Dr Sommer will retire from the Nutriview Editorial Board at the end of this year after a long and valuable participation in our newsletter. I shall certainly miss his pertinent remarks and encouraging suggestions.

As from the beginning of 2008, the Editorial Board will have three members again. Ricardo Uauy will be joined by Dr Omar Dary, food fortification specialist at the USAID Micronutrient and Child Blindness Project A2Z in Washington DC, and Dr Noel W. Solomons, Director of the Center for Studies of Sensory Impairment, Aging and Metabolism (CeSSIAM) in Guatemala City. Both of these scientists are very active in advocating for greater efforts to eliminate malnutrition in the world, and are well known as leading specialists in their respective fields. Both of them have also been regular contributors to Nutriview in the past, and I look forward to working with them more intensively in the future.

With these changes, Nutriview can confidently continue as a communication medium between nutrition science and the workers in the front line of national development activities, assured that everything is still under the control of a knowledgeable and reliable editorial team.



A. Bowley

Feature:

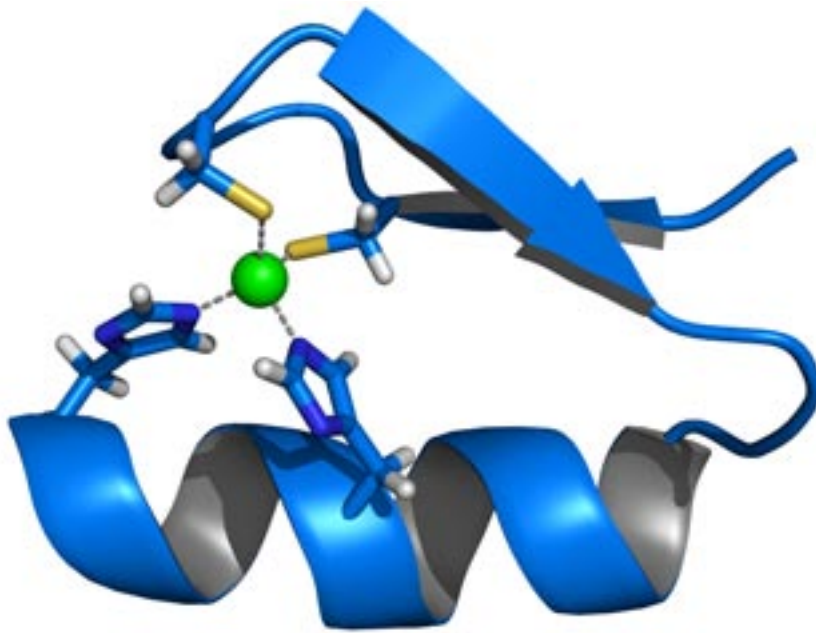
Update on zinc

Zinc, an essential nutrient of the transition metal family, has recognized roles in growth, fertility, immune function, taste, smell and wound healing, among others. Zinc deficiency results from insufficient intake, poor bioavailability and various clinical conditions. To date, there is no biochemical or laboratory indicator for assessing zinc status in clinical medicine. Red meat and shellfish are the best sources of zinc in terms of content and bioavailability. Zinc is more biologically available from human milk than from cow's milk or soy milk. Phytic acid forms insoluble complexes with zinc, making the zinc content of whole grains poorly absorbable. Recommended dietary allowances are 11 mg daily for adult men and 8 mg for adult women (11 mg during pregnancy and 12 mg during lactation). The upper tolerable level for all adults is 40 mg daily.

Genes involved in zinc transport

Recently, the discovery and elucidation of membrane zinc transporters from the families of ZnT

(zinc transporter) and Zip (from the technical terminology of protein chemistry 'Zrt- and Irt-like proteins') proteins have unraveled the intercellular and intracellular movement and metabolism of zinc. ZnT reduces intracellular zinc concentration by exclusion or sequestration of the metal, whereas Zip generally increases intracellular zinc concentration (uptake related). Some transporter genes have metal response elements (MRE). This makes them responsive to changes in dietary zinc availability. Acrodermatitis enteropathica, the once lethal metabolic zinc malabsorption syndrome, which presents as florid zinc deficiency, can now be attributed to a mutation in the Zip4 gene. This transporter has a specific function of zinc uptake by intestinal cells. Others have roles in the accumulation of zinc in the liver or its export from the pancreas, as well as its transport in the placenta and immune cells. Some of the transporters co-transport other divalent trace elements, such as iron and manganese.



Representation of a zinc finger (from: http://en.wikipedia.org/wiki/Zinc_finger) consisting of an alpha helix and an antiparallel beta sheet. The zinc ion (green) is crucial for protein stability. In this example, it is coordinated by two histidine residues and two cysteine residues.

Physiological functions

Zinc acts physiologically through enzymatic, structural and regulatory mechanisms. It is involved in catalytic functions of all six classes of enzymes. Over 200 zinc metalloenzymes are known. Most recent revelations, however, have come in the structural and regulatory domains.

At least 3% of the human genome codes for zinc-finger proteins, a sequence of amino acids with periodic insertion of cysteine (or occasionally histidine), in which zinc has a structural function. Zinc-finger proteins allow coordination with a zinc ion, and provide a defined, rigid (finger-like) conformation to that segment of the protein. About 40% of the known transcription factors are zinc-finger proteins. The chemical removal of zinc from the zinc-finger motif usually results in loss of function. The interest in zinc fingers is intense, because they are potential targets for the action of new therapeutic agents.

With respect to regulation, one of the first and critical regulatory functions of zinc is that of regulating its own homeostasis within the organism. This is vividly illustrated by control of the gene for metallothionein, an intracellular binding protein for zinc. A metal-binding transcription factor (MTF), interacts with a metal-response element. It is postulated that new zinc ions entering the cell direct MTF to translocate the MRE to the cell nucleus, where it induces the expression of metallothionein. Recent studies reveal potential roles for intracellular zinc in regulating the process of apoptosis (programmed cell death).

Additional functions of zinc have recently been brought to light in the domain of inflammation control and immune function. They could involve any or all of the three basic mechanisms. It has been observed that zinc increases peripheral blood

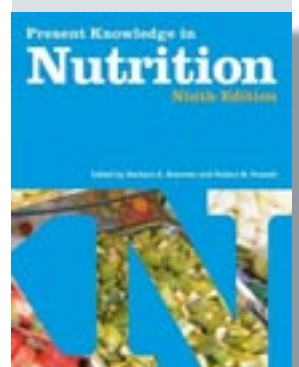
mononuclear cell synthesis of the immune factors interferon-gamma, interleukin-1, interleukin-6, tumor necrosis factor and IL-2 receptor. Zinc may control the secretion and/or production of these immune regulators within physiological concentrations, and could have therapeutic applications where monocyte activation is required. As mentioned above, evidence suggests that intracellular zinc may alter the cell selection process through apoptosis. For example, flow cytometry separation of white blood cells clearly shows that early B-lymphocytes are depleted in bone marrow in nutritional zinc deficiency.

Finally, zinc has a cell protective role. It has been associated with the induction of metallothionein (zinc-binding protein) by proinflammatory cytokines, the instigators of cellular inflammation and oxidation. The oxidation releases zinc from its binding on metallothionein and allows the molecule to be oxidized, buffering the oxidation and breaking the dangerous cycle within the cell. It has also been suggested that zinc might suppress the expression of the cyclo-oxygenase-2 (COX-2) enzyme.

Deficiency impairs growth, performance and immune function

Using dietary availability of absorbable zinc and the prevalence of short stature as population-level indicators, it is estimated that half of the world's population may be suffering from some degree of zinc deficiency. Stunting, poor cognitive performance and lethargy have been reversed after zinc supplementation. Improvement in immune function and disease resistance has also been achieved with zinc supplements in various geographical regions. A clear adjunctive, therapeutic benefit of oral zinc combined with

The 9th Edition of Present Knowledge in Nutrition (PKN), edited by Dr Barbara A. Bowman and Dr Robert M. Russell was published in 2006 by the International Life Sciences Institute (ILSI). For further details and to order, please see the ILSI web site: <http://www.ilsilife.org/Publications/Present+Knowledge+in+Nutrition> or contact: ILSI Press, One Thomas Circle, NW, Washington, DC 20005-5802; Telephone: 202-659-0074; Fax: 202-659-3859



oral rehydration therapy has been shown in the treatment of acute bouts of watery diarrhea. Zinc has not shown unequivocal benefits in shigellosis, however. Results have also been mixed in zinc interventions to treat tuberculosis and HIV.

Higher doses not always toxic

Acute effects of high doses of zinc are nausea, vomiting and gastric irritation, whereas chronic excess zinc ingestion may induce copper deficiency anemia, lowering of HDL cholesterol and suppression of T-lymphocytes. A previously unrecognized form of neural zinc toxicity is the stimulation of the hippocampus, a zinc-rich area of the brain. This might release zinc from stores, and damage the neurons of the region. In theory, chelating agents that permeate membranes could reverse such damage. The clinical significance of these observations has yet to be determined.

High doses of zinc might also have protective effects in certain populations. One example is the observation that zinc induction of metallothionein in the bone marrow can protect stem cells from the noxious effects of certain chemotherapeutic agents. In another study, patients with advanced age-related macular degeneration who took zinc

supplements had lower mortality at follow-up after 6.5 years than those not taking zinc.

Technical developments and future directions

Recently, fluorescent probes are increasingly being used to measure abundance of free zinc within cells during altered physiologic conditions. These probes fluoresce when Zn⁺⁺ is bound. Some probes permeate cell membranes, whereas others do not. Fluorescent probes may replace radioactive zinc isotopes as tracers in cell-level experiments.

Basic research on transport mechanisms and metabolism will continue using new genetic and biochemical tools. Gene regulation and modification of cellular responses to stress by zinc supplementation is an emerging inquiry with potential clinical application. Biomarkers for the assessment of individual zinc status remain elusive and in need of development. The public health value of zinc interventions (supplementation, fortification) in populations in developing countries where zinc bioavailability from the staple diet is low needs to be established.

A summary of the most important advances in knowledge from Chapter 35, Present Knowledge in Nutrition, 9th edition, by Dr Robert J. Cousins, Boston Family Professor of Nutrition, Food Science and Human Nutrition Department, College of Agricultural and Life Sciences; Director, Center for Nutritional Sciences and Joint Professor of Biochemistry and Molecular Biology, College of Medicine, University of Florida, USA. General Editor for this series is Dr Noel W. Solomons of the Center for Studies of Sensory Impairment, Aging and Metabolism (CeSSIAM) in Guatemala City. This article closes the series of PKN9 summaries in Nutriview.

Feature:

GAIN-funded project catalyzes wheat flour fortification in Pakistan

The population of Pakistan suffers from significant and widespread nutritional deficiencies. The nutritional status of children under five years of age is extremely poor; almost 38% are underweight, 37% are stunted and 13% are wasted [1]. Although regional variations exist, it is estimated that 39% of pregnant women and more than 50% of children under-five years of age are anemic [1].

Food fortification provides an opportunity to address these deficiencies, and to complement other more targeted public health initiatives such as micronutrient supplementation for the populations most at risk. In Pakistan, small-scale fortification initiatives and pilot programs have been successfully undertaken by the Micronutrient Initiative (MI), and fortification of staple foods has been welcomed by the government as well as the general population. Flour fortification with iron and folic acid is among the key strategies of Pakistan's 10-Year National Nutrition Strategic Plan (NNSP) to improve overall nutrition and health status.

Pakistanis' staple food is atta wheat flour. They consume about 15 million metric tons of

it annually. The average Pakistani consumes around 300 grams every day [2], making flour an appropriate food vehicle for fortification with key vitamins and minerals. The country is currently self-sufficient in domestic wheat production, and more than half of its atta wheat flour is produced by medium to large-scale mechanized mills, where the product can be fortified relatively easily.

Nation-wide fortification of atta wheat flour with key vitamins and minerals provides an excellent opportunity to address the significant and widespread nutritional deficiencies affecting the Pakistani population.



Millers' support assured

GAIN, the Global Alliance for Improved Nutrition, is a Swiss foundation established in 2002. Its mission is to improve the health and nutrition of at-risk populations around the world through support for food fortification and other nutritional strategies. GAIN builds alliances of public and private partners and provides financial support and technical expertise. It currently delivers funding and technical assistance through multi-sector National Fortification Alliances in 17 countries.

In July 2005, GAIN signed a three-year project agreement with Pakistan's Minister of Health. The grant (worth almost US\$3 million) supports the first phase of the National Wheat Flour Fortification Project, and enables fortification with 10 ppm of NaFeEDTA iron and 1.5 ppm of folic acid at 300 roller mills. The GAIN grant has galvanized support from a diverse array of partners, and helped obtain an additional US\$ 8.3 million from the public and private sectors to extend fortification to all 600 roller mills nation-wide by the year 2010. Millers have committed significant resources to the program, including covering 100% of the costs for necessary equipment upgrades, and for the iron and folic acid premix after the project provides initial supplies. The government has likewise committed resources to on-going quality control and demand creation.

Strong partnerships mobilized

A strong partnership has been formed among the private and public sectors, and civil society. The National Fortification Alliance (NFA) that developed, monitors and governs the program includes members from all these sectors. The NFA is chaired by the Ministry of Health and includes members of the Pakistani Flour Millers Association (PFMA) and other wheat flour industry representatives, the Ministry of Industry, the Ministry of Food and Agriculture, international development partners such as MI, WFP, WHO and UNICEF, and industry representatives of other fortifiable foods such as ghee and salt. These partners are working together on all components of the flour fortification program including: expanding production, establishing quality control and assurance protocols and testing, social marketing and communication to raise consumer demand, and monitoring and evaluation in the four major Provinces of the country (Punjab, Sindh, Balochistan and North West Frontier Province). In particular, in addition to its earlier support to fortification efforts,

MI remains a key partner in providing technical expertise. The GAIN funding also includes support for adopting a mandatory fortification standard by the Pakistan Standard and Quality Control Authority.

To date, two baseline surveys have been carried out: a wheat flour market analysis and a consumer "knowledge attitude and practices" survey to improve the project's understanding of the market and consumer demand. A Memorandum of Understanding has been signed with the PFMA to formalize roles and responsibilities. It includes assurance of price stability and quality control. Initial consignments of fifty micro-feeders and 64,800 kg of premix have been procured and imported. A far-reaching media campaign has been developed and launched. Quality control mechanisms have been developed and initiated, including the upgrading of testing laboratories. Training of laboratory and mill staff is underway. Various program management activities are on-going, laying the foundation for a sustainable program that will continue after GAIN funding ends.

In short, the GAIN-funded project has catalyzed nation-wide wheat flour fortification in Pakistan. It has mobilized partners in all sectors to commit significant resources to a sustainable program that will improve the health and nutritional status of Pakistanis for years to come.

GAIN mobilizes public-private partnerships to fight malnutrition, and enables large-scale market-based solutions to make people and economies stronger, healthier and more productive. www.gainhealth.org

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Dr Regina Moench-Pfanner, Senior Manager for Food Fortification Programs at the Global Alliance for Improved Nutrition (GAIN), Geneva, Switzerland and Dr Imtiaz Malang, National Coordinator for the National Wheat Flour Fortification Project, Ministry of Health, Islamabad, Pakistan.

Review:

Controlling nutritional anemia

Following the workshop that was held in Barcelona, Spain, on September 27, 2006 (see Nutriview 2006/4), SIGHT AND LIFE has published a manual summarizing the findings, and a guide-book that helps health workers, organizations and policy makers to make a real difference in the lives of millions of people affected by nutritional anemia.

The guide book summarizes some of the conclusions reached by the experts. It draws attention to the unchanged magnitude of the anemia problem and its resulting economic implications. It also determines the crucial points for addressing nutritional anemia by specifying critical factors for future research related to micronutrients, and by identifying key components to ensure that programs and interventions really work.

A massive health and economic burden

Estimates based on data collected by the World Health Organization between 1993 and 2005 indicate that almost half of all preschool-aged children worldwide suffer from anemia. Almost 42% of pregnant women and more than 30% of nonpregnant women are also anemic. The highest prevalence is in Africa, but the greatest number of people affected is in Asia.

Recent research indicates that functional consequences of iron deficiency (weakness and fatigue) can occur even before the clinical onset of anemia. More than 200 million children fail to reach their development potential, because chronic iron deficiency in infancy permanently retards cognitive, motor, and socioemotional development. These children are likely to fail at school and remain in the poverty trap. There is consensus among scientists that global and national priority should be given to the prevention of even mild anemia in infants and young children because of this. All infants need iron supplements, because breast milk provides only about half of their iron requirement.

In the past, iron deficiency and anemia have primarily been dealt with as a medical problem. While anemia at all ages is associated with a significant health burden, it also has a potentially large negative impact on productivity and income; current loss estimates are as high as US\$50 billion. The cost of individual physical and cognitive impairments due to nutritional anemia is considerable when compared to the modest costs of prevention (Table 1).



The most vulnerable segments of the population for nutritional anemia are pregnant/lactating women and infants. Measures to prevent iron deficiency and anemia should include food fortification with multiple micronutrients, and the treatment of infectious diseases, intestinal parasites and inflammation.

Improving iron alone is not enough

Iron deficiency is not the only cause of anemia, so the problem cannot be solved simply by increasing iron intakes. Interventions must correct other nutritional, health and socioeconomic deficits as well.

It is important to correct other micronutrient deficiencies that impair iron metabolism

It is important to correct other micronutrient deficiencies that impair iron metabolism. These occur mainly as a result of a poor diet with limited intake of fruits, vegetables and foods from animal sources. Plant-based diets with a high phytate and polyphenol content also inhibit the

Table 1: Costs of nutritional anemia and benefits of treatment

1. The cognitive effects of anemia potentially reduce adult earnings by 2.5%.
2. Iron interventions in adults improve productivity by around 5% in light manual labor and as much as 17% in heavy manual labor.
3. Iron fortification is one of the most cost-effective public health interventions. The annual cost for food fortification is in the range of US\$0.10–1.00 per person, with a cost-benefit ratio of 1:6 (physical benefits to adults) or 1:9 (including estimated cognitive benefits to children).
4. Supplementation costs around US\$2.00–5.00 per person annually. However, the cost per disability adjusted life year (DALY) saved is five times that of fortification. Large-scale supplementation programs to date have not been very successful.
5. More research is needed to quantify economic losses from mental retardation due to iron deficiency anemia.

absorption of iron and other minerals. Diseases such as tuberculosis, HIV/AIDS, malaria, other parasitic infections and some forms of chronic inflammation also impair nutritional status and contribute to anemia. It is therefore important to treat underlying disease.

The effects of malnutrition start in the womb and continue throughout a person's lifetime. The most vulnerable segments of the population for nutritional anemia are pregnant and lactating women, infants, children and adolescent girls. Corrective measures should take the specific requirements of each target population into account.

It is still unclear which micronutrients are involved in iron metabolism, and what dosage is needed for an optimal effect. It is important to consider possible risks due to interactions between micronutrients, and the effects of iron absorption inhibitors. Existing prevention programs, such as high-dose vitamin A, iron/folic acid supplements and parasite control, have to be integrated, and monitored carefully.

An integrated approach is essential

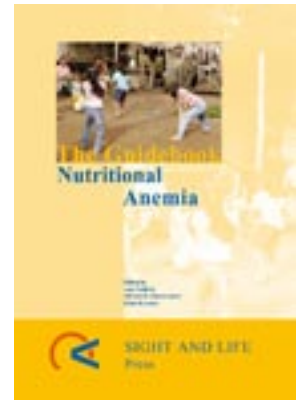
Iron deficiency cannot be controlled in the same way as deficiencies of vitamin A or iodine, where approaches using supplements and salt fortification have worked. The key message is that, in anemia, all causes and approaches must work together; supplementation, food fortification, biofortification, food-based approaches and public health measures have to be viewed and practised as complementary to each other. For the long-term success and sustainability of nutritional anemia control programs, all factors and options must be

viewed as a whole and be adjusted to suit specific local conditions and requirements.

A key hindrance to achieving the global goal is the fact that operational components of controlling iron deficiency are less well developed than research and development efforts, neither of which is generally linked to communication (including political advocacy, funding, motivation for acceptance of better nutrition practices, health education and promotion). In fact, the greatest challenge probably does not lie in the need for more scientific research, but rather in communicating and interpreting the research findings and exceptions so as to fine tune programs.

Advocacy needs to focus on the benefits of interventions throughout the life cycle and the associated impact on productivity, which ultimately leads to the economic uplift of both individuals and countries. To mobilize action across a wide range of sectors for the eradication of iron deficiency and anemia, it is essential to emphasize the irreversible damage caused to intellectual development in early childhood and the loss of GDP incurred by them. We need effective bridges between science and technology, service providers, as well as political and financial decision makers.

The problem is not the lack of knowledge about tailored solutions but rather a lack of clear political and financial commitment to undertake interventions to match the magnitude of the problem. The problem is clearly described. What remains is to accept the challenge and accelerate the action.



Nutritional Anemia. SIGHT AND LIFE Press 2007. Edited by Dr Klaus Kraemer, SIGHT AND LIFE, Basel, Switzerland, and Dr Michael B. Zimmermann, Swiss Federal Institute of Technology, Zurich, Switzerland. Both the manual and the guide book can be downloaded from: <http://sightandlife.org/aaHTMallg/News.html>

News in brief:

Dissolution rate best for iron bioavailability screening

Lynch et al. [1] evaluated possible ways to screen commercial iron powders (carbonyl, electrolytic, hydrogen reduced, carbon monoxide reduced and other reduced) for bioavailability, to identify those with the potential to improve iron status, and to ascertain whether bioavailability is related to the method of manufacture. After determining the structure and physical properties of all powders, they subjected selected samples to five screening procedures advocated for predicting bioavailability in humans (dissolution rate in HCl, dialyzability, iron uptake in Caco-2 cells, relative bioavailability with respect to ferrous sulfate by the Association of Official Analytical Chemists (AOAC) rat hemoglobin repletion test, and plasma iron tolerance tests in human volunteers).

They found that the dissolution rate in HCl under

standardized conditions was the most reliable and sensitive screening procedure for predicting and monitoring the bioavailability of commercial elemental iron powders. Its predictive value was confirmed by both the rat hemoglobin repletion test and the human efficacy trial. This assay is also attractive from the practical point of view: a single criterion could be used for all powder types; the apparatus required is inexpensive and is already available in most laboratories. Plasma iron tolerance tests in humans provided bioavailability estimates similar to those based on physical properties, dissolution in HCl and/or relative bioavailability in rats, but were not more precise than these. Powders stored under adverse environmental conditions were difficult to disperse evenly in the fortification vehicles. This could be a greater problem than low bioavailability.

These results suggest that Electrolytic/A131

iron (added at twice the concentration of ferrous sulfate, as recommended by the WHO) would be a satisfactory substitute for ferrous sulfate. However it is substantially less effective than ferrous sulfate in correcting iron deficiency in vulnerable women.

The authors conclude that commercial iron powders used for food fortification vary significantly in their bioavailability, and that this is related in part to the way they are produced. Some of the carbonyl and electrolytic iron powders may be adequately bioavailable, but the reduced iron powders tested are unlikely to have an adequate impact on iron nutrition at the fortification levels currently employed. The authors recommend that all products should be screened rigorously.

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Adults in Ireland benefit from voluntary fortification

To measure the effect of voluntary food fortification on the dietary intakes of vitamins and minerals of Irish adults, Hannon et al. [1] determined the intakes of micronutrients from fortified and non-fortified foods in 1379 Irish adults on the basis of a seven-day food diary recorded during the North/South Ireland Food Consumption Survey. Fewer than 2% (54) of the 3000 foods recorded as consumed were fortified, mainly breakfast cereals and beverages; a typical serving provided 18–33% of the European Commission 1990 RDA.

Around two thirds of the population surveyed (65% of men and 68% of women) regularly consumed one or more fortified foods. Fortification contributed the following amounts to the mean daily intakes of men/women respectively: energy 4/5 %; iron 16/19%; folates 18/21%; B1 14/16%; B2 16/18%; B6 12/15%; B12 5/7%; niacin 10/12%; D 5/11%. This significantly improved, in particular, the adequacy of riboflavin, folate, vitamin D and iron intakes in women, and did not increase the risk of adverse effects from excessive intake of any micronutrient.

This survey shows that voluntary fortification of foods in Ireland makes a significant contribution to the adequacy of intake of a range of micronutrients in the population.

In a commentary in the same issue of the journal, Rosenberg [2] notes that the best way of preventing micronutrient malnutrition is to ensure consumption of a balanced diet that is adequate in every nutrient. This is, however, far from being achievable everywhere, since it requires universal access to adequate food and appropriate dietary habits. From this standpoint, food fortification is a good alternative strategy. Depending on the nutritional quality of their basic diet, individuals who regularly consume fortified foods might well gain discernible benefits. However, it is important that governments exercise an appropriate degree of control over the process.

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- 2. Rosenberg IH. Further evidence that food fortification improves micronutrient status. Brit J Nutr 2007; 97: 1051–1052.*

Photos – Title page, page 2, page 6: DSM; page 3: ILSI; page 7: Sight and Life
Graphics – Page 3: Wikipedia, The Free Encyclopedia; November 2007

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