



2 Editorial: Check it

Recent food scandals show the importance of regulation, monitoring and control in food processing.

2 PAHO Code of Practice

This book aims to help build effective food fortification programs to eliminate micronutrient deficiencies.

3 Premix quality may be critical for fortification effectiveness

Reliable premixes can be recognized by the comprehensive documentation supplied with the product, and the fact that they have been certified as reaching internationally recognized standards.

4 Update on vitamin D

Vitamin D₃ (the more bioactive form) can be synthesized endogenously. Few foods are good sources of vitamin D. Knowledge about membrane-based reactions and endocrine aspects continues to grow. Higher dietary intakes are advocated.

6 Vitamin D deficiency a global threat?

Vitamin D deficiency appears to be a global problem that has not been adequately recognized in the past.

7 News in brief

A renewed call to increase dietary recommendations for vitamin D

Reasons for colorectal cancer after folate fortification need clarification

Prevalence of neural-tube defects in Canada decreased by 46% after folate fortification.

Editorial: Check it

How sure are you that the ingredients used in food processing are, indeed, what you think they are? In these days of online trading it has become much easier to buy food ingredients from international sources. Often, you cannot be certain that the seller is also the manufacturer, or that the claims made for a product are valid. Some recent experiences show that, if the food processor and the controlling authority are not especially vigilant, foods can be adulterated with ingredients that are dangerous to the extent of causing bodily harm or even death.

One of the most serious events in recent years has been the use of 'antifreeze' (diethylene glycol) instead of glycerine in cold remedies in several countries in South and Central America, Asia and Africa. The importers of the ingredient and the manufacturers of the cold syrup, trusting the label on the container, had not tested what they were using. As a result, many people's condition worsened, or they died. Earlier this year, another scandal was discovered in which the industrial chemical melamine was sold as protein enhancer

for use in pet food. The powder had passed through the hands of numerous intermediate traders, who had modified the accompanying documentation each time, so that it was almost impossible to trace the source back to the original manufacturer.

Another event that shows the importance of regulation, monitoring and control was the discovery, by the Nigerian Food and Drug Authority, that one of the country's millers was selling flour that was not fortified with vitamin A as labelled, and required by law. These events confirm once more that some people are more interested in increasing profits than in contributing to people's nutrition and health. The wisest course is to take everything with a pinch of salt and check it first!

A useful guide for anyone responsible for a food fortification program is the 'PAHO Code of Practice for Food Premix Operations' summarized below. This book is available at no cost from the PAHO web site.



A. Bowley

Review: PAHO Code of Practice

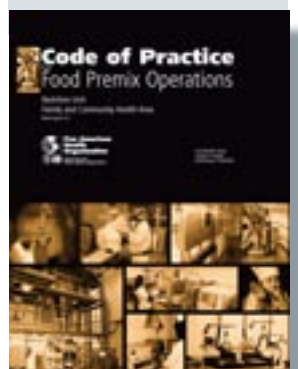
This Code of Practice for Food Premix Operations was published in 2005 as the first response to a need raised by implementers of food fortification programs. Its aim is to help build effective food fortification programs to eliminate micronutrient deficiencies. The first step to assuring premix quality will be the adoption of this Code by premix operators for their internal audit. The next steps will include developing a system of external auditing and certification of premix quality by regulatory agencies at the regional or sub-regional level.

The book is the result of efforts by PAHO/WHO and various partner organizations, beginning with a technical consultation in 2001 to develop practical guidelines on the types and levels of iron compounds recommended for food fortification. A second consultation in 2003 established guide-

lines for levels of fortification with folic acid and vitamin B12. These were followed by a regional meeting to exchange ideas with policy makers and program implementers on how to optimize flour fortification. It resulted in the formulation of country-specific recommendations.

The book points out factors for the limited success of food fortification programs (such as weak or no regulations, suboptimal types and concentrations of fortificants, poor manufacturing practices, poor standards for fortified foods, weak or no quality control/quality assurance systems, and lack of demand generation through consumer awareness and participation). It recognizes the need for guidelines and mechanisms for assuring the quality of nutrient premixes.

The PAHO Code of Practice is available online at <http://www.paho.org/english/AD/FCH/NU/COPPremixOperations.htm>



Feature:

Premix quality may be critical for fortification effectiveness

When embarking on a food fortification project, numerous factors have to be considered to ensure that the fortified food delivers the chosen fortificants in the correct amounts, and is safe for regular consumption at a reasonable cost. The quality of the micronutrient premix is one of the most critical factors for the success of a fortification program.

Of course, to ensure program sustainability, it is necessary to obtain the fortificants from the most economical supplier, as long as the micronutrients have the same bioequivalence—in its broadest sense—as other alternatives in the market, and as intended by the program design. Recent experience has shown that many ingredient sources cannot be trusted. By using fortificants that are substandard, or maybe even containing foreign materials that are dangerous to health, populations are placed at risk, the fortification program is doomed to failure, and a great deal of money will be lost.

A valid solution to this problem is to externally source food ingredients from reputable companies that fulfil basic quality requirements.

Reliable premixes:

- ◆ are designed individually for specific foods;
- ◆ use raw materials from manufacturers that offer full traceability and comply with international standards (e.g. Food Chemical Codex and Pharmacopoeia);
- ◆ deliver micronutrients in a homogeneous and stable system;
- ◆ are produced in clean, efficient plants according to good manufacturing practices;
- ◆ are tested for content, purity, bioavailability and stability;
- ◆ are packaged and stored under controlled conditions;
- ◆ are certified by internationally recognized organizations.

In this way, they also help to reduce costs and ensure peace of mind.

Good premixes have optimized characteristics

When individual nutrients or simple premixes are added to a food, there is a high risk that their distribution will be irregular (Figure 1a). This could result in the dosage being too high in one part of a batch and too low in another. The risk is particularly great in the case of nutrients added in minute amounts (such as vitamin B12). The nutrient forms in high-quality premixes are homo-

geneously diluted and stabilized. When mixed with the food, the fortification levels achieved are similar in all samples (Figure 1b).

In addition, to improve and simplify fortification procedures, a reputable company will provide different forms of micronutrient premix for different types of food. Flour, for example, needs a premix with different ingredients and characteristics than vegetable oil, sugar or rice.

Premix homogeneity depends in part on the design and construction of the equipment used, the operating and cleaning procedures applied, and the achievement of an optimal mixing time that is validated for each type of premix in each particular mixer. It requires expensive machinery that is unlikely to be found in a plant producing low-cost commodities.

High quality assured at all stages

For reputable companies, premix quality also relies on adherence to good manufacturing practices, and especially to effective plant hygiene. This means that buildings are designed for easy cleaning; rooms provide clean air at an adequate humidity and temperature; the manufacturer takes precautions to avoid external contamination (e.g. with microbes) and cross-contamination between batches.

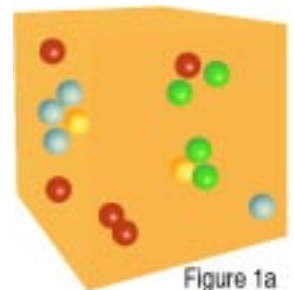


Figure 1a

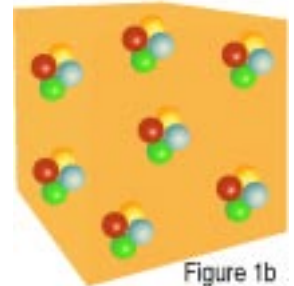


Figure 1b

Distribution of nutrients in simple premixes may be irregular (1a). Use of high-quality premixes ensures a homogeneous and stable distribution of nutrients in the fortified food (1b).

Premix homogeneity depends in part on the design and construction of the equipment used, the operating and cleaning procedures applied, and the achievement of an optimal mixing time.

Manufacturers of high-quality premixes carefully test all ingredients and finished goods at different stages of production to ensure they contain the desired bioavailable nutrients and necessary excipients in a stable form, and nothing else. This simplifies the analyses needed at the food fortification stage, making such premixes easier and less expensive to use.

Reliable premixes can be recognized by the comprehensive documentation supplied with the product, and the fact that they have been certified as reaching internationally recognized standards.

The packaging of high-quality premixes meets the same high standards of quality to minimize deterioration during storage as a result of physical or microbial influences, humidity and oxidation. Labelling identifies the lot number and the exact

weight of the contents, as well as the date by which the premix should be used. Until delivery, the packaged goods are stored, properly labelled, in separate areas under controlled temperature and humidity.

Saving wisely

It is important to remember that the micronutrients added to a food increase the price by only a negligible amount. A high-quality premix with about 30% of the RDA adds between 0.1% and 0.5% to the price of unfortified flour, for example, depending on the number of micronutrients involved. This means an increase in cost to the consumer of between 2 and 11 US cents annually. This affordable amount is not an acceptable reason for fortifying staple foods with substandard ingredients that will hamper the success of public health programs and may endanger the health of the consumer.

Héctor Cori, DSM Nutritional Products

Feature:

Update on vitamin D

Vitamin D refers to two inactive, fat-soluble, precursors—cholecalciferol (vitamin D₃) and ergocalciferol (vitamin D₂)—of a regulatory hormone. Vitamin D₃ (shown to be more bioactive) can be synthesized in the skin by the action of ultraviolet light on 7-dehydrocholesterol. Dietary sources of vitamin D₃ are foods such as oily fish, egg yolk and liver. Ergocalciferol is derived from UV irradiation of plants and fungi. In various countries, milk and/or margarine are fortified with vitamin D.

A liver enzyme (25-hydroxylase) converts cholecalciferol to 25-hydroxyvitamin D₃ (25(OH)D₃). A kidney enzyme (1-alpha hydroxylase) then metabolizes 25(OH)D₃ to the biologically active hormone 1-alpha,25-dihydroxyvitamin D₃ (1α,25(OH)₂D₃), which regulates the absorption of calcium from the diet and the calcification of hard tissues. Nutritional status is best assessed by measuring circulating levels of 25(OH)D₃. D₂ was used for decades to fortify milk and in nutritional supplements. It was recently demonstrated that oral vitamin D₂ has less than one third of the biopotency of vitamin D₃ in supporting the vitamin nutriture of humans. Our knowledge about endocrine aspects of vitamin D continues to grow wider and deeper as research advances.

More than a bone regulator

In the intestine, bone and kidney, 1α,25(OH)₂D₃ is largely involved in the regulation of calcium homeostasis, which is important for normal

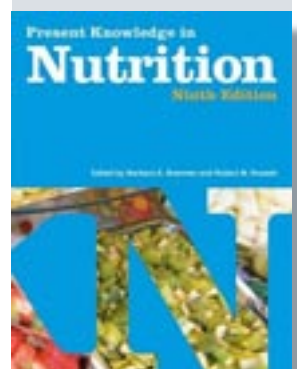
bone metabolism. Parathyroid hormone plays a complementary role in this endocrine system. The vitamin D endocrine system embraces an assortment of tissues beyond intestine and bone; these include pituitary gland, pancreas, breast, placenta, bone marrow and skin, as well as in proliferating cancer cells.

Interesting experiments have appeared using transgenic mice with a gene mutation that eliminates the expression of the nuclear vitamin D receptor (VDR). This produces the condition of (type 2) vitamin-D-dependent rickets. However, even in the absence of vitamin D action, these animals are normal at birth, and feeding them diets high in calcium and lactose can retard the development of overt rickets throughout early life. Furthermore, the finding of impaired insulin secretion in these mutant mice suggests a possible linkage of vitamin D status to glucose homeostasis.

“Rapid response” in membrane signalling

The vitamin D hormone acts like other steroid hormones (such as aldosterone, cortisol and sex hormones) in an interaction with a receptor in the cell nucleus. The receptor-hormone complex then acts in the classical mechanism of up-regulation and down-regulation of the transcription of proteins coded in nuclear DNA, which leads to the biological response. A realm of vitamin D₃ knowledge that has exploded in recent years is in our understanding of another domain of action for the vitamin, the so-called “rapid response” (non-

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



genomic response). This is a signalling system at the level of cellular and intracellular organelle membranes that operates on the time frame of seconds to minutes. A membrane-associated VDR forms a complex with its ligand $1\alpha,25(\text{OH})_2\text{D}_3$ to activate intracellular signalling events such as rapid uptake of calcium by intestinal cells, opening of calcium and chloride channels in skeletal muscle and modulation of a host of regulatory phosphorylation-dephosphorylation reactions in diverse tissues. Some of these reactions are instrumental in the programmed death of cells after many cycles of division.

Recent studies on the three-dimensional structural conformation of active vitamin D in its differential interaction with nuclear receptors and membrane receptors show that the shape of the vitamin preferred in each instance is different. The rotation in the carbon-6-to-carbon-7 bond on the vitamin D molecule can vary. The nuclear VDR links preferentially with a moiety with a crescent-shaped molecule (6-s-trans conformation), whereas the membrane VDR prefers to ligand with a more ellipsoid-shaped molecule (6-s-cis conformation).

New insights into 24,25-dihydroxyvitamin D function

A second metabolite of $25(\text{OH})\text{D}_3$, formed by the enzymatic action of a 24-hydroxylase in the kidney, is 24,25-dihydroxyvitamin D_3 . From the time of its discovery, this metabolite has been suspected of having a physiological role. Only recently have insights advanced. Evidence suggests that two dihydroxylated forms are needed in concert in the diet to produce the complete spectrum of biological responses that we ascribe to vitamin D. This need for synchrony or synergy was first shown in hens deprived of dietary 24,25-dihydroxyvitamin D_3 , when their fertile eggs failed to hatch, and from the demonstration of a unique membrane receptor, specific 24,25-dihydroxyvitamin D_3 in avian bone-fracture healing and rat cartilaginous tissue cells.

Higher intakes advocated

At least as far as the USA and Canada are concerned, there is no established Recommended Dietary Allowance (RDA). What is expressed, instead, is an "Adequate Intake" (AI), which represents the average intake that a specific segment of the population should consume daily. In North America, the AI for vitamin D is set at $5\ \mu\text{g}$ from infancy to 51 years for both sexes. From 51 to 70 years, the AI is $10\ \mu\text{g}$, and this rises to $15\ \mu\text{g}$ in the eighth decade and beyond. In order to generate a legitimate RDA for vitamin D, we would need a firm estimate of the average nutrient requirement for the population in all age-groups

beyond 6 months. Hampering such an assessment is the fact that oral vitamin D needs are variously dependent on age, sex, degree of solar exposure, season of the year and race, as reflected in the density of the skin pigment, melanin.

Recent studies indicate that a substantial portion of the population living at latitudes greater than 42° is exposed to suboptimal levels of sunlight, particularly during the winter months. Wintertime vitamin D insufficiency is common in young Canadian women, and the levels of vitamin D in foods do not prevent the deficiency. Insufficient vitamin D status has also been shown to be widespread through all latitudes in the Republic of China. These findings have prompted calls for vitamin D intakes substantially higher than those currently recommended.

One of the potential mechanisms by which augmented vitamin D status might prevent chronic disease relates to an extrarenal action of the 1-alpha hydroxylase that can convert $25(\text{OH})\text{D}_3$ to $1\alpha,25(\text{OH})_2\text{D}_3$ within cells in peripheral tissues susceptible to carcinogenesis. These tissues include breast, prostate and colon. Such local generation of the dihydroxylated vitamin has putative beneficial anticancer effects, to prevent both the initiation and progression of cancerous transformation.

Overdosage may cause diverse symptoms

The current upper tolerable intake level (UL) for vitamin D_3 is $50\ \mu\text{g}$ daily; advocates of enhancing vitamin D status, however, attest to the safety of such an intake. Case reports of vitamin D toxicity from ingesting improperly (over)fortified milk or from table sugar contaminated with vitamin D are well documented. The manifestations include excessive levels of calcium in the blood and urine, loss of appetite, nausea, vomiting, thirst, excessive urination, joint pains, general disorientation, muscular weakness and loss of mineral from the skeleton. The more calcium that persons with excessive oral vitamin D intakes consume, the more severe are the symptoms.

Future directions

Drs Norman and Henry see future developments in the increased application of chemical analogs of vitamin D in the treatment of human diseases, and further discussion and resolution of the emerging human nutritional issue as to whether the daily requirements for vitamin D_3 from the diet need to be adjusted upwards.



At high latitudes many people do not get enough sunlight for adequate endogenous production of vitamin D, particularly during the winter months.

A summary of the most important advances in knowledge from Chapter 14, Present Knowledge in Nutrition, 9th edition, by Drs Anthony W. Norman and Helen L. Henry, Department of Biochemistry, University of California at Riverside, Riverside, CA, 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.

Feature:

Vitamin D deficiency a global threat?

A lack of sunlight has been recognized as a cause of rickets since the end of the nineteenth century, when rickets prevalence was found to increase with the distance from the Equator. Until recently, daily sunlight exposure of 10–15 minutes to the hands and face was considered sufficient in the temperate zone to produce adequate levels of vitamin D for normal bone metabolism. However, there is an increasing amount of scepticism about this recommendation. Newer studies show that people who avoid the sun or apply sun-protection to reduce the risk of developing skin cancer, tanned and dark-skinned individuals, pregnant women, elderly women and women who cover themselves for religious reasons have an increased risk of vitamin D deficiency, even in tropical countries (high skin pigmentation and sunscreen can reduce synthesis of vitamin D in the skin by as much as 99%). As an alternative to sunbathing, it has been suggested to increase dietary vitamin D intakes. However, a 2005 global review [1] showed that the current foods, supplements and dietary patterns in most countries cannot adequately compensate for the lack of solar exposure. The authors therefore suggested that food fortification with vitamin D should be practised more widely.

High rates in sunny countries

Eis et al. [2] evaluated serum 25(OH)D concentrations in regions outside North America to determine the global prevalence of vitamin D inadequacy in 1163 postmenopausal women with osteoporosis. Prevalence was 42% in South America, 53% in Europe, 57% in Asia, 59% in Australia, 61% in Central America and 82% in the Middle East. It did not appear to be influenced strongly by latitude or season. At the same symposium, Blau et al. [3] reported on the prevalence of vitamin D inadequacy in 252 osteoporotic women living in Southern California. In 53% of them 25(OH)D levels were below 30 ng/mL; 42% below or equal to 25 ng/mL; 29% below or equal to 20 ng/mL; 13% below or equal to 15 ng/mL, and 4% below or equal to 9 ng/mL. Mean 25 OHD levels were not significantly different between women under 65 years and those 65 years and older, or between Caucasian and non-Caucasian.

A recent review published by the Middle East Group of the International Osteoporosis Foundation and endorsed by the leading members of the region's osteoporosis associations confirms that hypovitaminosis D is highly prevalent in the Middle East [4]. It reports on studies from Lebanon, Saudi Arabia and Iran. The study

performed in 316 Lebanese aged 30–50 years found that 72.8% (women 83.9%, men 48.5%) are affected by vitamin D insufficiency (defined by a 25(OH)D value below 15 ng/mL). In women, veil wearing and high parity were predictors of hypovitaminosis D. Another study on 385 schoolchildren aged 10–16 showed that 52% of them were vitamin D insufficient (defined by a 25(OH)D value below 20 ng/mL). Girls, especially those with a lower socio-economic status, were at particular risk. A study in 321 Saudi women with a mean age of 35.4 years, identified severe hypovitaminosis D (25OHD level below or equal to 8 ng/mL) in 52% of them. In Iran, 1210 subjects aged 20 to 64 were studied; 81.3% of them were found to be vitamin D insufficient (25(OH)D levels below or equal to 14 ng/mL). The prevalence of severe and moderate forms was 9.5% and 57.6% respectively. In that study, neither sun exposure nor clothing habits were predictors of vitamin D deficiency.

Also in Iran, Moussavi et al. [5] demonstrated a high prevalence (46.2%) of vitamin D deficiency in students (153 boys and 165 girls aged 14–18 years). Serum 25(OH)D levels were below 20 ng/mL in 72.1% of the girls and 18.3% of the boys. According to the survey by Meddeb et al. in Tunisia [6], accumulated prevalence of hypovitaminosis D in 389 people aged 20–60 years (mainly women) was 47.6%, increasing with age. Prevalence was also associated with multiparity, menopause, wearing the veil, and dietary intake.

Hatun et al. [7] measured 25(OH)D concentrations in 89 Turkish girls aged 13 to 17 years. At the end of winter, 39 girls (43.8%) had serum 25(OH)D between 25 and 50 nmol/L (vitamin D insufficiency) and 19 (21.3%) had 25(OH)D <25 nmol/L (vitamin D deficiency). Girls who wore concealing clothes had significantly lower 25(OH)D concentrations (28.13 ± 12.53 nmol/L) than girls who did not; 50% of them were vitamin D deficient. At the end of summer, vitamin D status improved significantly in the girls who did not follow the Islamic dress code, whereas girls who did showed no change; 70% of them had vitamin D insufficiency and 30% had vitamin D deficiency. Grover and Morley [8] screened 82 veiled or dark-skinned pregnant women attending an antenatal clinic in Melbourne, Australia, for vitamin D deficiency. Sixty-six of them (80%) had 25(OH)D values below the reference range (22.5–93.8 nmol/L).

Response to sunlight varies

A new study [9] suggests that individual response to UVB radiation varies, causing some people to



Women who wear concealing clothes, people with dark skin, and those who regularly use a sunscreen may not produce enough endogenous vitamin D for good health, even when they live close to the Equator.

have low vitamin D status despite abundant sun exposure. Binkley et al. investigated serum 25(OH)D levels in 93 young men and women living in Hawaii. The participants spent an average of 28.9 hours per week outdoors (22.4 hours without sunscreen). Despite this abundant sun exposure, 51% of them had serum 25(OH)D levels below 30 ng/mL; the highest observed level was 62 ng/mL. Overall, vitamin D levels did not correlate with age, skin pigmentation or amount of sun exposure.

The consensus of vitamin D experts at the 2006 vitamin D Workshop in Victoria, British Columbia, Canada [10], was that current governmental guidelines in all countries with respect to how much daily vitamin D is required to maintain bone health and health in general are too low, and do not reflect the many scientific advances made in vitamin D research over the past 10 years. The level of 25(OH)D in the blood should meet or exceed 50 nmol/L (20 ng/mL). As reviewed at the workshop this level is not achieved by half of the North American elderly population and by two-thirds of the rest of the world, and the situation is not much better in younger people. Considering that vitamin D might play a role in the development of some cancers, multiple sclerosis, infection, hypertension and diabetes mellitus, as well as being important for bone health, it can no longer be assumed that individuals with abundant sun exposure have an adequate vitamin D status.

From this evidence vitamin D deficiency appears to be a global problem that has not been adequately recognized in the past.

References

1. Calvo MS, Whiting SJ, Barton CN. Vitamin D intake: a global perspective of current status. *J Nutr* 2005; 135: 310-316.
2. Eis SR, Rizzoli R, Eisman J, et al. Vitamin D inadequacy is highly prevalent globally in women with osteoporosis. *Sixth International Symposium on Osteoporosis: Current Status and Future Directions, April 6-10, 2005, Washington, DC.*
3. Blau EM, Brenneman SK, Bruning AL, et al. Prevalence of vitamin D inadequacy in an osteoporosis population in Southern California. *Sixth International Symposium on Osteoporosis: Current Status and Future Directions, April 6-10, 2005, Washington, DC.*
4. Maalouf G, Gannagé-Yared MH, Ezzedine J, et al. Middle East and North Africa consensus on osteoporosis. *J Musculoskelet Neuronal Interact* 2007; 7: 131-143.
5. Moussavi M, Heidarpour R, Aminorroaya A, et al. Prevalence of vitamin D deficiency in Isfahani high school students in 2004. *Hormone Research* 2005; 64: 144-148.
6. Meddeb N, Sahli H, Chahed M, et al. Vitamin D deficiency in Tunisia. *Osteoporosis International* 2005; 16: 180-183.
7. Hatun S, Islam Ö, Cizmecioglu F, et al. Subclinical vitamin D deficiency is increased in adolescent girls who wear concealing clothing. *J Nutr* 2005; 135: 218-222.
8. Grover SR, Morley R. Vitamin D deficiency in veiled or dark-skinned pregnant women. *Med J Australia* 2001; 175: 251-252.
9. Binkley N, Novotny R, Krueger D, et al. Low vitamin D status despite abundant sun exposure. *J Clin Endocrinol Metab* 2007; 92: 2130-2135.
10. Norman AW, Bouillon R, Whiting SJ, et al. 13th Workshop consensus for vitamin D nutritional guidelines. *J Ster Biochem Mol Biol* 2007; 103: 204-205.

A. Bowley

News in brief:

Call for higher intakes of vitamin D

Following a report on the high prevalence of vitamin D deficiency in the UK [1], an international group of experts has made a renewed call for increasing dietary recommendations for vitamin D [2]. Their arguments are based on the level of 25(OH)D needed to reduce fracture incidence in randomized trials. This level can only be reached with a daily intake of 700-800 IU vitamin D. A new assessment concluded that the safe, tolerable upper intake level of vitamin D for adults should be 10'000 IU/day. This gives a safety margin of more than ten times the currently recommended intake.

They recommend the following measures to correct low 25(OH)D concentrations: moderate exposure of skin to ultraviolet light; appropri-

ate increases in food fortification with vitamin D; higher doses of vitamin D in supplements for adults. The authors are convinced that an improved vitamin D status would benefit public health, and urge all those able to support this idea to undertake new initiatives as a matter of high priority to encourage the reassessment of dietary recommendations for vitamin D.

1. Hyppönen E, Power C. Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. *Am J Clin Nutr* 2007; 85: 860-868.
2. Vieth R, Bischoff-Ferrari H, Boucher BJ, et al. The urgent need to recommend an intake of vitamin D that is effective. *Am J Clin Nutr* 2007; 85: 649-650.

Colorectal cancer after folate fortification

Following the introduction of food fortification with folic acid in the USA and Canada, both countries experienced an abrupt reversal in the downward trend in colorectal cancer incidence seen in the preceding decade. Mason et al. [1] hypothesize that folate fortification might have been wholly or partly responsible for the observed effect.

On the other hand, emerging data suggest that folate may be protective against certain cancers (breast, uterine cervix and others). Studies indicate that the central role of folate in biological methylation and nucleotide synthesis is perturbed in folate inadequacy. Because aberrations in these mechanisms are among the most common pathways identified in carcinogenesis, this provides a biologically plausible explanation for the protective effect of folate.

However, cancer cells often have much higher growth rates than normal cells. This seems to be the case in colorectal adenomas and cancers. Thus, the pivotal role of folate in nucleotide synthesis also makes it a potential growth factor for cancer cells. It seems that folic acid is protective only before neoplastic changes occur. Once these are established, the more folic acid that is consumed, the faster the tumor develops. This would explain why the addition of substantial quantities of folic acid to the food supply could have facilitated the transformation of existing adenomas into cancers, or small cancers into larger ones, making them more obvious at the time of a routine screening colonoscopy.

It has been suggested that the folic acid used in supplements and food fortification might be detrimental, because it is not a naturally occurring coenzyme of the vitamin. Folic acid intake can lead to measurable levels of the unmetabolized form in the bloodstream.

By presenting these data, the authors wish to highlight the potential complexity of the response to folic acid. They stress that their observations do not prove a causal link between folic acid fortification and increased rates of colorectal cancer in the

mid-1990s. It is important that nobody misconstrues the observations or the nature of their interpretation. It would be a mistake to ignore or negate the compelling body of scientific evidence gained over the past 15 years indicating that supplemental folic acid protects against neural tube defects, and that habitually high intakes of dietary folate are protective against colorectal cancer. Clearly, further research needs to be conducted to determine whether the hypothesis is valid.

1. Mason JB, Dickstein A, Jacques PF, et al. *A temporal association between folic acid fortification and an increase in colorectal cancer rates may be illuminating important biological principles: A hypothesis. Cancer Epidemiol Biomarkers Prev* 2007; 16: 1325–1329.

Folate fortification halves NTD prevalence

To assess changes in the prevalence of neural tube defects in Canada before and after implementation of mandatory food fortification with folic acid in 1998, De Wals et al. [1] reviewed 2446 live births, stillbirths, and terminations of pregnancies because of fetal anomalies (recorded among 1.9 million births) to women in seven Canadian provinces between 1993 and 2002. The study, divided into prefortification, partial-fortification, and full-fortification periods, evaluated the relationship between baseline rates of neural-tube defects in each province and the magnitude of the decrease after fortification was implemented.

The prevalence of neural-tube defects decreased by 46% from 1.58 per 1000 births before fortification to 0.86 per 1000 births during the full-fortification period. The decrease was greatest in areas in which the baseline rate was high; geographical differences almost disappeared after fortification began. The Canadian food-fortification program provides an additional daily folate intake of about 150 micrograms.

1. De Wals P, Tairou F, Van Allen MI, et al. *Reduction in neural-tube defects after folic acid fortification in Canada. N Engl J Med* 2007; 357: 135–142.

Photos: DSM Nutritional Products; graphics: A. Bowley

Published by DSM Nutritional Products Ltd, Nutrition Improvement Program, Basel, Switzerland. Opinions expressed are those of the authors, and are not necessarily shared by the publisher. Unless otherwise stated, information published in Nutriview may be reproduced without permission provided that proper credit is given. Please send contributions and correspondence to the Editor, Anthony Bowley, at Mèlèzes 4, CH-1475 Montbrelloz, Switzerland (Email: nutriview@bluewin.ch).

Scientific advisers: Dr Alfred Sommer, Professor of Human Nutrition, Johns Hopkins University, USA-Baltimore MD21205

Dr Ricardo Uauy, Professor of Human Nutrition, Institute of Nutrition and Food Technology, University of Chile, Casilla 138-11, Santiago

Coordinator: Hector Cori, Scientific and Technical Director, Nutrition Improvement Program, DSM Nutritional Products Ltd, Switzerland

Internet: <http://www.nutritionimprovement.com/nutriview.html>