



## **Symposium Report: Effective and Safe Micronutrient Interventions, Weighing the Risks against the Benefits**

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### **Authors' contributions**

*This work was carried out in collaboration between all authors. Authors IB and MJB wrote the first draft of the manuscript. All authors have contributed to, read, and approved the final manuscript.*

### **Article Information**

DOI: 10.9734/EJNFS/2015/17357

**Review Article**

**Received 10<sup>th</sup> March 2015**

**Accepted 15<sup>th</sup> May 2015**

**Published 27<sup>th</sup> May 2015**

## **ABSTRACT**

Micronutrient fortification of staple foods can be an effective strategy to combat micronutrient malnutrition. When planning on fortification, challenges faced include the collection of essential information on population food and nutrient intake patterns, as well as the use of this information in a method to select appropriate fortification levels. A symposium was organized aimed at discussing the existing approaches to set effective and safe micronutrient fortification levels and to outline the challenges and needs in this area. Two different approaches to establish effective and safe fortification levels for food fortification were presented. In the first approach, the Estimated Average Requirement (EAR) and Tolerable Upper Intake Level (UL) are used as cut-points in the micronutrient intake distribution to evaluate and simulate effective and safe micronutrient intakes.

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This was exemplified by challenges encountered in Guatemala and Cameroon towards unequal vitamin A intake distribution and the impact of the food vehicle choice. Secondly, the risk-benefit approach was presented as an approach in which risks and benefits of micronutrient intakes can be quantified and balanced in order to optimize fortification benefits with the least risks and to allow decision making. This was illustrated by a case on folic acid fortification in The Netherlands. Irrespective of the approach, food and nutrient intake data are required to identify potential vehicles for fortification, quantify the nutrient gap to be addressed, and set the appropriate level of fortification based on consumption pattern. Such information is rarely available to the quality and extent ideal to set fortification levels and requires regular updating, as exemplified in the case of sugar fortification in Guatemala. While the EAR cut-point method can be used to determine the proportion of the population meeting their required and safe nutrient intakes and set goals, risk-benefit assessment may offer an answer to commonly-asked questions as to whether, and at which levels, the benefits of increasing micronutrient intakes outweigh the risks.

*Keywords: Public health; fortification; risk-benefit assessment; deficiency; toxicity; micronutrients.*

## ACRONYMS AND ABBREVIATIONS

<i>ADI</i>	: <i>Acceptable Daily Intake</i>
<i>BRAFO</i>	: <i>Benefit Risk Analysis of Foods</i>
<i>CeSSIAM</i>	: <i>Center for Studies of Sensory Impairment, Aging and Metabolism</i>
<i>DALY</i>	: <i>Disability-Adjusted Life Year</i>
<i>EAR</i>	: <i>Estimated Average Requirement</i>
<i>EFSA</i>	: <i>European Food Safety Authority</i>
<i>FAO</i>	: <i>Food and Agriculture Organization of the United Nations</i>
<i>GAIN</i>	: <i>Global Alliance for Improved Nutrition</i>
<i>HCES</i>	: <i>Household Consumption and Expenditure Surveys</i>
<i>IMAPP</i>	: <i>Intake Monitoring, Assessment and Planning Program</i>
<i>INCAP</i>	: <i>Institute of Nutrition of Central America and Panama</i>
<i>JECFA</i>	: <i>Joint FAO/WHO Expert Committee on Food Additives</i>
<i>IOM</i>	: <i>Institute of Medicine of the National Academies</i>
<i>IU</i>	: <i>International Units</i>
<i>LOAEL</i>	: <i>Lowest Observed Adverse Effect Level</i>
<i>NCI</i>	: <i>US National Cancer Institute</i>
<i>NOAEL</i>	: <i>No Observed Adverse Effect Level</i>
<i>QALY</i>	: <i>Quality-Adjusted Life Year</i>
<i>RAE</i>	: <i>Retinol Activity Equivalents</i>
<i>RDA</i>	: <i>Recommended Daily Allowance</i>
<i>RE</i>	: <i>Retinol Equivalents</i>
<i>RIVM</i>	: <i>National Institute for Public Health and the Environment</i>
<i>RNI</i>	: <i>Recommended Nutrient Intake</i>
<i>UL</i>	: <i>Tolerable Upper Intake Level</i>
<i>USDA</i>	: <i>US Department of Agriculture</i>
<i>WHO</i>	: <i>World Health Organization</i>
<i>WFP</i>	: <i>World Food Programme</i>

## 1. INTRODUCTION

When the level of micronutrient intake is insufficient to meet the requirement, this may result in typical signs and symptoms, which have been fully characterized for each of the vitamins and minerals [1]. For some micronutrients, excessive intake is also a risk factor [2]. The adverse effects related to long-term excessive intake of micronutrients are less-well understood.

Few data on human case reports or case-control studies are generally available to establish safe intake limits or sometimes insufficient to establish a safe limit.

Because of the obvious clinical benefit of overcoming micronutrient inadequacies, most fortification programs have been focusing on micronutrient inadequacies whereas overexposure received little attention, as there is

not yet a solid understanding of the risk that comes with excessive intakes. For most micronutrients there is little concern about excess intake from the amounts typically used in fortification programs. However, the growing number of foods being fortified and simultaneous micronutrient initiatives has risen concern about the safe upper intakes of micronutrients in some developing countries. When a micronutrient inadequacy is widespread, the benefits of addressing the inadequacy are likely to outweigh the risks of excessive intakes. Yet, it is critical to understand whether overconsumption of micronutrients with an upper safe level of intake is actually a true concern. Related to this, it is important to understand how to set micronutrient levels in food that are adequate and safe for the population.

The conference organizers identified a need to understand the risks related to inadequate and excessive intake of micronutrients with fortification. How to set effective yet safe levels of micronutrients in fortified foods is considered a major challenge when planning on food fortification, particularly in the case of micronutrients with a relatively narrow margin of safe intake between the actual intake and the UL, as for folic acid and vitamin A [3].

Sight and Life, the Global Alliance for Improved Nutrition (GAIN), and the Dutch National Institute for Public Health and the Environment (RIVM) organized a symposium titled "Effective and safe micronutrient interventions: weighing the risks against the benefits". The symposium took place on the 3rd of June 2014 on the second day of the Micronutrient Forum Global Conference, held in Addis Ababa, Ethiopia, from June 2-6, 2014. The symposium aimed to discuss existing approaches available to set micronutrient levels in fortified foods, and discuss their values, advantages, disadvantages, and shortcomings, including data needs. Practical examples were added to the program to provide insight into the benefits and challenges experienced in food fortification using these different approaches. This symposium report summarizes the presentations and the questions and discussion raised by the audience.

This report summarizes the five invited presentations and discussions that took place during the symposium. Prof Dr Lindsay H Allen (US Department of Agriculture (USDA), ARS Western Human Nutrition Research Center, Davis, CA, USA) presented on public health risks

and consequences of too low and too high micronutrient intakes in developing countries; Dr Reina Engle-Stone (University of California, Davis, CA, USA) presented on risks of vitamin A inadequacy and chronic or intermittent excess of vitamin A intake in Cameroon; Dr Noel Solomons (Center for Studies of Sensory Impairment, Aging and Metabolism, Guatemala) presented on vitamin A intake distribution among the Guatemalan population: contemporary perplexing perspectives; Prof Dr Hans Verhagen (National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands), presented on integrated risk-benefit assessment in food and nutrition; and Dr Maaïke Bruins (DSM Biotechnology Center, Delft, The Netherlands) presented on the challenge of setting micronutrient fortification levels.

## **2. PUBLIC HEALTH RISKS AND CONSEQUENCES OF TOO LOW AND TOO HIGH MICRONUTRIENT INTAKES IN DEVELOPING COUNTRIES**

Prof Dr Lindsay H Allen (US Department of Agriculture (USDA), ARS Western Human Nutrition Research Center, Davis, CA, USA).

Micronutrient deficiencies or excess intakes of micronutrients can exert a large impact on public health. The prevalence of inadequate and excess intakes can be assessed by making use of dietary intake data and comparing intakes to the recommended values. In addition, biochemical markers of micronutrient deficiency or excess may also be used to evaluate severity of a public health problem or the effectiveness of a public health intervention. Clinical and biochemical markers of deficiencies are generally available for most micronutrients, but are rarely available to detect excessive micronutrient intakes (Table 1). Clinical signs and symptoms of deficiency usually manifest only when the deficiency is severe, and they are often quite non-specific and therefore may be less useful. Biochemical markers of nutrient exposure/status usually change at an earlier stage of deficiency and are more nutrient-specific.

The goal of increasing micronutrient intake by fortification is to provide approximately 97.5% of individuals in a population group with an intake of each micronutrient that meets their Estimated Average Requirement (EAR) while no more than approximately 2.5% of individuals in that

population exceed their Tolerable Upper Intake Level (UL) (Fig. 1) [4].

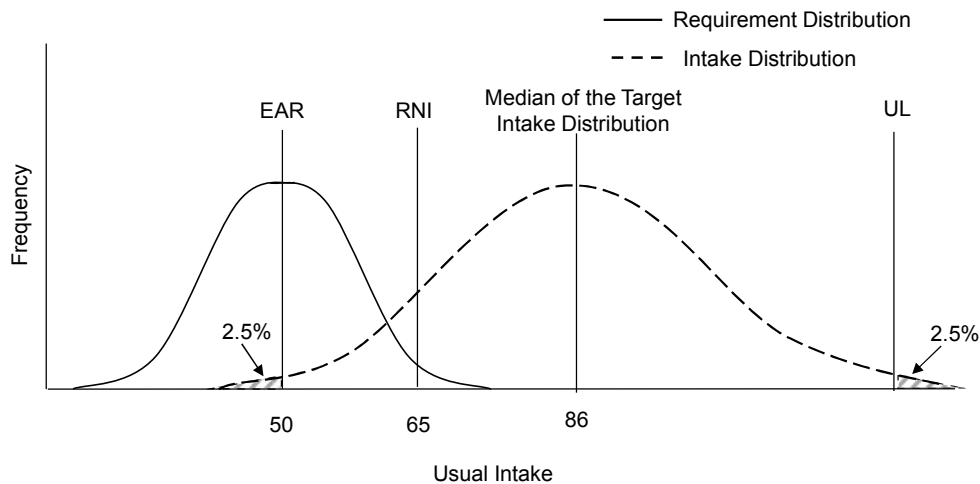
In other words, the probability of both nutrient inadequacy and excess must be acceptably low. In this regard, it is important to note that the UL is an upper safe level of intake within a margin of safety and not a “toxic” level. The UL is derived by dividing the No Observed Adverse Effect Level (NOAEL) or the Lowest Observed Adverse Effect Level (LOAEL) by an uncertainty factor, to account for the uncertainties associated with extrapolating from the observed data. The size of the uncertainty factor depends on features such as the severity of the adverse effect and level of uncertainty about the data, providing a margin of safety.

Biochemical and clinical data collected from a population do not provide quantitative estimates of how much of each nutrient should be added as a fortificant and which food(s) to use as vehicle for fortification. Collection of food intake data is critical before implementing micronutrient interventions [5]. It provides information on micronutrient intakes, shows prevalence of inadequate and excess intakes within a population, reveals the main food sources consumed and can therefore be used to identify the most suitable food vehicles for fortification and predict prevalence of inadequate and excess intakes after fortification (Fig. 2).

need to be added to the diet through fortification or dietary diversification, or possibly through supplementation in particular high-risk subgroups of the population. When planning on fortification, the gap between usual intake and the EAR needs to be identified for all micronutrients in vulnerable population groups. In addition, information on the usual distribution of intake of foods that could be fortified is needed. To this end, intake data need to be collected by food surveys over two days on approximately 100 people per group. Then the prevalence of inadequate intake of each micronutrient needs to be estimated, as well as the local intake of potential food vehicles.

Subsequently, the effect of fortification with different levels of micronutrients can be simulated, including scenarios that result in inadequate and excessive intakes. The software planning program IMAPP (Intake Monitoring, Assessment and Planning Program) can be used to simulate different fortification scenarios [6]. It requires entering nutrient intake data, but it corrects for bioavailability and day-to-day variation in intake and estimates prevalence of intakes below the EAR. The software also simulates the proportion of a population group with intakes below the EAR and above the UL assuming different levels of fortification of food vehicles under consideration.

Well-collected food intake data provide important information on the amount of micronutrients that

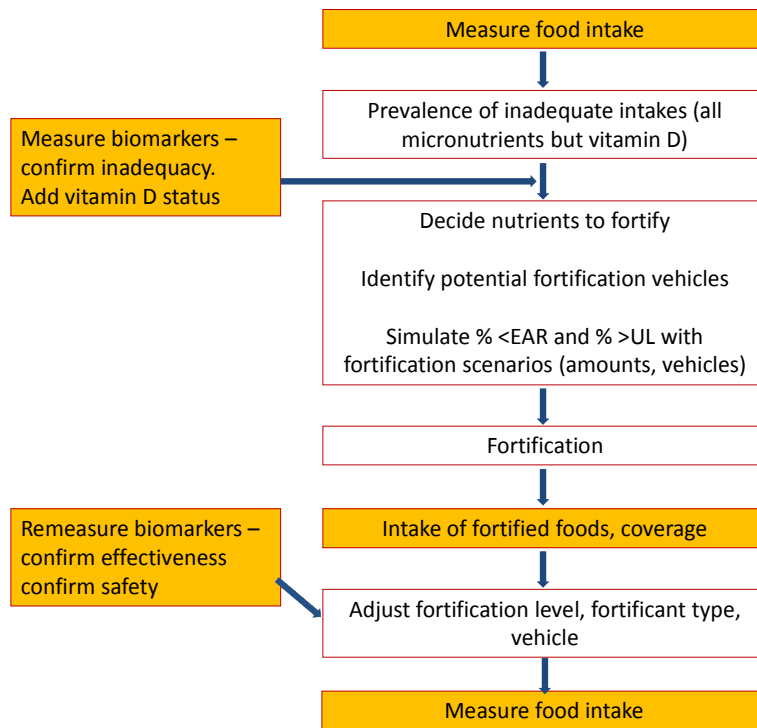


**Fig. 1. The principle of the EAR cut-point method**

For each nutrient, plan so that <2.5% of a population group has intakes <EAR and <2.5% exceed the UL. Modified from [4]

**Table 1. Micronutrients of concern – indicators of too little and/or too much**

Nutrient	Clinical symptom of severe deficiency	Biochemical marker of deficiency	Clinical symptom of excess intake	Biochemical marker of excess intake
Iron	√	√	√	No
Vitamin A	√	√	√	√?
Iodine	√	√	√	√
Zinc	√	(√)	No	No
Folate	√	√	No	√?
Vitamin B12	√	√	No	No
Thiamin	√	√	√	No
Riboflavin	√	√	No	No
Vitamin B6	√	√	√	No
Vitamin D	√	√	√	√



**Fig. 2. Key steps in food fortification programming**

*Food intake data are critical in defining the prevalence of inadequate micronutrient intakes in a population. Next to food intake data, biochemical data on micronutrient status may assist in confirming and complementing food intake data pre- and post-fortification*

Despite their usefulness and importance, nationally representative surveys of individual dietary intakes are rarely performed in developing countries as it is relatively time-consuming to collect all the data and to calculate nutrient intakes by converting food consumption data to nutrient intakes using a food composition database. The use of dietary intake data also has some limitations; the collected data can be

subject to recall bias and bias in recording “good/bad” foods [7]. Another limitation of food intake data is that recording of a single intake day is not usually representative of a person’s usual intake due to day-to-day variation. However, the IMAPP program corrects for day-to-day variation of intake, either by estimating this variation from two days of intake data per individual, or offering an estimate established in

other populations. Another limitation of relating intake data to the EAR and UL is the uncertainty around these reference values. For some micronutrients, the EAR, and especially the UL, is based on a limited number of data, or the data were considered insufficient to even establish an EAR or a UL.

Dietary intake data may not be available, in which case the World Health Organization (WHO) and Food and Agriculture Organization of the United Nations (FAO) method allows one to estimate the usual *per capita* intake of fortification vehicle(s) from household intake data or national food balance sheets [4]. However, the disadvantage of this approach is that prevalence of intakes below the EAR or above the UL is not estimated and vulnerable members of households or populations are not identified.

Biochemical data on micronutrient status may assist in confirming and complementing intake data concerning whether a micronutrient deficiency is a national problem (Fig. 2, Table 1) [8]. For vitamin D, no intake data can be used, thus for this nutrient status assessment relies on measuring plasma/serum 25-hydroxyvitamin D. Changes in biochemical indicators of status can also be useful in monitoring and evaluating the nutritional impact of a fortification program, provided that a suitable biochemical marker of status is available (Fig. 2). In addition, alongside food intake data, biochemical markers of excessive intake, if available, may assist in monitoring the safety of a micronutrient intervention program (Fig. 2). However, collecting biochemical indicators in a field-setting can be invasive, expensive, and laborious and for several micronutrients, no good biochemical markers are available. Biochemical markers such as plasma zinc, calcium, iron and retinol perform relatively poorly due to homeostatic regulation of blood levels and/or potential influence by infection or inflammation, not reflecting true micronutrient status.

Prevalence estimates of specific micronutrient inadequacies based on intake data and biochemical markers may not agree. For example, results may show a high prevalence of inadequate folate intakes accompanied by lower frequency of low plasma folate concentrations [8]. In this case, errors in food composition data might be responsible and should be checked. Moreover, the criteria used to define "inadequacy" in terms of EAR cut-off value versus biomarker cut-off value often differ,

particularly in at-risk groups such as infants and young children and pregnant and breastfeeding women. This may consequently result in different prevalence rates of inadequacy depending on the method used.

For most micronutrients, there is little concern about excess intake from the amounts typically used in fortification programs. However, concerns about exceeding the UL exist for some micronutrients due to the narrow range between the EAR and the UL, particularly when several micronutrient programs (supplementation, staple food fortification, home fortification with micronutrient powders or pastes) are implemented. Table 2 shows the particular cases of concern, which include overconsumption of iron from multiple oral supplements, of folic acid from oral supplements and food fortification, and of vitamin A from oral supplements and (multiple) fortified foods and micronutrient powder. Micronutrient imbalance may also be of concern; both folate and vitamin B12 are important determinants of fetal growth and development. During pregnancy, the increased requirement for folate is met with iron and folic acid supplements and often folic acid fortified flour as well, while vitamin B12 deficiency usually remains untreated [9].

The availability of valid and reliable data determines our ability to develop evidence-based micronutrient intervention programs and policies to achieve nutrition goals. Use of both intake data and biomarkers reflecting nutrient exposure, status, and functional effects is critical for assessing the problem and monitoring/evaluating the efficacy of a program. Current food consumption assessment tools may be subject to substantial measurement errors. Therefore, future efforts should invest in improved methods for collecting and analyzing food intake data. Prevalence of deficiency estimated from dietary intake data and biochemical markers should be compared; if the biochemical deficiency/inadequacy does not confirm the intake data, then a dietary deficiency is unlikely to exist. Research is needed to enable better comparison and interpretation of differences in biochemical markers compared to dietary indicators. Also investment in new technologies may lead to discovery of novel and suitable biochemical markers. We need consensus on the relative strengths or weaknesses and applicability of various biomarkers of micronutrient status under specific conditions. Many biomarkers have been identified; yet formal consensus is limited

regarding the best biomarkers for particular nutrients and applications. It has been recognized that a process is needed to harmonize decision making about which nutrition biomarkers are best suited for a given use, under specific conditions and settings, and whether and when to use infection and inflammation biomarkers to correct biochemical values. A number of concerted actions/programs/networks, such as EURRECA (EUROpean micronutrients RECommendations Aligned) and BOND (Biomarkers of Nutrition for Development), have been initiated aiming to provide further consensus on biomarker use and evidence-informed guidelines.

### **3. RISKS OF INADEQUATE VITAMIN A INTAKE AND CHRONIC OR INTERMITTENT EXCESS OF VITAMIN A IN CAMEROON**

Dr Reina Engle-Stone, University of California, Davis, CA, USA.

In Cameroon, dietary intake data have been used with success to predict the effects of large-scale micronutrient interventions on inadequate and excessive intakes [10]. In addition, a kinetic model of hepatic retinol concentrations was used to model the effect of multiple vitamin A interventions (fortification and supplementation) on liver vitamin A stores of young children.

A national micronutrient survey conducted in Cameroon in 2009 was used as the data source to simulate nutrient intakes prior to and after large-scale food fortification [11]. Dietary intake data were collected by 24-hour dietary recall interviews (with duplicates in a subset) from 1002 households with at least one woman 15-49 years of age and at least one child 12-59 months of age. Usual intake distributions of vitamin A were estimated according to the method developed at the US National Cancer Institute (NCI) [12]. Inadequate and excessive vitamin A intakes were estimated as the prevalence of vitamin A (pro-vitamin A and retinol) intakes below the EAR and the prevalence of retinol intakes above the UL.

The effects of different vitamin A intervention scenarios on vitamin A intakes and the prevalence of intakes below the EAR were simulated by adjusting individual nutrient intake values to reflect the new intervention scenario and then recalculating the distribution of usual intakes by the NCI method. Analyses were

conducted for women and non-breastfed children in three different regions of Cameroon. The following scenarios were simulated: 1) the effect of increasing the vitamin A content of refined oil (which is currently fortified in Cameroon); 2) the effect of fortifying a second food vehicle with vitamin A, i.e., wheat flour, sugar and bouillon cubes. The prevalence of intakes below the EAR for vitamin A in the Cameroonian population suggests a need for interventions to increase vitamin A intakes. The regional patterns of low intake are consistent with the data for low plasma retinol-binding protein concentrations that were measured among children and women as a biomarker of vitamin A deficiency [13].

Simulation of vitamin A intakes suggested that the current oil fortification program would increase vitamin A intakes, but complementary interventions are needed to meet the gap between the EAR and usual intake of vitamin A, especially in the north of the country. The simulations also indicated that fortification of additional food vehicles would not only increase dietary vitamin A, but may also increase excessive intakes of preformed vitamin A in subgroups of children, depending on the food vehicle and level of fortification. The simulations can be used to determine the optimal fortification level in different food vehicles that would result in the lowest prevalence of the population with intakes below the EAR and the lowest prevalence of intakes above the UL. Of the vehicles examined, bouillon cubes was considered the best selection for a second fortification vehicle with respect to balancing inadequate and excessive intakes because bouillon cube consumption was homogenous throughout the country.

It has to be noted that dietary intake modeling has some limitations, such as error in dietary assessments and uncertainty around cutoffs for inadequate and excessive intake, and the fact that physiological risks of intakes between the UL and the LOAEL are unknown. Because, young children in some countries are exposed to both fortification and periodic high-dose vitamin A supplements, any risk of these overlapping interventions should be investigated. The potential risk of excessive vitamin A intake via supplements is, however, difficult to estimate because high-dose periodic supplementation is difficult to translate into an equivalent daily intake value. For that purpose, an Excel-based kinetic model of liver vitamin A was developed at the University of California, Davis. The model can be

used to estimate the potential risk of inadequacy and toxicity (based on liver stores) of specific scenarios meant to improve the vitamin A status of deficient populations [14]. The model was used to assess the risk of intermittent excessive liver vitamin A through high-dose vitamin A supplements on top of multiple programs providing daily vitamin A at different fortification levels in Cameroon. The model's built-in parameters for children 1-2 years of age included: Average liver weight; 2.2% loss of hepatic stores per day [15] and retention of dietary vitamin A (50%). Hepatic retinol concentrations were then modeled for different daily intakes of vitamin A (derived from the dietary simulations), with or without high-dose supplementation. A sensitivity analysis was also performed by estimating the hepatic retinol concentrations, assuming 50% or 70% retention of vitamin A.

Fig. 3 shows an example of a sensitivity analysis for the effect of multiple vitamin A interventions on liver retinol concentrations over time for a young child. Although the upper safe limit of liver vitamin A stores is unknown, a physiologic range of liver vitamin A concentration is between 20 and 300 µg/g liver [16]. Even though some of the scenarios with multiple fortification vehicles resulted in retinol intakes greater than the UL, simulations using the liver model suggested that these intakes would not be associated with hepatic retinol concentrations greater than 300 µg/g liver, even following administration of a high-dose vitamin A supplement (although in some sensitivity analyses liver vitamin A concentrations transiently surpassed this threshold).

Assumed is a total daily vitamin A intake of 1700 µg RAE/d, 50% (blue line) or 70% (purple line) retention of dietary vitamin A, and administration of a high-dose vitamin A capsule (200,000 IU) at 12 months of age. The daily vitamin A intake represents the 95<sup>th</sup> percentile of predicted total vitamin A intakes of urban, non-breastfeeding Cameroonian children 12-59 months of age under a modeled program scenario including fortified oil (12 mg RAE/kg) and fortified wheat flour (5.9 mg RAE/kg). Hepatic retinol concentrations are shown in relation to the cutoffs (red lines) for inadequate and excessive liver vitamin A concentrations of 20 and 300 µg retinol/g liver, respectively [16].

In summary, dietary intake data are useful to predict the effects of micronutrient interventions

on risk of inadequate and excessive intakes, as shown in this case study of large-scale food fortification in Cameroon. Based on the dietary intake simulations, there is evidence that young Cameroonian children (1-4 years of age) may benefit from large-scale vitamin A fortification, but some subgroups may be at risk of exceeding their UL, when multiple food vehicles and/or high fortification levels are in place. The biological risks of intakes between the UL and LOAEL are unknown. In this respect, more research is needed to identify the risks of intakes at the high end of the intake spectrum. A kinetic model of liver vitamin A concentrations may assist in exploring the contribution of high-dose vitamin A supplements to liver stores in children, in combination with dietary intake data. The data from Cameroon suggested that there is a low risk of excessive liver stores under the scenarios examined. For both the intake simulation model and the kinetic model, the quality of the results depends on the quality of the data used. Moreover, empirical validation of the models is still needed. Using these models, the risk of inadequate or excessive intake will depend on whether the targeted population subgroup is reached, stressing the importance of targeted programming. Whether the target group is reached through fortification strongly depends on the choice of the food vehicle and its intake distribution among the population. Therefore, it is important to collect data on intake distribution and not just data on average amount consumed. Besides collecting dietary intake data and program coverage data, it is essential to monitor the actual nutrient content of fortified foods to ensure that the program has the intended impact.

#### **4. VITAMIN A INTAKE DISTRIBUTION AMONG THE GUATEMALAN POPULATION: CONTEMPORARY PERPLEXING PERSPECTIVES**

Dr Noel Solomons, Center for Studies of Sensory Impairment, Aging and Metabolism, Guatemala.

A national survey of Guatemala in 1965-1967 found that 27% of children under-five were deficient in vitamin A based on having serum retinol levels below 20 µg/dL. Starting at the end of 1975, sugar was fortified with vitamin A at 15 mg/kg to address public vitamin A deficiency owing to strong advocacy by Guillermo Arroyave of the Institute of Nutrition of Central America and Panama (INCAP). Mandatory sugar fortification took place from 1975-1977. From October 1975 through November 1977, surveys



were performed in children and lactating mothers showing that only 9% of children suffered low levels of vitamin A in their blood [17]. Immediately thereafter, fortification stopped due to a number of reasons, and vitamin A deficiency reappeared. By 1987, a general study found a situation similar to that of 1965. Voluntary fortification recommenced in 1987, and since that time until today, all sugar was to be fortified at the refinery level of about 15 mg/kg and household level has been constant at about 10 mg/kg. This fortification level of 10-20 mg/kg sugar was recommended such that it would add an average intake range of 400-800 µg retinol equivalents (µg RE/d). This rationale was based on an estimated average sugar consumption by pregnant women at that time of 40 g/d and aimed to provide them 600 (µg RE/d).

Nowadays, many foods are fortified with vitamin A in Guatemala. Many processed foods are fortified with vitamin A such as breakfast cereals and protein-rich *atoles* (e.g., Incaparina), or are made with vitamin A-fortified sugar (e.g. sweet bread, soft drinks). In addition, children could potentially receive vitamin A through special formulated products such as vitamin A-fortified

corn soy blend distributed by the government, micronutrient powders distributed by the World Food Programme (WFP), or fortified lipid spread. Moreover, when enrolled in a vitamin A supplementation program, children can receive six-monthly oral supplements of 200,000 International Units (IU) of retinyl palmitate.

The concern for adverse health effects does not only reside at the lower end of the vitamin A intake exposure or status spectrum. The upper end of the status or intake exposure continuum also can produce adverse consequences.

In order to be able to evaluate and manage potential inadequate and excessive intakes of vitamin A, several (inter)national committees, for example the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the European Food Safety Authority (EFSA) and United States Institute of Medicine's Food and Nutrition Board (IOM) used by both Canada and United States, have set nutrient intake values such as the EAR, the Reference Nutrient Intake (RNI) or Recommended Daily Allowance (RDA) (Table 3) and the UL (Table 4).

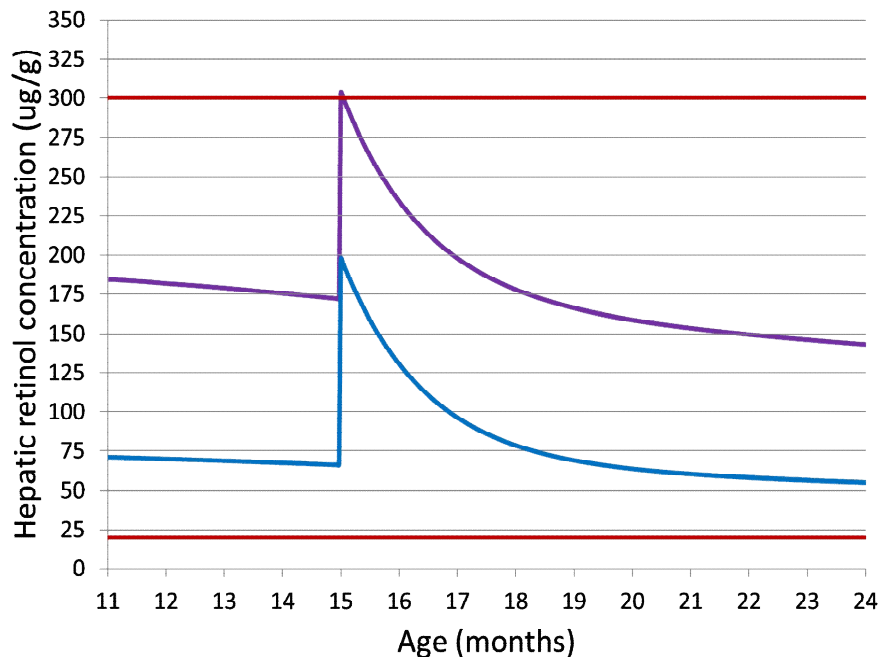


Fig. 3. Predicted changes in hepatic retinol concentration over time among young children

**Table 2. Risks of excessive micronutrient intakes involved in supplementation and/or fortification**

Nutrient	EAR/UL	Risk	Fortification or supplement
Iron	6/45	Inflammation, gastrointestinal discomfort	Supplement
Vit A	625/3000	Liver toxicity, 2X ↑ bone turnover markers, teratogenicity	High-dose supplement + fortification
Iodine	95/1100	Elevated TSH	Excess universal salt iodization, fortification
Zinc	9/40	↓ Copper status	Supplement
Folate	320/1000	↓ B12 status	Fortification, supplement, especially if both
Vit B12	2/–	None	
Thiamin/Vit B1	1.1/–	None	
Vit B6	1.1/100	Neurological damage	Supplement

- In a first step, information needs to be collected on the quantity of the food vehicle and micronutrients consumed in order to quantify the nutrient gaps to be addressed. Biochemical data on micronutrient status can be supportive in confirming whether a micronutrient deficiency is a national problem.
- In a second step the appropriate level of fortification based is determined based on consumption pattern micronutrient intake gap to be addressed. To that end, intakes above the EAR and below the UL are often used to estimate the proportion of the population meeting their required and safe intake, respectively.
- The same process is applied to monitor whether a fortification program is effective and safe, requiring regular updating of the data.
- The value and limitations of dietary intake data, nutrient reference values, and biochemical markers are discussed.

Dietary adequacy is the habitual consumption from all sources of the recommended amount of total vitamin (preformed vitamin A and provitamin A carotenoids) by the individual (RNI, RDA) or by the population group (EAR). The EAR of vitamin A for adults of 600 µg/d was derived from the requirements to maintain liver stores to meet vitamin A needs of a healthy population for 4 months, estimated to be approximately 20 µg/g liver [16]. The RNI or RDA is assumed to be the EAR plus twice the standard deviation of 20%, i.e., calculated by multiplying by 1.4 [20]. Dietary excess of vitamin A is the habitual consumption of dietary preformed vitamin A in excess of the UL in relation to the norms for different segments of the population by age and sex. Because little is known about the risks of excessive intakes, the UL is established by applying an uncertainty factor to the level where no or the lowest adverse effects were observed (NOAEL and LOAEL) from case reports or cohort studies. The UL of vitamin A relates to preformed vitamin A and not provitamin A from carotenoids. Provided it is from dietary sources, there is no UL to provitamin A carotenoid intake, with the only consequence being yellowing of the skin (carotenoderma).

However, there are some caveats related to the ULs for preformed vitamin A. The UL of 3000 µg/d for adults as established by the EFSA is based on a risk of congenital birth defects forming in the embryos during the first trimester of pregnancy [21]. This UL has been extrapolated to other age and gender groups based on relative body size (metabolic weight). However, the risk of congenital birth defects in pregnant women is not relevant to other life stages or gender groups. The IOM and WHO/FAO extrapolated the UL of 3000 µg/d only to all women of childbearing age. The UL established by IOM and WHO/FAO for other gender and life stage groups, is based on the risk of hepatotoxicity of which lowest effects were observed at 14,000 µg RAE/d with an uncertainty factor of 5 and a correction factor for body weight. Since the evidence of adverse effect risks in adults for bone demineralization and skeletal fracture risk for intakes of preformed vitamin A intakes exceeding 1500 µg/d was non-conclusive for adults and absent for children, the EFSA, WHO/FAO and IOM did not take it into consideration.

The EAR reflects the average requirement of vitamin A in a population group, i.e., the intake that meets the requirement of half of this group, whereas the other half is at risk of inadequacy (Fig. 4). The UL reflects an intake level of preformed vitamin A for a population group that is likely still to be safe in this group.

- Cameroon is among the countries that have used dietary intake with success to predict the effects of large-scale micronutrient interventions on the population proportions having inadequate vitamin A intakes and exceeding safe vitamin A intakes using the EAR and UL as cut-point.
- Children (1-4 years of age) may benefit from large-scale vitamin A fortification, but some subgroups may be at risk of exceeding their UL, when multiple food vehicles and/or high fortification levels would be implemented.
- This illustrates that for micronutrients with an UL close to the usual intake, shifting the intake distribution between the EAR and the UL is a challenge.
- Based on a kinetic model of liver vitamin A concentrations predicted that there is a low risk of excessive liver stores under the different scenarios of food fortification and high-dose supplementation examined.

**Table 3. Total daily recommended vitamin A intakes expressed as Recommended Nutrient Intake (RNI) by WHO/FAO and recalculated\* Estimated Average Requirement (EAR)**

Population group	RNI (µg RE**/d)	EAR (µg RE/d)
0-6 mo infants	375	--
6-12 mo infants	400	--
Toddlers (1-3 y)	400	286
Preschool (4-6 y)	450	321
Childhood (7-9 y)	500	357
Adolescent male (10-18 y)	600	428
Adolescent female (10-18 y)	600	428
Adult male (>18 y)	600	428
Adult female (>18 y)	500	357
Pregnancy	800	571
Lactation	850	607

\* EAR values are adjusted from WHO/FAO [4] by recalculating with 1.4 factor

\*\* RE: Retinol Equivalent

**Table 4. Tolerable Upper Intake Levels (UL) of preformed vitamin A established by The IOM (USA, Canada) [18] and the WHO/FAO [4], and the EFSA (Europe) [19]**

Population group	UL (RAE/d) IOM WHO/FAO	Population group	UL (RAE/d) EFSA
6-12 mo	600 <sup>a</sup> & #	6-12 mo	Not determined
1-3 y	600 <sup>a</sup> #	1-3 y	800 <sup>b</sup> §
4-8 y	900 <sup>a</sup> #	4-6 y	1000 <sup>b</sup> §
9-13 y	1700 <sup>a</sup> #	7-10 y	1500 <sup>b</sup> §
14-18 y male	2800 <sup>a</sup> #	11-14 y	2000 <sup>b</sup> §
		15-17 y	2600 <sup>b</sup> §
>18 y male	3000 <sup>a</sup>	>18 y	3000 <sup>b</sup>
14-18 y female	2800 <sup>b</sup> #		
>18 y female	3000 <sup>b</sup>		

\* RAE: Retinol Activity Equivalent

<sup>a</sup> Derived from a LOAEL for hepatotoxicity of 14000 µg RAE/d for adults and an uncertainty factor of 10

<sup>b</sup> Derived from a NOAEL for teratogenicity of 3000 µg RAE/d for adult women

<sup>c</sup> WHO/FAO has no UL established for the age 6-12 mo

<sup>#</sup> Corrected for body weight

<sup>§</sup> Corrected for metabolic weight

A public health problem of endemic hypovitaminosis A is declared based on evaluation of a representative sample (national, sub-national) of serum retinol levels from children aged 6-59 months [22]. Action to address a public health problem of endemic hypovitaminosis A is justified when more than 20% of the surveyed sample has a retinol concentration of  $<20 \mu\text{g/dL}$  ( $<0.70 \mu\text{mol/L}$ ). The Guatemalan nutritional survey of 2008-2009, encountered only 3% of retinol samples below  $20 \mu\text{g/dL}$ , with 1.8% remaining after an adjustment for inflammation [23]. Guatemala could therefore formally classified as a nation without a hypovitaminosis A problem, which can be attributed to the program of sugar fortification.

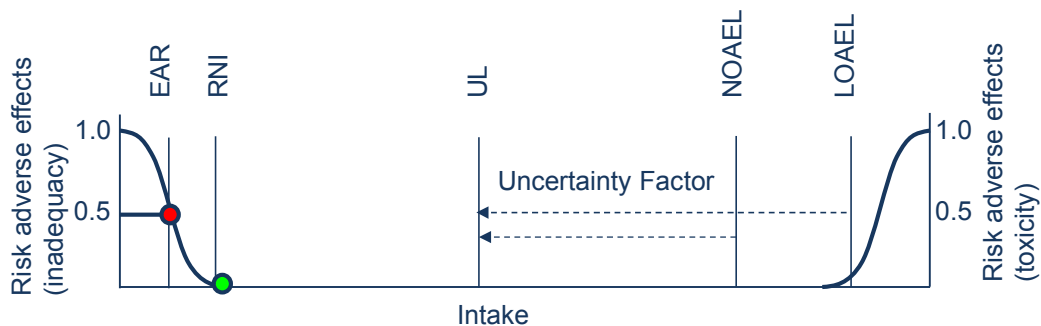
CeSSIAM has contributed what could be considered confirmatory data. This comes from a regional, convenience-sample survey conducted on the Pacific coastal plain; there was not a single sample among 582 serum specimens with a low retinol level below  $20 \mu\text{g/dL}$ ; meanwhile, 13 of 268 samples from children (4.8%) and 1 of 314 (0.3%) of adult women had a marginal retinol concentration below  $30 \mu\text{g/dL}$ . However, this survey may not necessarily tell us that vitamin A intake is adequate in the whole population. There may be geographically uneven intake distributions in the country and there may still be existing pockets of low vitamin A consumption with associated low status for any segment(s) of the Guatemalan population. Meanwhile, with all concurrent vitamin A initiatives available, there could be a summation of sources of preformed vitamin A in other pockets that poses risk of consumption in excess of the UL on an occasional or habitual basis. A survey in the Western Highlands of Guatemala showed that pockets of persistent sub-adequacy indeed still

exist. The Western Highlands of Guatemala showed that 25% of urban pregnant and lactating women had inadequate vitamin A intakes below their (WHO/FAO) RNI of 800 and  $850 \mu\text{g RE/d}$ , respectively (Fig. 5). Contrary to rural areas where inadequate intake prevalence was much higher; 84% of the women did not meet their RNI. This result should ideally be confirmed by the modified retinol dose response as a biomarker of vitamin A inadequacy.

Vitamin A intake data among women of reproductive age from fortified sugar alone has been collected. Fig. 6 shows that in urban populations, 70% of women consumed more than their RNI of  $500 \mu\text{g RE/d}$  of vitamin A from sugar (light-blue) whereas in rural populations, their consumption was less than their RNI of  $500 \mu\text{g RE/d}$  (dark-blue) (Fig. 6). Whether these women with intakes below their RNI were really at risk of inadequacy should be confirmed by the modified retinol dose response as a biomarker of vitamin A status.

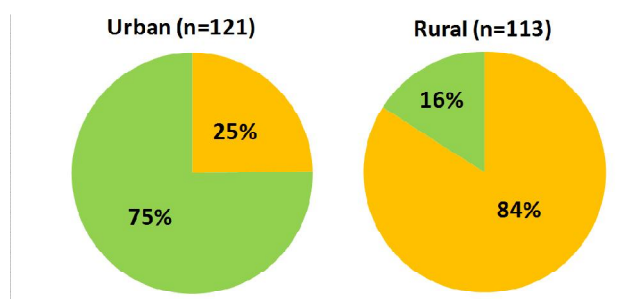
The survey data pointed out that five of the 40 women in the urban region consumed preformed vitamin A in excess of their UL of  $>3000 \mu\text{g}$  on the day prior to interview. This is the UL for vitamin A, edging toward the NOAEL of  $4500 \mu\text{g/d}$  [18].

With all the vitamin A initiatives, it is not unlikely that pockets of habitual excess exposure also exist for children. Hypothetically, a 4 year-old Guatemalan child could over consume with all of the sources of vitamin A superimposed in the diet and from the health care system. This would result in a maximal intake of  $3847 \mu\text{g RAE/d}$  of vitamin A (Table 5).

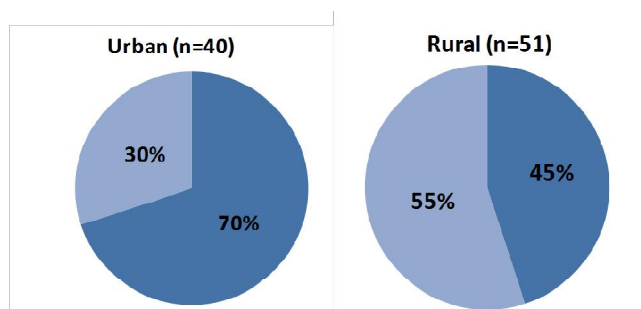


**Fig. 4. Relationship between dietary nutrient reference values and risk of inadequacy or excessive intakes**

*Adjusted from [2]. EAR: Estimated Average Requirement, RNI*



**Fig. 5. Adequate and inadequate vitamin A intakes among pregnant and lactating women in urban and rural Western Highlands of Guatemala**  
 Proportions with intakes above and below the RNI specific for lactating and pregnant women (WHO/FAO) are indicated in green and yellow, respectively



**Fig. 6. Vitamin A intakes from fortified sugar among women in urban and rural Western Highlands of Guatemala**  
 Proportions with intakes above and below the RNI specific for lactating and pregnant women (WHO/FAO) are indicated in light blue and dark-blue, respectively

**Table 5. Hypothetical high intake scenario of a 4-year old child over-exposed to vitamin A**

Source	Form	µg RAE/d vitamin A provided (% of total)
Basic Guatemalan family diet, containing predominantly herbs, fruit, carrots and squashes	Provitamin A carotenes	928 (24%)
Sugar	Preformed vitamin A	1014 (24%)
Other fortified foods	Preformed vitamin A	1636 (43%)
Oral supplement	Preformed vitamin A	267 (7%)*
<b>Total</b>		<b>3847</b>

\* Prorated per day over 183 days

Whether a child with intakes above the UL is at risk of excessive intakes is ideally not only based on food intake data, but also confirmed by elevation of one or another of the still not strongly validated putative indices for excessive vitamin A status. When retinol concentrations in the liver reach about 300 µg/g, circulating levels of retinol may rise in association with increasing circulating fasting retinyl esters [16]. Early studies proposed the use of fasting plasma retinyl ester concentrations greater than 10% of total serum vitamin A concentration (exceeding the

mobilization and transport capacity of Retinol-Binding Protein 4) as a biomarker reflecting excessive intakes [24,25]. However, this notion has been challenged by a study in 2001 with 6547 adults showing no relationship between high fasting retinyl ester concentrations and liver dysfunction [26]. More recently, retinoic acid metabolites like 9-cis retinoic acid have been studied as a function of vitamin A intake. Some of these metabolites mediate the functions of vitamin A required for growth and development but in high amounts may mediate some of the

adverse effects [27]. Despite the large amount of new understanding gained about vitamin A metabolism, the debate continues concerning the use of suitable vitamin A exposure biomarkers.

Since sugar fortification became a national program in Guatemala, vitamin A deficiency is officially no longer a public health problem. This could be considered a historical success story of addressing a nutritional problem in a developing country. However, preformed vitamin A is now consumed in Guatemala from many sources. Therefore, this may also be considered a potential adverse scenario of uncontrolled and uncoordinated summation of sources of preformed vitamin A.

Hypovitaminosis A still exists in pockets of the country, particularly in rural areas. The question now is, what is the way forward for Guatemala? INCAP has proposed a modification in the fortification based on two considerations. The first is the change in the fortification process for the nation. In the early years, all sugar was fortified at the time of its initial harvesting and milling, in the range of 10-20 mg/kg, taking into consideration a loss over the ensuing year. Indeed, sugar collected in households had a concentration ~10 mg/kg, as analyzed by the surveillance system at INCAP. The new procedure involves so-called *just-in-time* fortification, in which vitamin A is constantly being added to sugar just before it goes from the warehouse to market. No longer is post-fortification loss a consideration. The INCAP-recommended range, moreover, has moved down to 5-9 mg/kg, for a median of 7 mg/kg. Given the increase in median sugar consumption of adult women, to an estimated 75 g per day, the 7 mg/kg would provide 525 RE, close to their RNI of 500 RE. As of the moment, the Government of Guatemala is studying the proposed change.

If implemented, this would reduce preformed vitamin A intake by only 350-400 µg/d in the case of our example of the overexposed preschool child (Table 5), but would reduce the percentage of rural reproductive-age women with sugar-based intakes meeting their RNI by approximately 20%. Especially when the intake distribution is right-tailed, exposing a population to interventions with additional vitamin A will reduce the proportion with intakes below the EAR but may unavoidably result in a another (smaller) proportion exceeding their UL. Not allowing the UL to be exceeded may leave a

proportion of the population with intakes below the EAR unaddressed (Fig. 7). More understanding is needed in Guatemala on how adequate intakes for the majority at all ages can be promoted without causing excess intakes, and on how specific rural populations can be targeted for outreach in their moments of increased requirements. In summary, the complex situation requires a multifaceted approach based on the total diet and all available sources of vitamin A.

## 5. INTEGRATED RISK-BENEFIT ASSESSMENT IN FOOD AND NUTRITION

Prof Dr Hans Verhagen, National Institute for Public Health and the Environment (RIVM), The Netherlands. Risk-taking is normal in everyday life if there are associated (perceived) benefits. Risk-benefit assessment compares the risk of a situation to its related benefits and addresses the acceptability of the risk. Risk-benefit assessment in food and nutrition is relatively new. It weighs the beneficial against the adverse effects that a food (or food component) may have, in order to facilitate better informed policy decisions regarding public health issues. It is rooted in the recognition that good food and nutrition can improve health and that some risk may be acceptable if benefits are expected to outweigh such risk.

In the field of food and nutrition, risks are not accepted. In contrast, risks associated with drugs or medicines are generally accepted. Concepts of balancing risks and benefits is common in evaluation of medicines [28]. Moreover, for economics and marketing finance, financial risk management decisions are even a necessity [29]. In the field of food and nutrition, the health burden related to unsafe food is a lot smaller than the health burden related to eating unhealthily or eating too much. For example, the benefits related to eating fruits and vegetables and reduction of cardiovascular disease, cancer, etc, by far outweigh the risks of pesticide contamination [30]. Agricultural pesticides are monitored regularly by government authorities, and are below acceptable daily intake (ADI) levels. Yet residues remain a consumer issue and are mainly a perceived risk, unlike a real risk.

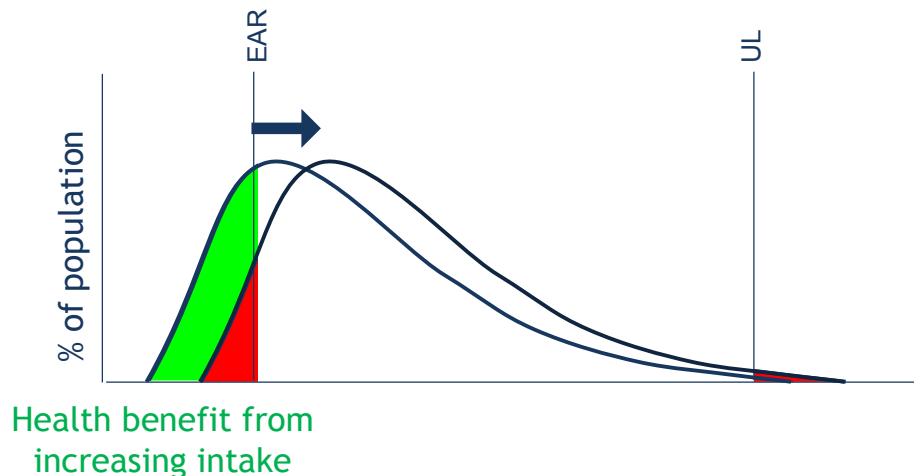
Traditionally, the prevalence of population intakes below the EAR is taken to reflect the risk of inadequacy and intakes above the UL are taken to reflect the risk of excess intakes.

Alternatively, more sophisticated risk-benefit assessments can be used to estimate health benefits and risks of increasing micronutrient intakes without making use of nutrient reference values. Risk-benefit models make use of a step-wise approach as support to decision making related to changes in risks and benefits of food or nutrient intakes. In each subsequent step, additional data on occurrence and consumption will allow the assessment to be refined.

Risk-benefit approaches differ from traditional cut-point methods. Cut-point methods use prevalence of population nutrient intakes below or above nutrient reference values as an estimate of “risk”. Risk-benefit approaches are rather based on intake dose-response effects rather than nutrient reference values as are cut-off points. Risk-benefit approaches use incidence data of adverse effects opposed to prevalence data exceeding a nutrient reference value. Incidence takes into account the number of people affected. Moreover, other dimensions of the magnitude of the risk, such as duration and severity of the adverse health effect, can be integrated into a common health metric such as the Disability-Adjusted Life Year (DALY) or Quality-Adjusted Life Years (QALY). Moreover, by making use of the DALY or QALY as a common metric of “health risk”, deterministic or probabilistic risk-benefit evaluations can be performed. Thus, in risk-benefit assessments,

benefits and risks are assessed in one approach and may conditionally be expressed into one metric. This allows the comparison of adverse and beneficial effects to be qualitative as well as quantitative.

For example, by using the Benefit Risk Analysis of Foods (BRAFO) risk-benefit approach, the risks and benefits of increasing folic acid intakes via bread fortification in the Dutch population were assessed [31,32]. In a first step (Table 6), an inventory was made of the established adverse health effects in the literature associated with increasing folic acid intake. Subsequently the change in incidence rates of these adverse health effects was estimated depending on the increasing folic acid level used to fortify flour for making bread (Table 7). Based on these estimates of changing incidence rates, the benefits may still not clearly outweigh the risks (Table 7). A next step can be performed in which also other dimensions of risk magnitude such as duration and severity of the adverse health effects are integrated into a common health metric such as the DALY. Table 8 shows the net health benefit of bread fortification with folic acid at the level of 70 µg/100 g of flour. The health loss resulting from masked vitamin B12-deficiency in terms of DALYs appeared to be negligible compared to the health gain resulting from prevented neural tube defects.



**Fig. 7. Shifting vitamin A intakes in a population may result in intakes above the Tolerable Upper Intake Level (UL) while leaving a proportion with intakes below the Estimated Average Requirements (EAR)**

- More than 25 years ago, after the vitamin A sugar fortification program was suspended in Guatemala, surveys pointed out that vitamin A deficiency was again a public health problem. Since fortification recommenced in Guatemala in 1987, first voluntary followed by a mandated program, remarkable progress has been made in reducing vitamin A deficiency.
- Nowadays, all sugar for table use and processing, as well as many commercial foods are fortified with vitamin A. Nevertheless, pockets of persistent vitamin A sub-adequacy may still exist in Guatemala as shown by a recent survey while it is not unlikely that pockets of habitual excess exposure also exist.
- The changes in sugar consumption, number of fortified foods, and fortification levels over the years illustrate the need to re-assess the situation on a regular basis.
- Since vitamin A deficiency in Guatemala and vitamin A post-fortification loss are no longer considered problems, lower sugar fortification levels are under consideration. Yet, this will not provide the full solution to the complex problem to address inadequate vitamin A intakes while avoiding excessive intakes.

**Table 6. Hazard–benefit identification: Established health effects of folate and/or folic acid**

<b>Benefits</b>
Reduced incidence of neural tube defects
Reduced incidence of megaloblastic anaemia
Reduced incidence of stroke
A reduced incidence in colorectal cancer
<b>Risks</b>
Increased incidence of neurological damage due to masking of vitamin B12 deficiency
Increase in the incidence of colorectal cancer
Accelerated progression of colorectal cancer

**Table 7. Benefits and risks of bread fortification with folic acid at 70 µg/100 g flour (in The Netherlands): Results as relative or absolute change in incidence rates with folic acid fortification**

<b>Benefits</b>	<b>Δ Incidence relative (absolute)</b>
Reduced incidence of neural tube defects	- 37% (-83)
<b>Risks</b>	
Increased incidence of neurological damage due to masking of vitamin B12 deficiency	+1% (53)

**Table 8. Benefits and risks of flour fortification with folic acid at 70 µg/100 g flour: results as change in DALYs\***

<b>Benefits</b>	<b>Δ DALYs</b>
Reduced incidence of neural tube defects	- 5474
<b>Risks</b>	
Increased incidence of neurological damage due to masking of vitamin B12 deficiency	+ 53

\*DALY: Disability Adjusted Life Year

Nutrients may confer both beneficial and adverse health effects. Measures directed at safety may lead to suboptimal or inadequate intake levels of micronutrients from a benefit perspective. However, not allowing benefits to occur in order to guarantee 100% safety is a risk-management decision much the same as accepting some risk in order to achieve more benefits. A risk-benefit assessment can help risk managers to make

more informed and balanced risk-benefit decisions.

One step further than risk-benefit considerations are cost-benefit considerations in which the costs of the respective options are compared one with another. A review on the health-related economic impact of nutrition interventions published in 2012 found that of the 56 published cost-benefit



studies, 24 studies related to micronutrient interventions, 25 to healthy diets, and 7 to functional foods. The majority of food and nutrition interventions were highly cost-effective [33], suggesting that investing in adequate nutrition can significantly contribute positively to public health and society.

In conclusion, risk-benefit assessment can be a valuable and transparent approach to provide the best possible science-based answer to complicated questions with a large, and potentially optimal, impact on public health. Risk-benefit approaches assist in calculating the risks versus the benefits for public health of food or nutrient interventions. When using common health metrics, the costs of the intervention versus the benefits for public health can be calculated. Ultimately, public health can profit from risk-benefit and cost-benefit assessments. Risk-benefit approaches can help us to understand the magnitude of the risks and assist in making evidence-informed policy decisions in nutrition for the betterment of public health (and reducing their costs).

## 6. THE CHALLENGE OF SETTING MICRONUTRIENT FORTIFICATION LEVELS

Dr Maaïke Bruins, DSM Biotechnology Center, Delft, The Netherlands.

Micronutrient deficiencies impose a major disease burden on the affected persons and the societies in which they live. Micronutrient intervention programs (as part of a broader approach) may be implemented to increase the micronutrients of concern. In addition to the conventional approaches of micronutrient supplementation and large-scale food fortification, novel products have been developed for fortifying foods or complementary foods in the household using fat-based spreads and micronutrient powders.

When setting micronutrient levels for foods or food supplements, the intake levels need to be effective in mitigating the adverse health effects from inadequacy while at the same time needing to be safe. A legal framework provides the means to regulate minimum and maximum limits for micronutrients in foods or food supplements. However, there is currently no broad scientific consensus on the general principles or approaches for the assessment of benefits and

risks to human health of micronutrient deficiency or overexposure and the two are usually conducted independently.

Two main approaches exist in assessing risks of inadequate and excessive intakes that can be used in setting effective micronutrient levels for foods or food supplements. The usual approach in nutrition planning makes use of nutrient reference values as cut-points to shift the population intake distribution. The planning goal for a population (life stage and gender) group is to achieve an acceptably low prevalence of intakes below the EAR, reflecting inadequate intakes and acceptably low prevalence of intakes above the UL, reflecting too high intakes [4,20]. This method requires an estimate of the nutrient intake distribution within the main population groups, rather than just mean intakes.

The EAR is the nutrient intake level that is estimated to meet the requirements of half of a population group, but is inadequate for the other half [20]. The EAR is based on adverse effect markers of inadequacy reported in literature. Evidence on adverse effects due to excessive nutrient intake is often scarce, and usually large uncertainty exists around the level of intake at which adverse effects start. The UL is the level of intake that is likely to pose no adverse effects from too high intakes as it is set a factor lower (depending on the uncertainty and severity) than the highest level at which no adverse effect is observed (NOAEL) or the lowest level at which a relevant adverse effect was observed (LOAEL) [20]. For some micronutrients, a high uncertainty results in a low UL close to the high end intake levels, particularly for children [20,34]. This may pose a dilemma as to whether fortification levels should be set relatively low to ensure a safety margin at the high end of the intake spectrum while leaving a proportion of the population at risk of inadequate intakes, or *vice versa*.

Another approach for deciding on raising nutrient intake levels via foods or food supplements is to apply a risk-benefit assessment [32,35,36]. The risk-benefit approach takes into consideration the differences in adverse health consequences at both ends of the nutrient intake spectrum. The adverse health consequences of inadequate and excessive nutrient intakes are balanced against each other. Decisions are made in steps; at each step, the benefits are weighed against the risks of the nutrient intervention; and a advanced step is invoked if uncertainty still exists [32,35,36].

The relevant adverse health effects related to inadequate and excessive intakes of the nutrient are inventoried in the different population groups. Positive and negative effects before and after the nutrient intervention are expressed as a semi-quantitative or quantitative measure. Modelling of the intake-response relationship of the adverse effects is an important aspect of risk-benefit assessments. Different dimensions of risks can be integrated into a common metric such as the DALY or QALY. These aspects include incidence of the adverse effect (number of individuals yearly affected), the age of onset and time lived with the adverse effect (temporarily, permanent), and the severity or disability of the adverse effect. The risk-benefit approach allows assumptions for the assessments to be made, as long as these assumptions are explicitly stated.

Different fortification levels can convey different types of benefits and risks as illustrated by a risk-benefit assessment case for folic acid fortified flour in The Netherlands [31]. When expressed as incidence rates, at 70 µg folic acid per 100 g of flour, neural tube defects, megaloblastic anemia, and colorectal cancer would be prevented by 83, 2425 and 405 cases/year, respectively, whereas undiagnosed vitamin B12 deficiencies would increase by 53 cases/year (Table 9). In terms of people yearly affected, prevented cases of megaloblastic anemia may appear the biggest benefit; however, when taking into account factors as severity and time lived with the adverse effect, by expressing in DALYs, it becomes clear that preventing neural tube defects has a far bigger positive health impact (5474 DALYs prevented) than reducing megaloblastic anemia (24 DALYs prevented). The largest public health impact was estimated to be achieved with levels between 140 and 240 µg folic acid per 100 g of flour.

Targeted micronutrient intervention programs can be a strategy if the target population at highest risk of micronutrient deficiency is well-defined, usually young children and women of childbearing age [4]. Mass fortification is usually more cost-effective than other strategies, particularly if the micronutrient deficiency is widespread among the general population [4]. The success of mass fortification largely depends on the choice of the food vehicle; the food should be affordable to the target population and be

consumed regularly and in constant amounts by the whole population [4].

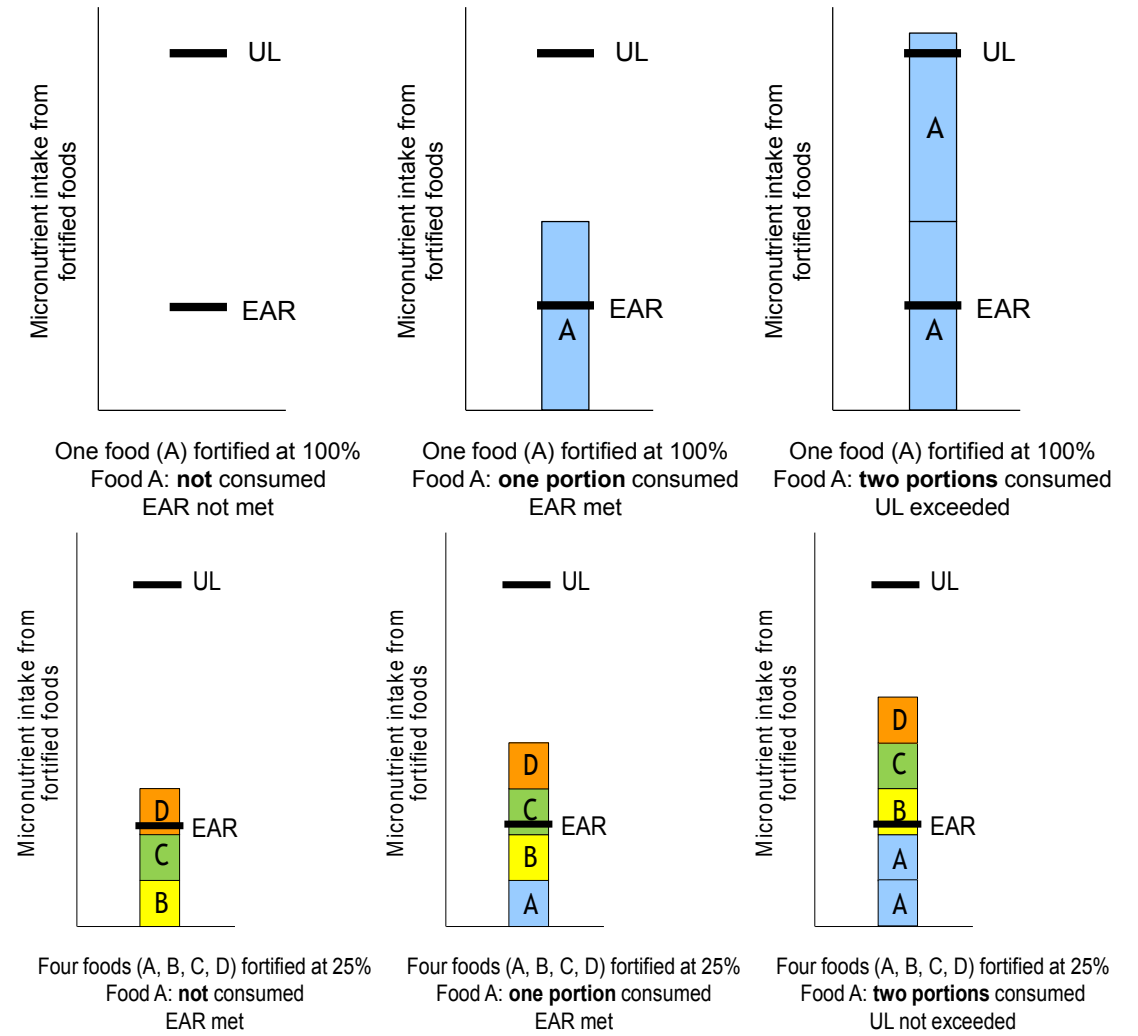
Usual intake distributions of most micronutrients tend to be skewed. For example, a large proportion of the population may consume a small amount of the micronutrient, while a small proportion of the population may consume a large amount. In micronutrient programming, the challenge is to reach the populations at risk of inadequacy while avoiding intakes in those segments that do not need it. I.e. the ideal food carrier has a normal and narrow intake distribution within the population with little excessive low and high intakes. Preferably, the quantity of micronutrient required to address a deficiency is divided over multiple instead of one food [37]; lower micronutrient levels in different foods reduces the chance of excessive intakes while increases the likelihood that a food is consumed by the group most in need (Fig. 8).

In conclusion, methods to assess micronutrient levels in foods and food supplements taking into account risks of inadequacy versus risks of excess differ in approach and concept. Table 10 summarizes the differences in the two main approaches. Consumption data of micronutrients from the usual diet and other sources are required for both approaches but unfortunately are rarely collected. Estimating the additional levels of micronutrients to foods or supplements that are effective in compensating micronutrient deficiencies and meanwhile safe, can be challenging when using the UL as the UL does not give any indication of the magnitude of any risk associated with intakes that exceed the UL [2]. Gaining understanding of the benefits and risks associated with increasing micronutrient intakes, and how serious a risk is, may assist in making decisions. Implementation of micronutrient interventions inherently requires policy decisions on the acceptability of risks of too low or too high intakes.

## 7. AUDIENCE DISCUSSION

The presentations were followed by a general discussion between the audience and the presenters, who took place in the discussion panel. The specific remarks and questions from the audience and the presenter's answers are summarized.

- The principle of risk-benefit assessment is that one must decide what risks to accept in order to get the benefits.
- Decisions are made in a step-wise approach, continuing as uncertainty exists, each step being more refined.
- Risk-benefit approaches are based on the concept that adverse health effects dose-dependently change in response to shifting (micronutrient) intakes.
- In risk-benefit approaches, different dimensions of risks are considered including incidence, duration and severity, in order to quantify and balance the benefits against the risks.
- The use of quantitative measures allows to assess the cost-effectiveness of a food or nutrient intervention.



**Fig. 8. Fortification of one food or multiple food vehicles at lower level: likelihood of exceeding the Tolerable Upper Intake Level (UL) and meeting the Estimated Average Requirement (EAR)** Intake if one food at 100% (upper panels) or four foods at 25% (lower panels) would be fortified. When fortifying only food A at 100%, and food A is not consumed, the EAR would not be met while consumption of two portions of food A would exceed the UL. When fortifying four foods at 25%, and food A is not consumed, the EAR would still be met while consumption if two portions of food A would not exceed the UL. This figure is published in: [38]

**Table 9. Changes in DALYs\* (prevented: Minus, increased: Plus) when fortifying flour with folic acid at 70, 140, 280, 420 µg/100 g flour**

		Δ DALY			
		70 µg	140 µg	280 µg	420 µg
Neural tube defects	Absolute Δ in incidence	-83	-118	-150	-166
	Change in DALYs	-5474	-7710	-9812	-10855
Megaloblastic anemia	Absolute Δ in incidence	-2425	-3197	-4012	-4432
	Change in DALYs	-24	-32	-40	-44
Undiagnosed vitamin B12 deficiencies	Absolute Δ in incidence	53	76	121	166
	Change in DALYs	53	76	120	165
Colorectal cancer	Absolute Δ in incidence	-405	-749	-445	1954
	Change in DALYs	-2217	-4146	-167	21740
Total	Total change in DALYs	-7662	-11812	-9899	11006

\*DALY: Disability Adjusted Life Year

**Table 10. Methods and approaches to set micronutrient levels to foods and supplements**

	Method using nutrient reference cut-points	Risk-benefit approach
Risks	% population intake below EAR* or above UL**	Health impact Semi-quantitative Quantitative
Input	Intake distribution	Intake distribution Intake-adverse effect incidence curves Severity, duration
Simulation	Intake distribution	Intake distribution Relationship intake vs. adverse effect incidence Health impact/disease burden (increased or prevented)

\*EAR: Estimated Average Requirement

\*\*UL: Tolerable Upper Intake Level

Intervention 1: One of the messages that was not made clear from the presentations is that often, the vulnerable group that is used to compare intakes against the EAR is different from the groups that are at most risk of excessive intakes. For example: we may not need to be concerned with pregnant women not reaching their EAR for nutrients but the group that may be at most risk of excess will be adolescent boys who eat a lot of unhealthy foods. That wasn't made explicit, but it is important. If we do these calculations even though pregnant women may be our target group and we want to get 200 samples of dietary intake for the women, we also need information on diet for the other groups who we think are at risk of excess.

Answer Prof Allen to intervention 1: Typically the group that runs the highest risk of exceeding the upper limit is adult men, because their overall food intake is higher. It turns out that adult men are, indeed, the issue.

Intervention 2: We should make sure that we choose the right food vehicle for fortification with

the right levels and the right nutrients in the food and I wanted to comment on the work that has been ongoing in many different regions on the harmonization of fortification levels of staple foods for many different regions. I wanted to hear your thoughts on that sort of process. How to balance between having harmonized standards for country versus individual levels?

Answer Prof Allen to intervention 2: There is value in at least setting a range of harmonized values of reference nutrient intakes to give people some guidance on what is unlikely to ever be useful and what would be too much. Each country and population is so different. The presentations by Dr Engle-Stone and Dr Solomons exemplify how, in a single population, you have these major groups and not tiny little groups that have similar food patterns. I feel strongly you should collect all the information and act upon it. Harmonized reference intake values are designed for populations rather than for individuals; for most individuals in that group they may apply whereas for some individuals may not.

- At intakes equal to the EAR half of the population is at risk of inadequacy. Intakes equal to the UL are unlikely to cause adverse effects as they comprise a margin of uncertainty.
- The usual method to set fortification levels is to minimize inadequate intakes and optimize safe intakes by minimizing the proportion of the population with intakes below the EAR and above the UL, respectively.
- When doubt exists about the benefits versus the risks of increasing micronutrient intakes, a risk-benefit approach may assist in decision making by balancing benefits against risks
- It is important to consider different dimensions of (reduced) risks involved with increasing micronutrient intakes, i.e. (reduced) incidence, duration and severity, when balancing benefits against risks.
- Dividing the quantity of micronutrient -required to fill the micronutrient gap- over multiple instead of one food (i.e. fortify multiple carriers at a lower content) is a suitable strategy to reach groups at risk of inadequacy while avoiding excessive intakes in other groups.

Intervention 3: I think we are handicapped with the approach to figure out what risks and benefits are. Simply, we often do not know the distribution in a population, this may be bimodal in Guatemala, which is one thing. The other thing is if you go out and simulate then you consider everything at an average level. Moreover, there is a lot of intra-individual variation, heterogeneity; I feel we do not exactly know what we are doing. I do also not have an answer, I have that observation. Can we find a way out? I think it is impossible but as Prof Allen was saying we need to collect all the data.

Answer Dr Solomons to intervention 3: I give you praise for the term "heterogeneity". I am interested in heterogeneity in response to nutrient exposures, I think it is the underlying background that we are only now beginning to be able to identify with techniques such as 'omics' where there are explanations for the different responders; but we do not have the money or the technology to identify them, so we treat them as a mixture with a distribution that is smooth. But you have tremendous heterogeneity in genetic, ethnic, life experience features, etc. I am an opponent of "one size fits all". Targeting and screening are important parts of public health that have been neglected. This arises more as a philosophical issue of a misguided notion of equity with which public health began. When it comes to fortification and supplementation, if you do not respect heterogeneity it will come back to bite you with instances of excess.

Answer Prof Allen to intervention 3: We dealt a little bit with heterogeneity of requirements but what we haven't dealt with is the heterogeneity in response to excessive levels. I work in a center that can measure exquisitely small changes in response using 'omic' methods to almost any one single food intervention, or one single

nutrient intervention. In that context, I would like to say that I utterly reject using the LOAEL as a criterion for balancing risk-benefit; we just do not know what we are doing. There is no reason to feed anybody anything that leads to excess exposure in 1% of the population, there is chronic exposure when dealing with fortification. Gene expression changes in response to excess nutrient intakes every minute. Maybe I am exaggerating, but that is the way I see it. A body that is having to deal with this all the time and we should never get on that excessive end because we do not know what is happening.

Intervention 4: Addresses question to Prof Allen; In your presentation, you said something about fortification of flour and you wondered why people do not add vitamin B12 because you think it should be there. You have done work in Kenya and found high rates of deficiency in schoolchildren; meanwhile, we have just finished work in Kenya in pregnant women and there was no evidence of deficiency. So I wonder with fortification policy and guidelines, you are talking about national level? We have a lot of diversity in terms of regions and target groups, e.g., children, women, tribes, dietary patterns. When you say that we should just add vitamin B12 because we can, how would you comment on your bases for that?

Answer Prof Allen to intervention 4: This is a complicated question. Which cut-point method did you find deficiency with? There is a fair amount of debate about that. I actually mentioned folic acid – not vitamin B12 - because there is a substantial amount of data. We have some data too, that folic acid is not masking diagnosis of vitamin B12 deficiency: it is rather exacerbating vitamin B12 deficiency, it makes status worse and we have seen this in a number of populations. In Bangladesh and India, they

often give 2000 µg/d of folic acid along with supplements in pregnancy and sometimes fortification as well but no vitamin B12. Safety of vitamin B12 has no tolerable upper intake level. At least people should get their requirements for these nutrients. Therefore, if you know that intake is low and there is a high prevalence of deficiency, it should be given. If you do not have deficiency, then do not give it as a fortificant or supplement. I am not saying always give it by any means.

Answer Dr Solomons to intervention 4: In Guatemala, because there is no other preparation that is cheap and available, we give children 5000 µg of folic acid with iron every week as part of our national norm. I do not know about their genomics and epigenetics: but because it is cheap and available, they give it. There is no real reason; children are not that fast growing that they are going to run out of their red blood cell folate. In my opinion, what we fortify - folic acid the chemical, totally oxidized form - is different from food-folate forms. So what we fortify with, is folic acid and is 100% oxidized. Preformed vitamin A is as incomparable to carotene provitamin A as oxidized folic acid is to the folate naturally found in food.

Answer Prof Kraemer to intervention 4: Folic acid is the totally oxidized form and usually not occurring in the body, so depending on the dose, it is reduced and methylated when taken up into the body. The dilemma is that the evidence on neural tube defect reduction is coming from folic acid and not from other forms. So it is still used and it might be unethical to use other forms without evidence that other folate forms reduce neural tube defects. I agree, the ideal form in the diet is 5-methyltetrahydrofolic acid, but oxidized folic acid is used for technical reasons primarily.

Intervention 5: It is a really important discussion. You are making this analysis targeting with step one: perfect food intake data, perfect data on neural tube defects, perfect data on compliance in your country. Some countries do not have any of those things. So how can we make a model to go back one more step? How much money should we spend trying to get the data to make the right decision?

Answer Prof Verhagen to intervention 5: If you look at the original paper by Hoekstra from 2008 [28] on folic acid fortification in The Netherlands, it already identifies that there are a lot of things that we do not know. We have to make

assumptions and deal with uncertainties even in The Netherlands, yet, in research what we always say that more research is necessary otherwise we wouldn't be here. What I think is that we should work on the basis of what we have, in real risk-benefit it is the challenge to come to a quantitative basis including all the limitations and uncertainties. Step away from qualitative considerations because that is what we have done in the past with folic acid fortifications. We have prevention of neural tube defects and masking of vitamin B12 deficiency, which are good and bad. So we did not undertake any action based on qualitative findings. Make it quantitative, even with all the uncertainties, so you can indicate that potentially it is good for public health, and you should not ignore the limitations but realize there are limitations and work on that basis. This is considered in The Netherlands, because we did perform a study for the Dutch government, and they were aware of the data; they knew that the fortification of flour with folic acid would be good for public health, but they did not do it for political reasons. We would expose everybody in the population to get benefit, but only a subset of females can get pregnant, not males. There is also another way of getting folic acid in women that can get pregnant, that is - by supplementation. That was the national policy decision following calculations. In summary, for risk-benefit considerations -go quantitative- even with all the limitations, otherwise you will not do a proper job.

Intervention 6: I want to hear your opinion on the use of proxies for dietary intake and add a comment. I chaired the group in 2008 that had to deal with consumption for the guidelines. We did not use availability from FAO food balance sheets because that is useless insofar as it does not have a distribution. In 2008, we decided what dietary intake data was available in the world. Available to us in 2008 were 75 national household consumption and expenditure surveys (HCES). We used those to establish ranges of intake of flour with which to set recommended levels later on. We used the food fortification formulator [34], because Dr Omar Dary was part of the working group, in order to check on potential excess. We had to do a national representative survey, a 24-hr recall with 2 measurements in order to move forward. This implies another question for Dr Solomons, I am also not for a one fits all. We should do a screening. But are we going to have all the tools to do so and individualize public health

interventions? Why do we need national guidelines? They are not recipes? I have not used the risk-benefit method and I like it a lot. Without using DALYs, once you put them quantitative, the whole conclusion changes and we should apply that for public health reasons.

Answer Prof Allen to intervention 6: These proxy countrywide data, how would they handle the description of the differences across Cameroon for example? I do not know a country in which that situation doesn't exist, and that bothers me. These proxies give no textural context: not by poverty strata, not by region, not only by whatever. I would rather have a proxy of percentage energy intake from animal source foods than I would something from a survey like the HCES. I think there probably could be other proxies. I have done dietary intake data surveys, and the fact is that they are not so bad. On the Disability-Adjusted Life Year issue, again I think we do not have the data. The neural tube defects is an easy problem, whereas others are more difficult and you have a lot of different nutrients to be concerned with.

Answer Dr Solomons to intervention 6: The Hippocratic dictum "First do no harm" applies not only to the individual in the clinical setting of medicine, but to population sectors in public health as well. We do not have to screen every single person, but rather find the regions in the country where there are gaps - gaps in any way, e.g. by geographic, ethnic, and economic characteristics. The dosage or coverage needs to be compensated - up or down - whatever the intervention is that is affecting their lives.

Intervention 7: I was interested to hear about the idea of multiple fortified foods at low levels. I was confronted the whole time with the question of having enough and not too much. About 10 years ago, the European Commission was considering legislating maximum safe levels of fortification in Europe. In order to get ready for that, the ILSI Europe model authored by Prof Albert Flynn et al. [35] was used. If you have got reasonable intake data, one may simply calculate the 95th percentile of intake of a micronutrient from food, and add the 95th percentile of the micronutrient from a supplement until you have a certain level of intake. In all cases below the UL, take the difference between this intake value and the UL and divide it into 20 slices of 100 kcal and make some corrections for percentage of food that is fortified. After that, you come up with a maximum safe fortification level per 100 kcal. It doesn't go

into risk assessment beyond using the UL. I can imagine this could be useful in a context with good intake data. In the end the European Commission decided not to legislate. Is this a reasonable model? Maybe a little bit less complicated than doing the risk benefit assessment?

Answer Prof Verhagen to intervention 7: I know this Flynn model. This model provides for safe levels of fortification by 100 kcal and why that works best. Risk-benefit of micronutrients is something different insofar as it also takes into account the risks of deficiency. What you are rightly doing is comparing intakes with an UL, and passing beyond the UL is still safe. If you want to do real risk-benefit calculations, you do not need to compare with an UL: ignore the UL and go for lowest adverse effect level. Then you can really compare. The UL is just a safe limit. If you go for risk benefit, ignore the UL, it is a risk management issue, but only at the LOAEL does an adverse effect start that is where you focus on. That constitutes a completely different comparison.

Intervention 8: When I hear about excess intake, the evaluation point has just been pointed out as the UL. If we were to apply this to developing countries the UL is inappropriate. In the sense that it is very much based on Western ideas of how to measure excessive intakes. In developing countries, the issue is not so much excessive intakes in people alone, but also risk of infectious diseases. The risk of excessive folic acid intakes in a person with malaria may be different from that in a healthy person. Folic acid supplementation may reduce the efficacy of anti-malaria drugs. The anti-malaria drug Cotrimoxazol is given as primary drug intervention for malaria and prophylaxis in HIV-infected adults, but folic acid supplementation may impair its effectiveness and increase the risk of malaria. For neural tube defects, folic acid may be of benefit; in Africa, the number of neural tube defects is more than 6000 per year [36], but for malaria-treated individuals folic acid may not be effective and malaria is more prevalent than neural tube defects. Some sort of risk-benefit analysis could be applied to assess the risks and benefits of folic acid fortification in developing countries.

## **8. SUMMARY**

Several key messages emerged from the symposium. Before considering a micronutrient

fortification program, it is essential to collect food and nutrient intake data in the different population groups, supported by ancillary information such as biochemical data on nutritional status, and possibly clinical data. This helps to gain insight into the groups to be targeted, target intake levels and the most suitable food vehicles for fortification. In a second step, the data are used to simulate the effect of different food vehicles and micronutrient food contents. The EAR and UL can be used to estimate the effect of different fortification scenarios on the proportion of the population with adequate and safe intakes, or a more elaborated risk-benefit approach can be used to model the benefits and possible risks. Repeated food intake data collection after implementation allows for subsequent monitoring and evaluation of the programs' efficacy and safety.

At intakes equal to the EAR, 50% of the population is at risk of inadequacy and intake equal to the UL is unlikely to represent a risk of adverse effects. Shifting micronutrient intakes such that the EAR is met in the target population without exceeding the UL in any of the population groups is a challenge in mass fortification. In order to decide on fortification strategies, and acceptability of risks, understanding of the potential risks below the EAR and above the UL and their magnitude in terms of health impact is essential.

In Cameroon dietary intake data and biochemical markers have successfully been used to inventory the public health problem of vitamin A deficiency. Simulation of the current oil fortification in Cameroon suggested that vitamin A intakes would increase, however, insufficiently to meet the requirements. Fortification of additional food vehicles would help to meet the dietary gap, however, depending on the food vehicle and level of fortification, also increase intakes in subgroups of children in excess of their UL. When modelling the effect of different fortified foods and high-dose supplements on the contribution of vitamin A to liver stores in children, minimal risks of excessive liver stores were shown. In Guatemala, most of the sugar and many foods are nowadays fortified at levels that deliver effective vitamin A amounts for preschoolers. This has been important in reducing prevalence rates of vitamin A deficiency and related adverse health effects. Still, intakes below the EAR associated with low status exist for vitamin A in segments of the Guatemalan population. Meanwhile, it cannot be excluded

that the expanding number of vitamin A-fortified foods puts some preschoolers at risk of exceeding their UL. This illustrates the difficulty of shifting the intake distribution such that both intakes below the EAR and above the UL are minimized.

The choice of the food vehicle and its distribution of intake in the population is important as illustrated for vitamin A fortification in Guatemala and Cameroon; the food should be consumed by the whole population, yet in constant amounts. However, fortifying one food at the target level may not adequately reach the target population and fortifying multiple foods at high levels may overexpose some groups. Dividing the target level over multiple foods can be a strategy to more equally distribute intake of the target micronutrient(s).

A risk-benefit assessment provides insight into the possible risks and benefits associated with increasing food or nutrient intakes. It can simulate how health benefits and health risks change as result of increasing micronutrient intakes; the benefits of reducing a micronutrient inadequacy versus the risks of excessive consumption. The approach has been used to evaluate the largest net health gain with different food fortification scenarios as exemplified by folic acid-fortified flour in The Netherlands. The risks and benefits are quantitatively expressed by considering the number of people affected, severity, and duration of the health effect. By expressing the benefits and risks quantitatively, they can be balanced, allowing decision making on the most appropriate fortification level.

Given the potential of long-term health benefits of successful fortification programs, it is essential to ensure proper investment in collection of food intake data and preferably biochemical and clinical markers to evaluate and monitor whether intakes are adequate and safe. Population intake distributions in relation to the EAR and UL provide rough estimates of adequate and safe intakes, while risk-benefit approaches can provide more in-depth assessment of quantitative health benefits and risks at the two ends of the intake spectrum. Risk-benefit modelling offers an important answer to the most commonly-asked question as to whether the benefits of increasing micronutrient intakes outweigh the risks. More data collection and advanced modeling will lead to smaller uncertainties around the benefits and risks. Lessons can be learned from experiences in different countries implementing micronutrient



programs, that knowledge can be applied to provide guidance to public health policy and program design.

## 9. CONCLUSION

In conclusion, risk-benefit assessment can be a valuable and transparent approach to provide the best possible science-based answer to complicated questions with a large, and potentially optimal, impact on public health. Risk-benefit approaches assist in calculating the risks versus the benefits for public health of food or nutrient interventions. When using common health metrics, the costs of the intervention versus the benefits for public health can be calculated. Ultimately, public health can profit from risk-benefit and cost-benefit assessments. Risk-benefit approaches can help us to understand the magnitude of the risks and assist in making evidence-informed policy decisions in nutrition for the betterment of public health (and reducing their costs).

## ACKNOWLEDGEMENTS

We acknowledge the contributions of Kenneth H Brown and Marjorie J Haskell (UC Davis) and Martin Nankap and Alex O Ndjebayi (Helen Keller International) to the Cameroon vitamin A analyses and the assistance of Marieke Vossenaar (CeSSIAM) in the data-analysis and presentation preparation for the Guatemalan setting.

## COMPETING INTERESTS

Maaikje J Bruins is an employee of DSM. Ingrid Bielderman, Klaus Kraemer, and Jane Badham are employees of Sight and Life, a humanitarian nutrition think tank of DSM.

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