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Risk of excessive intake of vitamins and minerals delivered through public health interventions: objectives, results, conclusions of the meeting, and the way forward

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The excessive consumption of certain vitamins and minerals could have deleterious consequences on health and development of individuals and populations. Simultaneous micronutrient-delivery interventions could be challenging in terms of safety as the target populations may overlap, posing a risk of excessive intake of certain micronutrients. The Evidence and Programme Guidance Unit of the Department of Nutrition for Health and Development of the World Health Organization convened a technical consultation on the risk of excessive intake of vitamins and minerals delivered through public health interventions in October 2017. The technical consultation's working groups identified important and emerging technical issues, lessons learned, and research priorities related to (1) planning, implementing, monitoring, and evaluating nutrition programs for the detection and control of the risk of excessive intakes; (2) safety, quality control, and assurance considerations; (3) coordination between public health nutrition interventions and other interventions and sectors; and (4) the legislative framework and policy coherence needed for simultaneous nutrition interventions. This paper provides the background and rationale of the technical consultation, synopsizes the presentations, and provides a summary of the main considerations proposed by the working groups.

Keywords: risk excessive intake; vitamins; minerals; public health interventions

Introduction

Policies and actions to address micronutrient deficiencies often face the challenge of coexisting integrated health programs with different levels of implementation and maturity, providing to the same or different segments of the population. Simultaneous micronutrient-delivery interventions pose several challenges in terms of safety as the target populations of different interventions may overlap, and thus these populations or individuals within these population groups may be at risk of excessive intake of certain micronutrients. This is principally relevant in stable settings where multiple stakeholders work jointly or separately delivering micronutrients through public health interventions, such as universal or targeted fortification of staple foods, provision of fortified complementary foods, or daily or intermittent micronutrient supplementation consumed alone or added onto prepared foods immediately before consumption (e.g., point-of-use fortification).

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The excessive consumption of certain vitamins and minerals could have deleterious consequences on health and development of individuals and populations. The Food and Agriculture Organization of the United Nations (FAO)/the World Health Organization (WHO) Expert Consultation on Human Vitamin and Mineral Requirements held in Thailand in 1998[1] reviewed the concept of upper tolerable nutrient intake level or upper level (UL) as the "maximum intake from food, water and supplements that is unlikely to pose risk of adverse health effects from excess in almost all (97.5%) apparently healthy individuals in an age- and sex-specific population group." The term tolerable upper intake level (UL) is also defined by the Institute of Medicine of the United States as "the highest level of nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population. As intake increases above the UL, the risk of adverse effects increases."[2]

It is important to highlight that the UL is not a limit for excess or toxicity, but a level of security for healthy populations. Intakes between the recommended nutrient intake (RNI) (or the recommended dietary allowances (RDAs)) and the UL should be sufficient to prevent deficiency while avoiding toxicity. ULs should be based on long-term exposure to all foods (including fortified or biofortified items), any other intervention providing micronutrients and nutrition sensitive measures aimed to improve their bioavailability. For most nutrients, no adverse effects are anticipated when they are consumed as foods because their absorption and/or excretion are physiologically regulated.

With a view of providing policymakers with the best available evidence to inform policies and programs simultaneously providing micronutrients across the population or specific population groups, the WHO Evidence and Programme Guidance Unit of the Department of Nutrition for Health and Development convened the technical consultation "Risk of Excessive Intake of Vitamins and Minerals Delivered Through Public Health Interventions–Current Practices and Case Studies" held in Panamá City, Panamá on October 4–6, 2017. Existing evidence on the safety of the provision of micronutrients to vulnerable populations in settings where a combination of interventions include micronutrients was examined, along with programmatic evidence of successful implementation experiences, best practices, and lessons learned.

The objectives of the consultation were to:

(1) Examine the current estimates for the total intake of vitamins and minerals (e.g., calcium, folic acid, iodine, iron, vitamin A (VA), vitamin D, and zinc) through diet and by different interventions implemented simultaneously in order to predict risks of excessive intake of vitamins and minerals and potential adverse effects while focusing on experiences of micronutrients delivered through public health interventions;
(2) Analyze national and subnational case studies of existing policies and programs delivering vitamins and minerals through integrated interventions, particularly considering the risk of excessive intake of micronutrients;
(3) Identify implementation considerations that could be useful to member states when considering simultaneous interventions that deliver vitamins and minerals through public health interventions and evaluating the use of upper tolerable nutrient intake level as a reference level to not be exceeded by all interventions simultaneously applied at a particular moment; and
(4) Identify monitoring, evaluation, and communication strategies for constant surveillance and information about the initiation or termination of programs.

Before this technical consultation, the Evidence and Programme Guidance Unit launched a call for authors interested in preparing review papers on diverse topics related to the risk and consequences of excessive intake of vitamins and mineral delivered through public health programs. The papers and case studies reviewed existing evidence on the provision of micronutrients to different population groups in settings where combinations of interventions include the provision of micronutrients. Gathering programmatic evidence including successful implementation experiences, best practices, and lessons learned could provide policymakers with the best available evidence to inform policies and programs simultaneously supplying micronutrients across the different population groups.

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The consultation was based on, but not limited to, the background papers and case studies that were commissioned through the public call for papers. It included the presentation of the commissioned papers and other topics of interest, plenary discussions, and a session for working groups. The participants were organized into four working groups to address topics relevant for discussions and presented their conclusions in a plenary session that was finalized with further discussions. The topics for working groups were:

Group 1: planning, implementing, monitoring, and evaluating nutrition programs for the detection and control of the risk of excessive intakes;
Group 2: coordination between public health nutrition interventions and interventions from other sectors;
Group 3: safety, quality control, assurance considerations, emergency settings, and ethical issues;
Group 4: regulatory framework and policy coherence.

This paper provides the background and rationale of the technical consultation, synopsizes the presentations, and provides a summary of the main considerations proposed by the working groups.

Technical consultation

Dietary reference values: estimated average requirements, recommended nutrient intakes, and upper limits

The initial objective of dietary reference intakes was to support assessment and design of diets for individuals, groups, and populations that provide adequate but not excessive amounts of micronutrients required by human physiology.[3] This acknowledges that more is not always better, meaning that the function and effect of micronutrients depend on concentration, not on quantity. The concentration depends on the size and volume of the person.

The difference in the percentage of coverage between estimated average requirement (EAR) and RDAs or RNI is 50% versus 97%, respectively. EAR is an average daily nutrient intake level that is estimated to meet the requirements of half of the healthy individuals in a particular life stage and gender group. RNI or RDA is an average daily nutrient intake level that is sufficient to meet the nutrient requirements of nearly all (97.5%) healthy individuals in a particular life stage and gender group.[1,3,4] If there is no information about EAR or RDA, adequate ingestion (AI) should be used. AI is based on experimental observation with healthy individuals and is usually a larger number than the RDA/RNI.

Above a certain threshold, the higher the intake, the greater adverse effects at the individual and population levels, but the UL is located before adverse effects. It is the highest level of intake that poses no risk to almost all individuals. The UL is not a determinant; it does not mean that there is no problem but there is not enough information. It is important when planning an intervention to consider that the largest volume of people would have a final micronutrient intake above the RDA and below the UL.[2] As a first step, it is key to analyze the diet, and then to plan the intervention considering the inadequacy; this way, it is possible to include only the nutrients in need and not aiming to cover 100% of the requirement, since there are always dietary contributions for each nutrient. The goal of nutrition programs is to complement the diet in order to satisfy nutrient requirements; it is not to supply 100% of the RNI/RDA with each intervention, which would risk excess of consumption.

The challenges associated with excessive intake of vitamins and minerals using a risk assessment model

As ULs are meant to apply to diverse populations, they are set conservatively in order to protect the most sensitive members of the population. Risk assessment has become internationally accepted as the best approach for setting ULs. Risk assessment framework has four steps: (1) hazard assessment, (2) dose–response assessment, (3) intake assessment, and (4) risk characterization.[5,6] There are both merits and drawbacks of the risk assessment methodology.

Results from a literature search to find published UL sets and their methodologies resulted in eight UL recommendations from governments, FAO, and WHO. The analysis using a risk assessment framework provided the consistency of approach, but variability in the application of the framework and differences in outcomes. In the analysis, all organizations considered a critical endpoint (CE), which is the most sensitive indicator of toxicity. There are different CEs for each micronutrient but the CEs for adults were fairly consistent in the recommendations. CEs for infants and children were

less consistent, possibly because ULs are calculated by extrapolating downward from adult values.[7] This is due to the uncertainty factor—a very subjective value that depends on the amount of evidence available. Larger uncertainty factors mean smaller ULs.

There is considerable uncertainty in UL values, especially for children. ULs were developed to apply to healthy populations and should not be assumed directly applicable to malnourished populations. Caution must be exercised in interpreting risk for populations receiving public health interventions, for example, high-dose vitamin A supplementation (VAS). For nutrients with limited evidence of toxicity in children, population intake data may provide a better insight for setting ULs than inappropriate extrapolation from adult ULs.[2,8]

Perspectives on excessive iodine intakes: interpreting the spectrum of thyroid disorders caused by excess iodine

The number of countries reporting excessive iodine intake has increased from 5 to 11 between 2003 and 2017.[9] In most countries with excessive intakes, this is due to salt over iodization and/or poor monitoring. In rare cases, excessive population intakes come from groundwater sources with high native iodine or areas with excessive seaweed consumption.

Thyroid dysfunction is due to both underconsumption and excessive consumption, the relationship is U-shaped, and both extremes may provoke adverse health effects.[10] The most vulnerable groups are fetuses and pregnant women, and there is no "one size fits all" approach; the question is whether it is possible to extrapolate data from adults to children.[11,12]

Considering the regulation of the thyroid gland against excess iodine, there is still much to be researched. The mechanism by which the gland tries to regulate levels is not known though there is evidence of adaptation to chronic excess. Iodine in urine is a strong biomarker because 90% is excreted within 24–48 h after consumption and measurement of iodine is relatively easy. Thyroglobulin is a sensitive biomarker of excessive iodine intakes and complements urinary iodine concentration for the evaluation of population iodine status, which should precede any review of salt iodization policy.[12,13]

Two recommendations to manage the risk of iodine overconsumption include strengthening salt iodization programs through monitoring and surveillance because benefits of iodization policies outweigh the risks of implementation, and generating more observational data to revise and refine the cutoffs, especially in relation to vulnerable population groups.

The biological impact of multiple VA interventions in both adults in the United States and children in Zambia and South Africa

At present, 22% of the U.S. population suffers from VA deficiency and 33% from excess.[14,15] Studies performed on cadaver livers ($n = 27$) showed that hypervitaminosis A is evident in a microscopic liver analysis, with evidence of toxicity at concentrations as low as 3.4 mg/g, when previously the threshold for toxicity was thought to be 10 mg/g. This could be due in part to diet, supplementation, or prescriptions from doctors.[16]

Hypervitaminosis A was documented in a large proportion of Zambian children who had been exposed to high-dose VA supplements, sugar fortification, maize biofortification, and diets generally adequate in VA through consumption of mango, fish, or green leaves.[17] Assessing VA status in communities exposed to more than one intervention is necessary to evaluate the potential for excessive intakes of preformed VA using biomarkers of status that are sensitive to hypervitaminosis. Guatemala started a sugar fortification program with VA in 1975. It stopped for 2 years and has been running since 1988.[18] In a 2011 survey from the Ministry of Health, no child had serum retinol <0.7 μmol/L and only 5% of women had values <1.05 μmol/L.[19] Additionally, Guatemala also has a VAS program with megadoses of VA and distribution of micronutrient powders and fortified complementary feeding programs that included VA, among other micronutrients.

When considering the addition of VA as a fortificant to multiple products in some countries, VA status needs to be evaluated with the most sensitive methods available. While serum retinol concentration can be diagnostic in cases of severe deficiency, it has no utility in diagnosing hypervitaminosis A. Previous research supported using circulating serum retinyl esters as a percentage of total serum VA as a measure of VA intoxication.[20] Other methods to evaluate overlapping coverage of programs include

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economic models that use cost-effectiveness and household consumption data.[21,22]

Super Cereal Plus and the well-being of children from 6 to 24 months in the context of the nutrition transition in El Salvador

To accelerate the progress in reducing stunting, anemia, and other micronutrient deficiencies, the government of El Salvador launched several interventions, including mandatory fortification of staple foods, distributing micronutrient supplements to all children, and distributing fortified-blended foods in most municipalities.[23] This last category includes the widespread distribution of Super Cereal Plus (SC+), a fortified-blended food, to fill nutrient gaps in children from 6 to 23 months who are breastfed and also receive food prepared at home. SC+ contains maize (58%), dehulled soybeans (20%), dried skimmed milk powder (8%), sugar (10%), vegetable oil, and a vitamin and mineral premix per 100 g of dry product. SC+ provides 410 kcal per 100 g of dry product and 100% for the RNI for 14 vitamins and minerals. Its macronutrient composition is 16% protein, 9% fat, and 75% carbohydrates.[24]

The Super Cereal program overlaps with other initiatives designed for nutritional emergencies and there is a concern it could be contributing to an excess of vitamins and minerals consumption among young children because SC+ is energy dense and likely to contribute to excessive energy and protein intakes among children aged 6–12 months. There is no evidence of the contribution of the SC+ to the prevention of anemia, or the reduction of iron deficiency or other micronutrients. Additionally, there is no evidence of deficiency of all other micronutrients provided by the SC+, so it could be responsible for excessive micronutrient intakes. This is even more likely considering the overlap of programs.[25]

The experience with SC+ in El Salvador was to implement a program before it was known whether the measure was necessary. Distribution of SC+ as part of a national nutrition program, especially in countries not experiencing humanitarian emergencies, or living in countries/regions where underweight and wasting are not public health problems should be a careful decision. When there is proof of need, criteria should be developed about which children to target; when the child reaches the median weight-for-length, the food assistance program should be discontinued.

The SC+ distribution should be limited in El Salvador to the most vulnerable population, not to the entire population. For example, it could be supplied to the dry corridor population in times of drought but not widely distributed since it may not contribute to diminishing deficiency but might increase the risk of excessive intake.

A successful story of VA fortification to eradicate VA deficiency in Guatemala: the continuous need for monitoring and surveillance

A long-term effort has been made to combat VA deficiency in Guatemala.[26] The achievements have been maintained over time thanks to monitoring systems and epidemiological surveillance. This has been an effort of committed actors from the National Commission for Food Fortification, Enrichment and/or Equivalent, an intersectoral commission including Ministry of Public Health and Social Assistance, Ministry of Economy, Ministry of Finance, Ministry of Agriculture, Livestock and Food, the Institute of Nutrition of Central America and Panama, Pan American Health Organization, the United Nations International Children's Emergency Fund, the World Food Programme, companies, and universities. Currently, fortified foods are salt, sugar, and wheat flour. The monitoring system includes various steps and stages, such as concentration, coverage, quality control in factories (packaging, shelf life, and vitamin limits), coverage of VA and other micronutrients in the diets in children under 2 years and their mothers, receipt of supplementation in the vaccine card, serum retinol monitoring, and inflammation trends over time.

Universal VA fortification by law has resulted in a population that is 100% covered. Guatemala has also considered voluntary fortification, which is evaluated in household surveys. There is concern about overlapping of fortification and supplementation programs[27,28] and high concentrations of retinol in the liver have been detected.[19] This could be a reason to stop the program but there are not enough sources of VA in the habitual diets of a large proportion of the population and canceling the program may put many back at risk of deficiency.[29] Varying concentration levels to avoid overconsumption and as a solution to a potential problem with high sugar

consumption could be done. The levels of sugar fortification can be increased if consumption decreases as part of the efforts to combat chronic noncommunicable diseases. It is of the utmost importance to maintain monitoring and updating. Guatemala currently has a project on excess markers to monitor the potential risk of excess VA.

Iodized salt fortification and risks of excess iodine intake in Ghana

A national universal salt iodization program was initiated in Ghana in 1996.[30] Apart from this program, there are multiple initiatives implemented to address iodine deficiency disorders without evidence about the impact of the interventions. A review to assess the risk of excessive iodine intake among Ghanaians and to identify policy and program implementation using mixed methods was developed to include a systematic literature review, validated questionnaires and conversations with key stakeholders, such as teaching hospitals, and source biological data. Results show that Ghana has a strong policy environment and there are ongoing interventions providing iodine or iodized salt at the national and subgroup level, including national mandatory salt iodization, voluntary fortification programs, and targeted interventions.[31]

In spite of all these efforts, iodine deficiency is still a greater problem in Ghana than iodine excess. Although there are several studies,[32–34] more information is needed to help with the implementation of public health programs. A national surveillance program would be key to improve the quality of data as well as for developing a progressive study of urinary iodine concentration and collecting data on iodine consumption including sources of intake in the diet. There is government support of voluntary iodine fortification, but it still requires funding. There is not enough staff to carry out a quality control program to improve standards.

Weighing the risks of excessive intakes against insufficient intake of vitamins and minerals delivered through public health interventions: a model from Cameroon

In Cameroon, existing fortification programs (addition of 12 mg/kg VA to refined vegetable oil, and addition of 60 mg/kg iron, 95 mg/kg zinc, 5.0 mg/kg folic acid, and 0.04 mg/kg vitamin B12 to wheat flour) would not be expected to contribute to excessive intake.[35,36] However, fortifying multiple food vehicles without modifying ongoing programs could have varying effects on excessive intake. In particular, fortifying sugar or wheat flour in addition to oil was predicted to increase the prevalence of excessive VA intakes among young children, while fortification of bouillon cubes with VA, in combination with an oil fortification program, was not predicted to cause excessive intakes.[35]

When assessing excess consumption, it is necessary to identify biomarkers of excessive intake/status, which are not well characterized for most nutrients and the identification of a suitable biomarker since some of them are used in research with little feasibility for routine monitoring, except perhaps urinary iodine content. There should be a clear knowledge about the relationship between biomarker and health outcome, and about the factors influencing biomarker interpretation (e.g., fasting status and infections).

The most common way to assess the risk of excess is measuring intakes above the UL. This could not be a single measure or a single event and requires a replicate 24-h recall or similar method to capture total diet and must include supplement use and exposure to micronutrient fortification programs.[37,38]

In the absence of detailed data on the risks and hazards of excessive intake, programmatic decisions will require judgment regarding both the risks and relative severity of deficiency and excess.[39] The decision may be straightforward for some nutrients, such as zinc, for which the consequences of intakes above the UL appear to be minimal, and the consequences of deficiency (increased morbidity, mortality, and stunting) are quite severe in low-income settings. The decision may be more complex for nutrients such as iron when considering the case of children in settings with a high burden of diarrheal morbidity where program managers must weigh the benefits of resolving iron-deficiency anemia against the potential risk of increased diarrhea incidence.

Regulatory aspects and legal framework to identify risk of excessive intake of vitamins and minerals delivered by nutrition interventions

Concerns about excessive intakes of micronutrients due to food fortification were first addressed in 1987 by the Codex Alimentarius,[40] intending to provide

guidelines and legal texts to country authorities for implementation of rational and safe fortification programs. One of these principles clearly states, "The amount (of micronutrient) added should not result in either an excessive intake or an insignificant intake of the added essential nutrients, considering total daily intakes from all relevant sources, including supplements." Later, a WHO document on food fortification[41] highlighted the relevance of setting fortification levels of micronutrients around the EAR and considering ULs.

Mandatory mass interventions are clearly government regulated and the corresponding regulations are part of the country's food laws. Targeted interventions, on the other hand, like micronutrient supplementation to specific risk groups, follow existent international regulatory guidelines, often WHO guidelines, adopted by the country but are not in its legislation. This is the case of megadoses of VA to children, iron and folic acid supplementation to women, and the use of multiple micronutrient powders to fortify meals for children. Biofortification is currently unregulated but has become part of the country's nutrition policies or action plans to combat micronutrient dietary deficiencies.

There is a complete absence of regulations in terms of coordination among interventions. There are some interesting initiatives in Latin America, named national commissions for micronutrient fortification established by government mandate. Formed by different stakeholders, these collegiate organizations include government, industry, community organizations, and NGOs. A somewhat similar government-sponsored organization in Africa is the National Working Group for Food Fortification in Uganda.[42] One of the functions of all these collegiate bodies is to coordinate micronutrient initiatives and advise governments on micronutrient policies, and could be a mechanism of controlling excessive micronutrient intakes from multiple interventions.

Currently, the regulatory framework for the existing interventions to combat vitamins and mineral deficiencies in the selected countries lacks mandatory requirements to coordinate implementation of multiple interventions in such a way that excessive micronutrient intakes are minimized. In general, countries have regulations setting the addition of micronutrient levels to foods, and in some cases maximum limits, only within the individual program without considering the micronutrient contribution from other sources.

Web-based management information system designed to systematically capture program compliance indicators

While there are many different factors that affect a country's ability to effectively monitor the quality of their fortified foods, the lack of an easy and automated data management system able to inform food control agencies and government personnel of implementation challenges and product compliance issues has been identified as a gap in global programs.[43,44] In order to address this gap in global compliance information and the need for such data to improve programming, the web-based management information system for fortification programs, called FortifyMIS, is being developed by Project Healthy Children and the Global Alliance for Improved Nutrition (GAIN). The system will enable national regulatory agencies and food producers to more efficiently and effectively track product compliance ensuring fortified foods actually contain the correct amounts of vitamins and minerals per national standards, and will enable countries to act upon identified gaps to improve the program's outcome in a timely, cost-effective, and sustainable manner.

Users of this tool in a country will include those who routinely collect and use data on the quality and quantity of fortified foods, including the food producers, regulatory monitoring inspectors, and laboratory and central government staff. Key outputs from the FortifyMIS are national-level compliance reports needed to flag issues for quick action.

The implications to understand risk of excessive intakes of micronutrients will include the possibility of verification that foods contain the required quantity and quality of nutrients as outlined in the national standards and in terms of intervention harmonization a more accurate modeling of nutrient intake that can then be used to adjust fortification levels or other micronutrient interventions as needed. At the time of writing this article, this page was not widely available to all potential users.

Micronutrient supplementation programs in Sri Lanka: benefits versus risks

Substantial progress has been made in Sri Lanka over several decades to reduce the prevalence of iodine

and VA deficiencies and anemia. Also, the reduction of child mortality and stunting are suggestive of an important overall sustained improvement in health and nutrition status of children.[45] As a result of a strong health infrastructure in Sri Lanka, the Ministry of Health–driven interventions have reached high coverage (>70%). In order to achieve such a status, the dose provided has to be decided to take into consideration the EAR and UL.[46–48] As an average of all children 6–59 months of age, these mandatory programs are estimated to contribute the equivalent of 162.3%, 140.8%, and 19.1% of the EAR for VA, iron, and iodine, respectively, without accounting for the conventional diet. Additionally, the availability of multiple fortified foods (milk and margarine) which are voluntarily fortified may lead to higher intakes than that required, among selected individuals/groups.

Universal salt iodization was launched in 1995, and mandatory salt iodization at a level of 25 ppm (later reduced to 15 ppm) was enforced by introducing legislation preventing the sale of noniodized salt. A subsequent survey showed the benefits of this program indicating a decline in the prevalence of goiter and 68% of households having adequately iodized salt. As an average of all children 6–12 years of age, universal salt iodization and water sources are estimated to contribute the equivalent of 289.3% and 36.2% of the EAR and UL for iodine, respectively, without considering the share from commercially available fortified food in the market (estimated considering a double intake of children 6–59 months, i.e., 38% of EAR).[48,49]

Along with the provision of supplementation programs, availability of fortified foods at the community, and the availability of commercial fortified products, the risk of excessive micronutrients intake should be considered by implementers at all levels. With a high literacy level of the population, it is also necessary to create awareness at the community level.[47]

Integrating micronutrient interventions into health systems for program sustainability: a case study on VA supplementation in Ethiopia

In Ethiopia, VAS started in 1996 by integrating with polio and measles supplementary immunization campaign, which was conducted in house-to-house visits through health workers and volunteers. This approach was gradually expanded to include three delivery mechanisms: (1) enhanced outreach strategy for child survival, (2) child health days, and (3) routine health extension program.[50,51]

To maintain the high coverage achieved by this integration with immunization campaigns, a 4-year program (2011–2015) was created to integrate VAS into the Ethiopian health system to maintain the high VAS coverage, which had been achieved through vertically enhanced outreach strategy intervention. The plan focused on service delivery, human resources, procurement and supplies, monitoring and evaluation, financing, stewardship, and governance, aiming at addressing the identified bottlenecks in integration. Annual assessments to determine progress on the extent of integration and VAS coverage by integrated delivery strategies were conducted through program monitoring.

The integration of VAS intervention into the Ethiopian health system based on the WHO framework for integrating micronutrients into a health system improved from 17 to 27 point score during the transition program implementation, meaning a systematic transition from less to more VAS-integrated intervention. Health system support at all levels allowed relatively high VAS coverage to be maintained while shifting to an integrated routine system. Integration of VA capsule into local systems of procurement was not yet achieved, while monitoring and evaluation integration has greatly improved.

The integration of VAS into a health system has not negatively impacted the country's VAS coverage. Government ownership, strong health system support at all levels, and the clear framework for integration and readiness assessment contributed to the good results achieved so far. Coverage needs to be monitored continuously to avoid the risk of overconsumption.[50,51]

Strengthened coordination between public health nutrition interventions and other sectors to prevent excessive intakes of vitamins and minerals: a case for Zambia

In Zambia, there are an important number of public health interventions to address micronutrient deficiencies, which affect the entire country, especially women and children. There are ongoing programs on (1) VAS to infants, children, and postpartum women; (2) sugar fortification with VA; (3) salt iodization for human and animal consumption;

and (4) biofortified crops including orange-fleshed sweet potato, orange maize, and beans.

Despite the implementation of these interventions against micronutrient deficiencies, VA and iron deficiencies continue to be problems of public health significance in Zambia.[52,53] However, there is also evidence of high intake levels of vitamins and minerals beyond requirements. For example, in a study to determine the efficacy of biofortified orange maize among 5- to 7-year-old children with the use of stable isotope dilution, 59% were found to suffer from hypervitaminosis, defined as >1 μmol retinol/g liver.[54] Another study that investigated the association between plasma retinol and infection among preschool children in rural Zambia found that their diets were adequate in provitamin A carotenoids.[55] The iodine deficiency disorders impact study conducted in Zambia in 2011 revealed that 41.6% of the boys and 37.1% of the girls were found to have an excessive intake of iodine (≥300 μg/L of urinary iodine).[56]

It is important to review the current policies regarding dietary diversification, targeted supplementation, fortification, and biofortification in order to prevent or reduce the risk of excessive intake of micronutrients. Joint decision making among sectors will play a role in ensuring that current policies are carefully reviewed to understand their contribution to recommended dietary intakes of specific micronutrients. It will also help in revising the lower and upper limits of food fortificants to avoid excessive intakes.

Micronutrient content in presentations from industry: quality control and actual amounts

Understanding micronutrient safety requires taking a step away from the classic toxicological approach and toward risk assessment approach. Micronutrient intake exhibits a U-shaped curve of risk derived from insufficient and excessive intakes. The risk of low intakes derives from micronutrient deficiency and the risk of excessive intakes from adverse effects as opposed to the toxic effects described in toxicology.

This risk assessment demands a case-by-case or nutrient-by-nutrient analysis. For most of them, ULs or (safe) highest observed intakes have been established.[1,3,57] They are levels of micronutrient intake that pose no risk of adverse effects over prolonged periods of time. In the case of ULs, chronic intakes above these values increase the risk of adverse effects.

Since micronutrients exhibit a very wide array of a safe range of intakes (an intake range above the requirement and below the maximum safe level), it is difficult to issue one recommendation on the maximum amount to be allowed in food products. Some scientific bodies and regulators have divided micronutrients into three groups, according to their safe range of intake:[58,59]

Group 1 (no evidence of risk to human health at levels currently consumed): vitamins B1, B2, B12, and biotin, vitamin K, pantothenic acid, and chromium;
Group 2 (low risk of exceeding the UL): vitamins B6, C, D, and E, nicotinamide, molybdenum, phosphorus, selenium, folic acid, and potassium; and
Group 3 (potential risk of excessive intakes): VA, beta-carotene, calcium, copper, fluoride, iodine, iron, manganese, and zinc.

Fortified food systems are particularly safe because intake does not allow for orders of magnitude in excess. Thus, probably only Group 3 needs a careful evaluation of current intakes of the nutrient, in comparison with the ULs, which is the basis of most models for the safe fortification of foods.

Tool for reviewing national health programs: initiatives to control the risk of excessive intakes

The WHO seeks to improve program performance through concrete action to address health inequities, support gender equality and the progressive realization of universal health coverage and the right to health, and address critical social determinants of health.[60] The WHO tool for country support package has four components: (1) evidence and generation of evidence; (2) strengthening plans, health systems, and policies; (3) strengthening health programs; and (4) empowering WHO country offices.[61]

These components are to ensure that policies are based on gender equity and rights development. The goals of these tools are to support the work being done not to add more work. Also, to visualize those not well represented and to guide the planning oriented toward them. It can be adapted to nutrition without problems, both to help in prevention and at risk of excessive intake through

understanding inequity and its variables such as distribution. Health equity is unfairly absent, and it can be avoided and remedied. Excessive intake of vitamins and minerals is more pronounced in certain groups than in others. This discrepancy should be part of the discussions of universal health coverage and incorporating it into nutrition programs could help in managing the risks of excessive micronutrient intake.

Global Fortification Data Exchange

The Global Fortification Data Exchange webpage, an analysis and visualization tool for food fortification data, was presented by GAIN in 2017 (https://www.fortificationdata.org).[62] The main tools available through the platform include legislation status and fortification standards. There is country information on what food is fortified, whether fortification is mandatory or voluntary, concentrations, and technical specifications. This visualization can be downloaded and contains filters to facilitate the search by nutrients and food vehicles. This work in progress will include information on quality and concentrations of nutrients in future versions.

Breakout sessions

The breakout sessions aimed to obtain the conclusions of the meeting in four discussion topics in order to support the WHO's position on the risk of excessive intake of vitamins and minerals delivered through public health interventions.

Participants were placed in four groups according to their background and expertise. Each group had 1 h and 30 min for discussions and approximately 10 min to present their summary to the plenary, with 5 min for questions and answers. Each group selected a coordinator and a rapporteur; they were advised to address unresolved issues, to be relevant, to be realistic, and to identify research needs.

Group 1: planning, implementing, monitoring, and evaluating nutrition programs for the detection and control of the risk of excessive intakes

Some questions and aspects discussed by this group were how to identify and assess the needs and rationale for simultaneous implementation of nutrition intervention programs; how to obtain information on all ongoing nutrition intervention programs in a country or a setting (both stable and emergency settings), including the duration of the program and specifics about the intervention (e.g., dose of vitamins or minerals being delivered, and vulnerable groups); the need to establish if the information about all ongoing programs should be considered mandatory before initiating a new program; types and sources of data that should be included when calculating total micronutrient intake; conditions and rationale for not initiating or discontinuing a public health nutrition intervention/program; data on the coverage for decision making; and to identify indicators to assess and to monitor the risk of excessive intakes and organizations responsible for surveillance.

The group highlighted the importance of obtaining data on the risk of excessive intakes and the consequences. Although the group recognized the importance of population surveys (at the regional or country level of significance), it is not always possible or data are not always reliable. Countries must prioritize their needs, what decisions should be made, and the available information for that. They need to decide if they can use data from current or previous surveys or if a new one is needed and what indicators are relevant. There has to be an order of priorities to make decisions.

The group proposed that a clear identification of sources and proportions of intakes should be included, identifying the proportion of each nutrient coming from a regular diet, and supplementation or fortification (including all possible sources of fortified items). This could be done by creating a decision tree adapted for each country that includes aspects as conditions, rationalization, nutritional intervention programs, and evaluation of costs and benefits.

Monitoring systems need to be promoted and updated constantly. They should allow determining the contributions from the diet and all other possible sources of the micronutrient of interest (supplements, voluntary fortification, and biofortification), considering local industry and imported products.

Group 1 concluded that country efforts to implement program monitoring systems and populations surveys on food consumption are needed. The surveys should be available and adapted to each country in terms of dietary specifications, nutrition policies, and actions. The identification of biomarkers, the inclusion of vulnerable groups from urban and rural areas, detailed identification of dietary patterns, and

the key importance of surveillance systems were also highlighted.

Group 2: coordination between public health nutrition interventions and other interventions and sectors

The relevant aspects addressed include the identification of country experiences, successful or not, implementing simultaneous nutrition interventions; the levels of responsibility for reporting and centralizing information about ongoing nutrition-sensitive and -specific interventions; the availability of these data when planning an intervention; the strategies that can be used by countries to consolidate programs providing micronutrient interventions and other public health interventions; the best way to pilot such strategies; how to overcome implementation barriers, particularly among low-income groups; when to initiate a new program and who should be informed; who should be in charge of consolidating the information and develop a roadmap; and steps needed to improve communication and data sharing between sectors involved in nutrition programs.

The need for coordination and how to coordinate was discussed, identifying as main points: (1) the creation of a steering group composed of key actors including government, private sector, stakeholders, and other actors in nutrient supply; (2) the need for an agreement on the strategies to coordinate multiple interventions and consolidate them; (3) establishing clear responsibilities for each member of the group (for instance, data analysis or performing a report); and (4) regular meetings and discussions to evaluate the need for adjustments or finalization of a program.

The group also highlighted that efficacy and safety must be interconnected to achieve good coordination. A strategy is needed to map the situation and it requires the creation of a monitoring system that includes roles and responsibilities for accountability.

The group concluded that there is a need to coordinate timeframes of the different interventions, the actors involved in implementation, the coordination mechanisms, the development of policies, the training of the workforce, and the results or impacts achieved by these simultaneous interventions in terms of the nutritional status of the targeted population.

For example, Ethiopia created a coordinated group between all sectors involved in nutrition. This coordinating body is cochaired by the Ministries of Health and Agriculture and they are responsible for leading all nutrition-specific interventions and activities that include supervision of the national nutrition technical committee composed of the government, academia, NGOs, and the private sector. All the strategies, interventions, and the people that implement them are under this committee.

Although most monitoring systems in place in countries were designed with micronutrient deficiencies in mind and although biomarkers of deficiency and excess could be completely unrelated, there are some characteristics of monitoring systems already in place, which could help with surveillance of risk of excessive intakes: (1) disaggregate data helps with data sharing and identifying who is at risk of deficiency and who is at risk of excess, and if there is an overlap; (2) take advantage of existing mechanisms to begin monitoring and collecting baseline surveillance data, but thinking about excessive intakes; (3) look at how products are sold, marketed, and regulated; and (4) share these data and create a multicountry coordination system.

Group 3: safety, quality control, and assurance considerations—emergency settings and ethical issues

This group discussed how to adequately evaluate the risk for excessive micronutrient intakes in a timely and cost-effective way; the existence of surveillance systems for food safety that may be useful in monitoring micronutrient intakes; the greatest concerns in terms of the quality control of products used to deliver micronutrients in public health programs; the existing surveillance systems for food safety that may be useful in monitoring micronutrient intakes, if any; the importance or need for protocols in the emergency; and the approach to be taken for nutrients or age groups that do not have a UL stated.

Regarding ethical considerations, the group analyzed: (1) how social determinants of health are accounted for in the design, implementation, and evaluation of public health nutrition interventions that distribute micronutrients; (2) if public health nutrition interventions that distribute micronutrients are properly informed by a gender-responsive, equity-enhancing, and human-rights-based approach; (3) how the balance of benefits and

harms is conducted; and (4) the consideration of values and preferences of populations when planning and implementing multiple programs, and how to address these ethical challenges.

Monitoring intakes from all sources is the key issue to address the risk of excessive intakes of micronutrients. The group recognized the limitations of using ULs as a set point and the difficulties of obtaining data from countries and concluded that each country must have monitoring and reporting mechanisms to evaluate trends, despite the fragility of monitoring and surveillance systems for food safety.

This group also discussed limitations and variants since the determination of risk depends on the exposure time and each individual situation, also that it is different in regular versus emergency zones, that the emergency could become a chronic situation and how to decide when to stop a program.

Group 4: legislative framework and policy coherence

The main aspects covered by this working group include international standards and national laws regarding program implementation, content information, and health claims, which help drive policies being effectively implemented worldwide; identifying if there is a need for a guided process to help countries select which interventions to implement as part of their national nutrition strategy; what needs to be in place for multiple nutrition programs that are implemented simultaneously to be successful from a regulatory standpoint; assessing the need for a model process to help countries to coordinate multiple micronutrient interventions at the same time; major benefits and drawbacks for a legal framework establishing minimum requirements for voluntary and mandatory food fortification; and identifying legal aspects to implement nutrition interventions/programs in emergency settings.

The group concluded that there is a need for international guidelines to help countries consider whether to initiate an intervention and to facilitate the assembly of a regulatory committee and the request of a dossier. This regulatory committee should be assembled by a decree or a resolution, and it should be built on something that already exists rather than creating something new. The Ministry of Health will make the final decisions but this commission will be indicated by law as the technical assistant to the Ministry of Health. The proposed dossier should contain a justification for the measure to be taken and data on food composition, nutrient intake, coverage, compliance information, other existing programs, the contribution of micronutrients from other interventions, and nutritional patterns (because they change constantly influenced by industrial marketing).

The major benefit for a legal framework establishing minimum requirements for voluntary and mandatory food fortification is security. Regulation of nutrition programs, especially fortification, is a big help to control intakes, especially for multiple, simultaneous programs. Drawbacks of a legal framework could include the reduction in the number of commercial products.

There were some controversies about a legal framework for emergencies. It is necessary to define if there is a risk of excessive intake when attending emergencies. A detailed analysis of food consumption indicating fortified foods or supplementation programs is necessary. The regulatory committee mentioned above could advise what to introduce in an emergency although some participants considered that this commission should not act in times of emergency and that there must be a special committee for emergencies. In any scenario, the group agreed that constant monitoring in emergency settings is mandatory.

Implications for countries

There were country representatives from the Ministries of Health of Brazil, Colombia, Costa Rica, Peru, and Panama. They briefly commented about the implications of the aspects discussed during the technical consultation. All agreed it was a useful experience and that the meeting was important for rethinking and redesigning practices. Each representative briefly described their advances, and identified their weaknesses and next steps. They identified a need for more evidence, regulation of voluntary fortification, strengthening interactions between intersectoral organizations and actors, and a shared instrument to evaluate the risk of excessive intakes, as important issues to address.

Research needs

The research needs identified by Group 1 included identification of surveillance systems and indicators and biomarkers of excess and generating

dose–response data for an in-depth review of ULs. Group 2 recognized the need to develop an economic modeling that allows a cost-effective implementation of multiple interventions, setting up a system for monitoring intakes, generating cost–benefit information on targeted preventions versus treatment, and developing tools to communicate effectively with end users, and a research agenda that includes universities and research institutions. Group 3 highlighted that given the difference between the reference levels in different countries especially for young children, more evidence is needed to establish stronger baseline data on toxicity and health parameters. It is essential to carry out a scientific review of the current values and health parameters, even on toxicity. Group 4 recognized the lack of articulation of the monitoring of all the interventions in an integral way, as a problem to be solved. Also, there is a need for a tool, a guide, or regulation that supports countries that implement micronutrient interventions and takes into consideration the unique context of a country, as well as the strengthening of the analytical capacity in countries or regional reference laboratories.

Concluding remarks

The WHO keeps track of member states adopting its guidelines on specific micronutrients delivered through public health interventions. However, there is a lack of knowledge and understanding of how countries and other nonstate actors implement concurrent interventions delivering different micronutrients to the same population groups, or on how state and nonstate actors interact with each other when planning, designing, and implementing interventions that may either complement or overlap in terms of the micronutrients delivered. There is a need to work with people of different expertise, such as plant breeders, molecular biologists, food technologists, nutritionists, experts in the food product development/marketing, communications, and economists, among others. Common implementation strategies between nutrition and other health interventions have a key role in preventing the risk of excessive intake of micronutrients. For example, when common strategies are utilized, there is a reduced risk of mixed messages, which may impede smooth program implementation.

It is important to differentiate between toxicity and adverse effect. The UL values are based on different outcomes for different nutrients, and that outcome and its significance should be considered in order to decide how the UL would be used. The ULs are for healthy individuals not for sick or small people, as are RNIs, but those values were set in order to reach an adequate average representation of a group of people. Those who suffer from diseases are excluded, but the average accounts for differences by gender and physical structure, and it should account for increased nutrient needs in sick people.

One of the problems in most settings is the lack of data about intakes and actual deficiencies prior to interventions; therefore, in some instances, it is possible that people are receiving more than is necessary. How to get a real picture considering the knowledge gap between theory and practice? This is a challenge especially considering that values are set for healthy people and the markers are weak. To solve this problem, it is necessary to have more accurate surveillance, monitoring, and evaluation systems, which take into account other environmental factors that can influence micronutrient levels.

The consultation group highlighted the need to understand and make clear to stakeholders the concept of ULs. The group highlighted the need to clarify that UL is not synonymous of toxicity but rather a level not to surpass chronically, but also recognized the need to review and determine ULs especially in children and for some nutrients. Regarding the determination of the risk of excessive intakes of vitamins and minerals, there should be a risk evaluation in a timely manner and a strong monitoring system to detect and control the risk resting on a cooperative multisectoral group with clear responsibilities. It is possible that the development of an ample general model is needed. This could be a tool for countries to plug their data into, because each country has different interventions and they need to know how to appropriately monitor and interpret the data, and government can refer to it to ensure that it is not getting out of the range of safety.

The outcomes of this technical consultation will contribute to the member states' efforts to strengthen their health systems and provide them with a summary of technical considerations and lessons learned, which could be useful in the implementation and monitoring of programs delivering micronutrients. It will also contribute to the WHO's continuous activities for future normative work in this field.

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Statement

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Competing interests

The authors declare no competing interests. M.N.G.-C., R.M., L.R., and R.G. are the WHO staff members.

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