# A conversation with Dr. Ekin Birol, Keith Lividini, and Bho Mudyahoto, July 27, 2018

## Participants

- Dr. Ekin Birol – Director, Impact and Strategy, HarvestPlus
- Keith Lividini – Head, Strategy and Policy Research Unit, HarvestPlus
- Bho Mudyahoto – Head, Monitoring and Evaluation, HarvestPlus
- Dr. Stephan Guyenet – Senior Fellow, GiveWell

**Note:** These notes were compiled by GiveWell and give an overview of the major points made by Dr. Birol, Mr. Lividini, and Mr. Mudyahoto. Dr. Erick Boy, Head of Nutrition at HarvestPlus, provided feedback and additional information for the draft conversation notes.

## Summary

GiveWell spoke with Dr. Birol, Mr. Lividini, and Mr. Mudyahoto of HarvestPlus as part of its investigation into micronutrient biofortified crops. Conversation topics included the strengths of biofortified crops and methods for estimating their effectiveness, including absorbed incremental micronutrients, bioconversion and bioavailability, nutritional status indicators, and impact on morbidity and mortality.

## Biofortification

HarvestPlus breeds staple food crops that have higher levels of vitamin A, zinc, and/or iron than typical cultivars and disseminates these crops to populations in developing countries. HarvestPlus believes that biofortification complements supplementation and fortification, which are other methods of combating micronutrient deficiencies. This is primarily because it provides micronutrients to individuals who might not otherwise be reached by the other two methods. This occurs through its coverage of:

- **Rural areas –** Fortification and supplementation programs may not reach very rural areas, which HarvestPlus targets.
- **All members of a household –** While supplementation programs target specific groups, biofortification is more likely to provide micronutrients to all members of a household. In addition, in some households, animal products, fruits, and vegetables are preferentially given to men and boys. In contrast, all members of a household, regardless of age or gender, consume the foods that are biofortified in HarvestPlus' programs.
- **Staple foods –**The staple foods that are biofortified in HarvestPlus' programs are widely consumed and do not require processing beyond traditional cooking practices.

As biofortification programs scale, their cost per person is decreasing. This derives from the fact that most costs are incurred initially in crop development, nutrition efficacy trials, and initial advocacy and scale up. Once biofortified crops are reasonably widely available, there is no additional cost to farmers and consumers to produce and purchase biofortified crops, as compared with non-biofortified varieties. This is in contrast to supplementation and fortification, which incur the same recurrent costs every year (e.g. 10 billion vitamin A supplements have been distributed to preschool children in developing countries over the past 20 years). Biofortification treats the underlying cause of the failure of food systems to provide adequate vitamins and minerals at an affordable cost to poor farmers/consumers. The initial fixed costs of biofortification are lower than the recurrent costs of supplementation and fortification. High benefit-to-cost ratios for biofortification, after discounting, assume reasonably significant adoption rates.

## Absorbed incremental micronutrients

The estimated average requirement (EAR) of a micronutrient is the intake level of that micronutrient that will meet the needs of 50% of the population. To quantify the nutritional value of its biofortified crops, HarvestPlus calculates the absorbed incremental micronutrient, which represents the amount of additional micronutrient that is absorbed as a result of replacing a standard staple crop with a biofortified version of the same crop. It is expressed as a percentage of the EAR for that micronutrient. This number represents the amount of additional micronutrient that is absorbed, not simply ingested, through consumption of a biofortified crop.

HarvestPlus calculates this number for zinc (and iron) using the following two formulas:[1]

Additional nutrient delivered = Q x I x BV X R

Where:

- Q represents the average daily quantity of a crop consumed (g).
- I represents the nutrient increment, i.e. the additional concentration of nutrient in the biofortified crop (mcg/g).
- BV represents the bioavailability of that nutrient, i.e. the fraction that is absorbed from the biofortified crop.
- R represents the average nutrient retention after storage and cooking.

Percent of EAR delivered = (additional nutrient delivered)/EAR * 100

## Bioconversion and bioavailability

### Vitamin A bioconversion

HarvestPlus biofortifies crops with provitamins A, predominantly beta-carotene, which are converted within the body to vitamin A.  These provitamins A are

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[1] HarvestPlus uses a similar formula for vitamin A, except the bioavailability term is replaced with a bioconversion term representing the efficiency with which the body converts carotenes (provitamins A) in the crop into vitamin A.

converted with varying efficiency, depending on the crop as well as other factors including the degree of food processing, individuals' existing vitamin A stores etc.

Originally, HarvestPlus defined the bioconversion rate of each of its vitamin A biofortified crops using standard assumptions published in the National Academy of Medicine's[2] Dietary Reference Intake handbooks. It has since updated those rates based on its own absorption studies. For example, the initial bioconversion rate assumed for vitamin A biofortified maize was 12:1 (i.e. the value for beta-carotene), meaning that for every 12 units of provitamin A beta-carotene equivalents, one unit of retinol (the active form of vitamin A) is produced. HarvestPlus has found that its own vitamin A biofortified maize is more efficient than the standard rate would suggest, with a bioconversion rate of 6.5:1.

### Zinc bioavailability

The main determinants of zinc bioavailability are the amount of zinc and the amount of phytate in the crop or diet. Phytate is a naturally occurring mineral chelator that reduces zinc absorption.

As with vitamin A, HarvestPlus first estimates zinc bioavailability using existing assumptions. Specifically, it uses population-based average bioavailability values published by groups including the International Zinc Nutrition Consultative Group (IZiNCG), the World Health Organization (WHO), the Food & Agriculture Organization (FAO) of the United Nations, the European Food Safety Agency (EFSA), and the National Academy of Medicine[3]. These values define zinc bioavailability within standard diets. IZiNCG has published two sets of values: one for an unrefined, cereal-based diet containing more phytate and another for a diet containing more animal meats and less phytate. HarvestPlus uses the values corresponding to the unrefined, cereal-based diet and the EFSA physiological requirements in order to match typical diets within the countries where it works.

HarvestPlus then updates these values with data from its own diet and meal studies. Depending on the type of study and the data it collects, HarvestPlus can quantify bioavailability in two ways:

1. Some of HarvestPlus's studies do not collect data on the entire diet. For example, an effectiveness study that quantifies the amount of a biofortified crop being grown and consumed by its beneficiary households might not capture the entire diet. In these cases, HarvestPlus uses average values from its own work or other published work to estimate the bioavailability and total absorbed zinc from the additional zinc in the diet.

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[2] Formerly the Institute of Medicine.

[3] Most recently, Gibson RS et al (2018) reviewed this topic and recommended different dietary intakes of zinc according to average phytate consumption, gender and physiological status, following the EFSA's recommendations (Nutrition Reviews 2018; 76(11):793-804).

2. Some of HarvestPlus's studies do collect data on the entire diet. Such studies might implement a 24-hour recall assessment on consumption or a household-level survey on typical consumption. In these cases, HarvestPlus can use the Miller algorithm, which calculates zinc bioavailability and total absorbed zinc based on the molar ratio of zinc to phytate within the diet.

## Status indicators

### Limitations of status indicators

Both zinc status and vitamin A status can be directly measured from blood biomarkers, but these methods have limitations. The most common method for assessing zinc status is to measure plasma zinc. However, this method has limited value because it is not very sensitive to changes in zinc status, except when pharmaceutical doses of zinc are administered (i.e. zinc supplementation). Similarly, vitamin A status is sometimes assessed by measuring serum retinol, but this method has limited value because the liver stores vitamin A and regulates its concentration in the blood, maintaining it at a similar level until its reserves are depleted. Thus, measuring serum retinol only reliably detects severe vitamin A deficiency. In both cases, inflammation spuriously lowers the circulating levels of these biomarkers.

### Identification of better biomarkers of nutritional status

HarvestPlus's nutrition team is working with external experts to develop and test new biomarkers that are more informative indicators of nutritional status after exposure to lower (dietary) doses of these nutrients. These include measuring DNA strand breaks to assess zinc status and using the isotope dilution method to assess vitamin A status. Both of these methods are more sensitive to changes in nutritional status. The nutrition team has convened several consultations involving zinc biomarker experts, including those from IZiNCG. For its work on vitamin A, the team works closely with the International Atomic Energy Agency (IAEA) and a Newcastle University-led research team funded by the Bill and Melinda Gates Foundation which is studying the potential toxicity of too much preformed vitamin A in the food supply and better mathematical models to estimate vitamin A status. HarvestPlus provides its partners with opportunities to test these new methods in its efficacy and effectiveness studies. In turn, HarvestPlus aims for these methods and studies to generate evidence of changes in nutritional status that will supplement evidence from its consumption and socioeconomic impact surveys.

## Evidence of effectiveness of zinc biofortification

Currently, there is no published evidence of the effectiveness of zinc biofortification. HarvestPlus has completed two efficacy studies of zinc biofortified wheat. Results from the larger of these two trials were published recently[4]. The 6-month intervention trial found significantly reduced morbidity in children 4-6 years of age and their mothers. HarvestPlus will begin conducting an efficacy study of zinc

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[4] Sazawal S et al. BMC Nutr J 2018; 17:86

biofortified rice in 2018. These studies primarily measure changes in zinc status, and they have used new, exploratory measures of indicators associated with nutrient status to compensate for the unreliability of typical measures (i.e. immune function, growth, DNA strand repair, fatty acid metabolism markers, etc.). These studies also measure functional outcomes associated with zinc deficiency, such as susceptibility to respiratory infections or incidence of diarrhea.

## Measuring the impact of biofortification

### Lives Saved Tool

One method to quantify impact is the Lives Saved Tool (LiST), developed by the Institute for International Programs (IIP) at the Johns Hopkins Bloomberg School of Public Health. LiST synthesizes program coverage rates with published intervention effect sizes to estimate the number of lives that would be saved if different interventions were to scale. It also incorporates program cost estimates to calculate the cost-effectiveness of interventions at scale. HarvestPlus is exploring whether its research data can be entered into LiST in order to quantify the impact of biofortification.

### Disability-Adjusted Life Years

Biofortification can lead to improvements in both morbidity and mortality, with some nutrients leading only to improvements in morbidity. However, LiST only captures impact on mortality. Thus, HarvestPlus measures biofortification's impact on morbidity with disability-adjusted life years (DALYs).

To quantify the DALYs averted by biofortification, HarvestPlus uses DALY methodology that was adapted for this purpose during a 2005 workshop that convened relevant experts, including nutritional epidemiologists. Under this methodology, HarvestPlus surveys the nutrition literature to identify adverse health outcomes associated with a particular micronutrient deficiency and estimates the amount of each outcome that is attributable to that deficiency. It then applies the DALY formula and relevant statistics to estimate the micronutrient-specific DALYs incurred under the status quo (i.e. through consumption of standard crops). Finally, using data on the incremental micronutrient in a biofortified crop, it estimates the reduction in the incidence rates of the disease outcome and the corresponding DALYs averted through a biofortification program.

HarvestPlus is in discussion with colleagues at Cornell University, who have measured the effect of iron biofortified crops on adverse health outcomes. It wishes to use data from its own studies measuring adverse health outcomes in order to improve its DALY calculations.