Are low tolerable upper intake levels for vitamin A undermining effective food fortification efforts?

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Vitamin A deficiency (VAD) is a major health problem, particularly in low-resource countries, putting an estimated 125–130 million preschool-aged children at increased risk of morbidity and mortality from infectious diseases. Vitamin A supplementation reduces VAD and increases child survival; it is complemented by fortifying foods with vitamin A. Concern over increased risk of bone fracture associated with vitamin A intakes below the tolerable upper intake level (UL) among populations in affluent countries conflicts with the need to increase intakes in less developed countries, where populations are at greater risk of VAD and intakes are unlikely to reach the UL as diets include fewer foods containing retinol while vitamin A from carotenoids poses no risk of overdose. With the implementation of recently developed risk management tools, vitamin A can be used safely in food fortification, including point-of-use fortification in the context of supplementation among specific target groups in low-resource countries.

INTRODUCTION

Vitamin A deficiency is a major cause of morbidity, mortality and blindness in the developing world, affecting an estimated 125–130 million preschool-aged children and 7 million pregnant women in low-income countries.[1] An estimated 350,000 vitamin A-deficient children become blind every year,[2] and about half of them die within a year of becoming blind. The World Health Organization (WHO) estimated in 1995 that 3 million preschool children throughout the world present ocular signs of vitamin A deficiency and 254 million preschool children had mild-to-moderate vitamin A deficiency, indicated by low serum retinol levels.[3] The prevalence of low serum retinol levels among children under the age of 5 years in various regions of the developing world ranged from 15% to 60% at the end of the 1990s, with Latin America, the Eastern Mediterranean, and Western Pacific at the low end of this range, and Africa and Southeast Asia at the high end.[1,3] The impact of mild-to-moderate vitamin A deficiency on children's resistance to infectious diseases has been recognized but not fully captured in statistical reports; hence, the magnitude of the vitamin A problem may be underestimated. Vitamin A deficiency not only causes night blindness in pregnant and lactating women, it also contributes to maternal mortality and other poor health outcomes.[4] The recent 2005–2006 National Family Health Survey (NFHS-3) in India indicates that vitamin A deficiency is still a significant public health problem in the wider population, as about 9% of Indian women had night blindness during their recent pregnancy.[5]

Vitamin A supplementation reduces morbidity and mortality among preschool children in developing countries.[6] The scaling up of vitamin A supplementation has made progress over the last decade but is still not reaching all vulnerable children with the desired dose.[7,8] High-dose vitamin A supplementation is one of the most

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Table 1 **Tolerable ULs with criteria for derivation, RNIs, and EARs (calculated from RNIs) for vitamin A intake recommended by WHO/FAO.**

Group	Criterion for UL	NOAEL or LOAEL (μg retinol/d)	Uncertainty factor	UL	RNI (μg RAE/d)	EAR (μg RAE/d)
<1 y	Bulging fontanelle, other symptons	6,000	10	600		
1–3 y	Extrapolated from adults			600	400	286
4–6 y					450	321
4–8 y	Extrapolated from adults			900		
9–13 y	Extrapolated from adults			1,700		
14–18 y, male	Extrapolated from adults			2,800		
14–18 y, female	Teratogenicity	4,200	1.5	2,800		
14–50 y, female	Teratogenicity	4,500	1.5	3,000		
19–50 y, female					500	357
Pregnant women, second trimester					800	571
Lactating women 0–3 months					850	607
19–50 y, male					600	429
Other adults	Liver toxicity	14,000	5	3,000		

Abbreviations: EAR, estimated average requirements; LOAEL, lowest observed adverse effect level; NOAEL, no observed adverse effect level; RAE, retinol activity equivalents; RNI, recommended nutrient intakes.
Data compiled from Allen et al. (2006)[4] and Allen and Haskell (2002).[37]

cost-effective health interventions in developing countries. Fortification of foods with vitamin A is a complementary approach applying a valid technology to combat vitamin A deficiency where existing food supplies do not provide adequate amounts of the nutrient.[9] In doses of 200,000 IU (60 mg) of preformed vitamin A per child only transient undesirable effects (such as nausea) have been reported in a few cases, and the long-term protection against the severe pathologies related to vitamin A deficiency clearly outweighs such minimal risk. The difficulty of distribution at the community level, not the adverse effect, is the primary constraint on the use of high-dose vitamin A supplementation.

For safety considerations, combined continuous intakes from fortification and supplementation should not exceed the tolerable upper intake level (UL) which is defined as the highest level of daily intake that is likely to pose no risk of adverse health effects in almost all individuals. The UL is not pertinent to the intermittent high-dose vitamin A supplementation used in some intervention programs.

Recently, as reviewed by Penniston and Tanumihardjo,[10] new concerns about the safety of vitamin A intake have arisen from population observations in Western countries, suggesting an association between preformed vitamin A (retinol) intakes below 3,000 μg/day, the UL for adults, and increased risk of bone fracture. Therefore, the UK Expert Group on Vitamins and Minerals (EVM) has decided to assign a guidance level for long-term intake of vitamin A of 1,500 μg/day,[11,12] which is less than two times the recommended nutrient intake (RNI) of 800 μg/day for pregnant women. Table 1 provides an overview of ULs as well as RNIs and estimated average requirements (EARs) for vitamin A intake (μg/d). Following the recommendations of the UN Food and Agricultural Organization (FAO) and WHO, estimates of vitamin A requirements are expressed as "retinol equivalents" (REs), where 1 μg RE = 1 μg of retinol = 6 μg of β-carotene = 12 μg of other carotenoids with provitamin A activity = 3.33 IU of vitamin A activity from retinol. In contrast, the US Food and Nutrition Board recently concluded that the bioconversion of provitamin A carotenoids from plants is only half the previously assumed level, which led to the new designation of retinol activity equivalent, or RAE.[13]

The purpose of this paper is to review the safety of vitamin A in food fortification, including multiple food fortification, and in targeted high-dose vitamin A supplementation. It is not meant to be a systematic review of all the evidence; rather, it is designed to highlight issues for further discussion. It also aims to document recent developments in risk management with regard to vitamin A.

CHRONIC HIGH VITAMIN A INTAKES

Chronic hypervitaminosis A is relatively rare. It is, however, a potential concern with any vitamin A fortification program. The manifestations of chronic hypervitaminosis A are varied and non-specific, and include central nervous system effects, skin disorders, conjunctivitis, nausea, vomiting, teratogenicity, and hepatotoxicity in adults.[11,13,14] In infants and young children, skeletal and intracranial (e.g., transient bulging fontanelle) abnormalities are of particular concern.[13]

Bone abnormalities

Several studies in industrialized countries have suggested an association exists between chronic higher intakes of preformed vitamin A and bone fracture risk[15–18] or reduced bone mass in humans.[16,19] However, the relationship between vitamin A intake and bone fracture risk has been inconsistent, as several other studies have failed to show any such associations.[20–27] Although the adverse effects of toxic doses of vitamin A on bone fragility in animals have been established (as reviewed by Hathcock et al.[28]), studies suggesting such an effect in humans were retrospective and observational; since they did not involve the extremely high intakes used in animal studies, their results must be interpreted with caution. Most human studies were not specifically designed to examine the relationship between retinol intake and bone health.[12] Some studies used plasma retinol or fasting serum retinyl esters as biomarkers for vitamin A intake, although fasting serum retinyl esters do not correlate with total vitamin A intake.[29] They may reflect recent excess intake rather than long-term intake. In addition, dietary assessment methods used in most studies were inadequate for obtaining reliable estimates of total vitamin A intake. Retinol is found in high concentrations in a limited number of foods (e.g., liver), that are consumed infrequently by most populations. Thus, dietary assessment of preformed vitamin A intake can result in high inter- and intra-individual variance and reliable individual estimation requires either long-term assessment (>20 d)[30] or a semi-quantitative food frequency questionnaire.[31] In the only available randomized clinical trial, short-term high vitamin A supply (7,500 µg/day over 6 weeks) did not affect bone turnover in men.[32] Although very high doses of vitamin A clearly affect bone adversely (as reviewed by Dary and Mora[9]), it is still not clear whether those detrimental effects occur at usual intakes, such as <3,000 µg retinol/day.

β-carotene

β-carotene and other pro-vitamin A carotenoids have no vitamin A toxicity.[9,33] This may explain why no increased risk of bone fracture has been observed with high levels of β-carotene intake[15,16,21,26,27] or in association with high β-carotene serum levels.[17] However, prolonged high-level intake of β-carotene may cause carotenodermia, a yellow-orange discoloration of the skin, which is harmless and without other consequences. Two clinical trials reported an increase in lung cancer in heavy tobacco smokers and asbestos workers associated with daily β-carotene supplements of 30 mg and 20 mg, respectively, but these doses are much higher than those normally available in the diet.[34,35]

SETTING TOLERABLE U INTAKE LEVELS

Tolerable upper intake levels are set to protect the population from adverse health effects. They are derived from NOAELs (no observed adverse effect levels) or, if these are not available, from LOAELs (lowest observed adverse effect levels) by applying uncertainty factors.[13] A UL is only set with an identified hazard and typically when dose-response data is available; it is thus considered to protect virtually 100% of the population.[36] A transient increase above the UL is considered as safe for most people because of the built-in generous safety margin.

Table 1 provides an overview of ULs for retinol intake (µg/day) and the criteria upon which they are based. The US Food and Nutrition Board based the UL for women of reproductive age on teratogenicity and for all other adults on liver abnormabilities.[13] Based on possible birth defects as a critical safety issue, the US Food and Nutrition Board identified a NOAEL of 4,500 µg/day from food and supplements, and applied an uncertainty factor of 1.5 to arrive at a UL of 3,000 µg/day for women of reproductive age. In order to define a UL for men, a LOAEL of 14,000 µg/day for hepatotoxicity and an uncertainty factor of 5 were applied to arrive at a UL of 3,000 µg/day. The US Food and Nutrition Board judged that the conflicting results from the studies on bone fracture risk were not useful for setting a UL for retinol. To derive a UL for infants (aged 0–12 months), case reports of hypervitaminosis in infants were used. A LOAEL of 6,460 µg/day was identified and an uncertainty factor of 10 was applied to arrive at a UL of 600 µg/day. Due to limited case report data of hypervitaminosis A in children and adolescents, the UL values for them were extrapolated from those established for adults on the basis of relative body weight.

The EU Scientific Committee on Food (SCF) identified the following LOAELs: 7,500 µg/day for hepatotoxicity, 3,000 µg/day for teratogenicity and, tentatively, 1,500 µg/day for bone density/fracture.[14] These differ from those of the US Food and Nutrition Board.[13] The adverse effects on bone health were reported at lower daily intakes than the other effects. However, the EU Scientific Committee on Food considered that the data on fracture risk provided insufficient evidence and were not appropriate for establishing a UL. Therefore, the UL for adults has been set at 3,000 µg/day from foods and supplements, based on the LOAEL for teratogenicity. Post-menopausal women are advised to restrict their intake to 1,500 µg/day because of a possible higher risk of osteoporosis. The UL values for infants and children were extrapolated from the value of 3,000 µg/day for adults, with correction for differences in basal metabolic rate using scaling according to body surface area (body weight$^{0.75}$).

The UK Expert Group on Vitamins and Minerals decided there was insufficient evidence to set a "safe upper level", therefore a "guidance level" of 1,500 μg RE (correctly, RE in the form of retinol/day) was established.[11,12] As with the US Food and Nutrition Board and the EU Scientific Committee on Food, they judged it prudent to take 3,000 μg/day as the threshold for teratogenicity. The risk of hip fracture, in contrast, is a continuous, graded response associated with exposure levels that include average dietary intakes. Thus, they judged that total intakes of >1,500 μg/day may be inappropriate. Nevertheless, because of overlap with reasonable dietary intakes, a change in dietary advice to all consumers was not justified.[12] No guidance level was set for children.[11]

VITAMIN A INTAKE IN INDUSTRIALIZED AND DEVELOPING COUNTRIES

Natural sources of vitamin A include retinol and retinyl esters from animal products and provitamin A carotenoids (mainly β-carotene) from fruits, vegetables, and oils. Consumption of natural sources of vitamin A rarely results in toxicity, with the exception of excessive and continued consumption of liver over a long period of time.[37]

Industrialized countries

Vitamin A intake can be relatively high in specific segments of the population. The UK National Diet and Nutrition Survey (NDNS) for adults aged 19–64 years found that the diet of 9% of men and 4% of women include retinol at levels above 1,500 μg/day.[38] Liver and supplements (including fish liver oil) were the major sources for those with retinol intakes >1,500 μg/day, contributing 70% and 16–17% of total retinol intake, respectively. In the United States, about 25% of preschool children exceed the UL of 600 μg/day from foods, but remain below the LOAEL of 6,000 μg/d.[37] In nonpregnant and non-lactating women aged 19–30 years in the United States, however, the 99th percentile of retinol intake from food alone does not exceed the UL. Cases with clinical signs of vitamin A deficiency are rare but do occur in marginalized populations and need due attention (personal communication: Richard Semba).

In developed countries, several foods are being fortified with vitamin A. Important food vehicles include margarine, breakfast cereals, and milk.[37] The increased consumption of fortified foods and dietary supplements containing vitamin A may result in a larger percentage of the population with vitamin A intakes higher than recommended.[37] This may not, however, guarantee an adequate supply of vitamin A in all population groups, particularly in vulnerable groups, such as pregnant and lactating women. Health advice discourages pregnant women from consuming food sources rich in vitamin A, i.e., liver and some types of fish.[39,40] Recently, concern was raised about low vitamin A status in new mothers of high-to-moderate socioeconomic backgrounds in Germany.[41] Accordingly, mothers and their offspring of lower socioeconomic status may be at even greater risk.

Developing countries

Risk factors for vitamin A deficiency in developing countries include low dietary intakes of preformed vitamin A from dairy products, liver, eggs, and fortified foods. Vitamin A intake in developing countries mostly consists of provitamin A carotenoids from fruits and vegetables as vitamin A from animal sources is commonly not affordable for the poor. Hence, dietary diversification is regarded as inadequate for controlling vitamin A deficiency.[42] The presence of infections such as measles, diarrheal diseases and helminth infections also contribute to vitamin A deficiency.[6] Recently, the US Food and Nutrition Board concluded that the bioefficacy of provitamin A carotenoids of plant origin is only half of what was previously assumed.[13] Studies in developing countries estimate that 21 μg of β-carotene from a typical mixed plant-based diet of vegetables and fruits, 26 μg of β-carotene from green leafy vegetables or 12 μg of β-carotene from fruits yield 1 μg RAE. At these conversion rates, it is impossible for young children to consume sufficient quantities of vegetables and seasonal fruits to meet the RNIs or Recommended Dietary Allowances (RDAs). Moreover, most developing areas of the world neither produce nor consume adequate amounts of provitamin A-rich plants.[43]

There is limited information on the contribution of fortified foods to total dietary vitamin A intake in developing countries. Fortified foods have been shown to contribute substantially to vitamin A intake in children, to improve vitamin A status and to reduce the vitamin A-related anemia burden.[44,45] Data from Guatemala indicate that in the 1990s a maximum of 600 μg of vitamin A/day may have come from fortified foods.[44] Preschoolers who consumed fortified foods in addition to a diet that contained vitamin A-rich foods may have temporarily exceeded the UL of 600 μg/day, but this would have been well below the LOAEL of 6,000 μg of retinol. About 40% of Indonesian children aged 11–23 months obtained at least one-third of their RNI for vitamin A from retinol-rich animal-derived and fortified foods; the 95th percentile from all sources amounted to 500 μg/day.[46] Data were collected between 1999 and 2001 among urban dwellers having access to vitamin A-fortified foods (e.g., dry milk, instant noodles, complementary foods, and infant formula).

FOOD FORTIFICATION AND POINT-OF-USE FORTIFICATION IN THE CONTEXT OF SUPPLEMENTATION

In recent years, mass fortification with vitamin A has become more frequent in developing countries. The most common food vehicles for vitamin A fortification include sugar, margarine, vegetable oils, cereal flours, milk, and instant noodles.[4,47]

Excessive retinol exposure from a single source in developing country settings is unlikely. However, concerns about inadvertent excessive retinol intakes have arisen due to overly frequent periodic supplementation combined with concurrent use of multiple micronutrient supplements, point-of-use fortification with micronutrient powders, fortified staple foods, as well as voluntarily fortified commercial foods.

Periodic supplementation with high-dose vitamin A capsules is the approach commonly used for controlling vitamin A deficiency and reducing related morbidity and mortality among children aged 6–59 months in developing countries. Many countries also have policies to provide high-dose vitamin A capsules to women shortly after delivery. Over the last decade, progress has been made in efforts to increase the coverage of vitamin A supplementation programs, but these programs are still not reaching all vulnerable children with the desired dose.[8] In 2004, just 58% of all children under the age of 5 years received two doses of vitamin A per year. In 2005–2006, on average, only 18% of Indian children under the age of 5 years received a vitamin A supplement in the 6 months prior to the national survey.[5]

High-dose vitamin A supplements are used for prophylaxis in breast-feeding women and young children. The WHO and the International Vitamin A Consultative Group currently recommend two doses of 200,000 IU vitamin A administered at least 24 hours apart within 6 weeks after delivery to the mothers; their infants should receive 50,000 IU at 6, 10, and 14 weeks.[42,48] Between 6 and 11 months of age, a single dose of 100,000 IU is recommended, followed by 200,000 IU every 4–6 months between the ages of 12 and 59 months. However, in the Philippines, the prevalence of vitamin A deficiency (serum retinol <0.7 μmol/L) among children under 5 years rose from 35.8% to 38% between 1993 and 1998 despite a comprehensive biannual vitamin A capsule distribution program.[49] Moreover, the effect of the supplementation on serum retinol persisted in most areas and periods for only 1–2 months, rather than the recommended 6 months between doses.

Among malnourished children, only 30–50% of a high-dose supplement is retained.[6] Even the administration of 200,000 IU vitamin A monthly between the ages of 12 and 24 months is likely to be safe, with only mild, transient, adverse effects. Only in the highly unlikely situation that a child's catabolic rate is close to that of an adult and the child receives 200,000 IU monthly between 12 and 24 months of age will liver vitamin A concentrations exceed the proposed cut-off of 300 μg/g.[37] Hence, it appears likely that there is no risk from two high-dose vitamin A supplements per year given to a child under the age of 5 years in the context of concurrent fortification or point-of-use fortification programs.

Periodic high-dose vitamin A supplementation alone is inadequate to address vitamin A deficiency (see discussion on vitamin A intake above). Low coverage with vitamin A supplementation due to lack of supplements and poor compliance, low absorption rate, and the biokinetics of single high-dose vitamin A supplements point to the need for additional approaches to meet the vitamin A requirements of target groups. Moreover, other population groups that are potentially at risk of vitamin A deficiency are excluded from supplementation programs. Dietary diversification is regarded as inadequate to control vitamin A deficiency in this respect.[42] Fortification of food (mandatory and voluntary), use of low-dose supplements, and point-of-use fortification provide complementary approaches and should, on a mid- to long-term basis, replace high-dose vitamin A supplementation under developing country settings. This may encourage increased intake of vitamin A by other high-risk groups that are often unnecessarily excluded from vitamin A supplementation, such as pregnant women.

MODELS FOR SAFE ADDITION OF VITAMIN A

A comparatively narrow range of safe intake is a big challenge to setting safe levels for vitamin A fortification and supplementation. On one hand, there is a potential risk that some consumers may exceed the UL on a daily basis due to the consumption of a limited number of foods (e.g., liver and liver products); on the other, there are significant numbers of people at risk of insufficient intake.[10] Moreover, the UK National Diet and Nutrition Survey[38] demonstrated clearly that the range of intakes for different age and sex groups varies widely, reflecting the limited distribution of preformed vitamin A in foods, i.e., the intake distribution of vitamin A is skewed with median intakes typically 20–50% below mean intakes,[50] indicating that a significant proportion of the population is at risk of inadequate intake.

To ensure that the outcome of a fortification program is adequate and does not lead to harmful intakes, it is important to collect food intake data on all types of food consumed (fortified, unfortified, and point-of-use fortified), as well as other sources such as dietary supplements.[4] This should be supported by findings on nutritional status, including biochemical or clinical data.

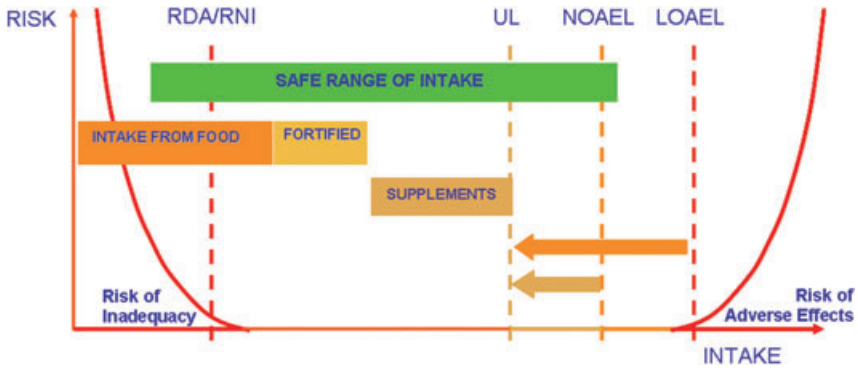

Figure 1 **Safe range of nutrient intakes: from all dietary sources and supplements.**
Abbreviations: RDA, recommended dietary allowance; RNI, recommended nutrition intake; UL, upper limit of tolerable upper intake level; NOAEL, no observed adverse effect level; LOAEL, lowest observed adverse effect level. Supplements also comprise micronutrient powders.

Quantitative food and nutrient intake data should be collected from different population groups. The fortification guidelines of the World Health Organization define the dietary goal of fortification as being to provide most (97.5%) individuals in the population group(s) at greatest risk of deficiency with an adequate intake of specific micronutrients, without causing a risk of excessive intakes in this or other groups.[4] Figure 1 depicts how a safe range of nutrient intakes from all dietary sources and supplements can be assembled.

The EAR cut-point method: model for mass food fortification

The WHO/FAO guidelines on food fortification with micronutrients recommend the EAR cut-point method (Figure 2).[4] This method has been proposed and described in detail by the US Food and Nutrition Board.[51] The method requires the assessment of food and nutrient intake data in specific population subgroups, particularly in the subgroups with the highest risk of deficiency and the highest risk of excess. The EAR is used to estimate the proportion of inadequate intake of a given nutrient in every population subgroup. The aim is to shift the intake distribution upwards so that only 2.5% of the target population remains below the EAR. Knowing the intake distribution of the chosen food vehicle also enables the effect of adding different levels of nutrient to the food vehicle to be simulated. This allows calculating the proportion of intakes below the EAR and above the UL for different fortification levels. Thus, the most appropriate fortification level can be identified, i.e., a level that prevents deficiency in a population at risk, but avoids a high proportion of very high intakes.[4]

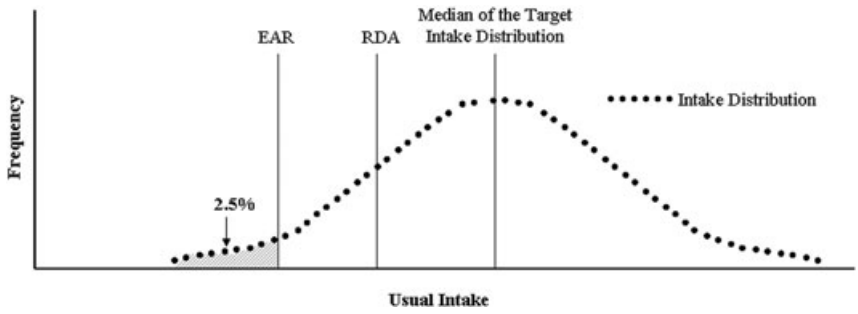

Figure 2 **EAR cut-point method for fortification programs taking benefit and safety into consideration.** Assessment of intake distribution among population subgroups and selection of EAR for planning of "target median intake" shows that 50% of the population is still below the nutrient requirement, which is not acceptable; selection of RDA for planning of "target median intake" reveals that 2.5% of population is below the RDA requirement, which increases the risk of exceeding the UL. Therefore, the recommended planning strategy is to shift intake distribution upwards so that only 2.5% of the target population remains below the EAR, as depicted in the figure.
Abbreviations: EAR, estimated average requirement (median); RDA, recommended dietary allowance.
Adapted from Allen et al. (2006)[4] with permission from The World Health Organization, Geneva, Switzerland.

For mass fortification, it is common practice to use staple foods as food vehicles. Staples are usually consumed in higher quantities by adults than by children. This is different for market-driven fortification. Market-driven fortified processed foods (e.g., breakfast cereals, beverages, nutritional bars) are usually marketed to all family members, and the same serving size may be consumed by all members of the family. Therefore, the maximum micronutrient content per serving size needs to be defined by taking into account the UL for the most vulnerable groups (e.g., children aged 4–8 years), the amount of nutrients provided by the diet and fortified foods (in the context of a concurrent mass fortification program involving this group), and the number of servings per day.[4]

$$\text{Maximum micronutrient content per 40 kcal serving size} = \frac{UL-(a+b)}{15}$$

In this formula, *UL* represents the UL for children aged 4–8 years; *a* represents the amount of micronutrients provided by diet at the 95th percentile of the 4–8-year group; and *b* represents the amount of micronutrients provided to the 4–8-year-old group by fortified foods in the context of a concurrent mass fortification program.

It is assumed that a maximum of 30% of an individual's daily energy intake (2,000 kcal) is derived from fortified processed foods. If the smallest dietary serving size is 40 kcal, the number of daily servings of children aged 4–8 years equates to at least 15.

International Life Sciences Institute Europe: model for voluntary fortification of processed foods

Flynn et al. [52] have developed a model for Europe to determine the safe maximum levels of voluntary micronutrient addition to foods. The maximum amount of a nutrient that can be safely added to foods can be estimated as the difference between the UL and the mean intake of the nutrient at the 95th percentile. The model calculates the amount of nutrient (FA_n) that can be safely added to each 100 kcal portion:

$$FA_n = \frac{[UL - CI_{95}]}{0.5 \times 36 \times PFF_n}$$

In this model, *UL* represents the UL for adult males; CI_{95} represents the intake of micronutrients from non-fortified foods of adult males at the 95th percentile; PFF_n represents the proportion of food in the market that is available for fortification.

The 95th percentile of daily energy intake by adult males in Europe is estimated to be about 3,600 kcal, which corresponds to 36 portions of 100 kcal. Further, it is assumed that no more than 50% of food energy is suited for food fortification because some foods, such as non-processed, non-packaged or traditional foods, are unlikely to be fortified. Other factors limiting food fortification include technological, cost, organoleptic and other constraints. In the development of the model, intakes from supplements were not taken into account because supplement users were considered to represent only a minority of the population.

In Europe, the 95th percentile intake of retinol of adult men exceeds the UL.[52] Therefore, there is no need to fortify other foods or to increase the fortification level of retinol in Europe. More recently, the International Life Sciences Institute model was applied to propose maximal levels for fortification in the Netherlands.[53]

CONCLUSION

In developing countries, the most common nutritional problem is still inadequate provision of vitamin A. Rarely, if ever, is overly frequent dosing or vitamin A intake from too many sources a problem. Indeed, vitamin A supplementation is important to alleviate vitamin A deficiency. However, it remains a short-term solution for practical and economic reasons. In the mid- and long-term, an integrated approach is required that combines low-dose supplementation, food fortification, point-of-use fortification, and promotion of locally available and culturally acceptable vitamin A-rich foods. This will enable the delivery of vitamin A tailored to the needs of all groups in the population. This approach may potentially put some individuals at risk of excessive intake but, in recent years, models have been developed for the safe addition of nutrients to foods. These models should be applied and further adapted to the situations in developing countries, where quality data on vitamin A intakes and status are frequently lacking.

Public health nutrition interventions need to accommodate potential benefits and risks, i.e., achieving optimal nutrient intakes with low prevalence of both inadequate and excessive nutrient intakes. Narrow safety margins for nutrients between desired effects in target populations and potential hazards in others require that public health specialists and policy makers familiarize themselves with simultaneous analyses of hazards and benefits. Thus, an overly cautious setting of the UL, at as low as 1,500 µg retinol/day, would create a substantial barrier to supplementation and fortification with vitamin A in developing countries, because it would conflict with an efficacious intake of the vitamin from all sources. The well-documented and widespread problem of excessive mortality and morbidity in children and mothers as a result of vitamin A deficiency in low-resource countries contrasts sharply with the speculative and inadequately documented risk of osteoporosis in old age in industrialized countries.

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Declaration of interest. KK manages a humanitarian initiative of a vitamin manufacturer that assists in combating micronutrient deficiencies in developing countries. JNH is employed by a vitamin and dietary supplement industry trade association. MW, SDP, RMP, MWB, and RDS have no interests to declare.

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