The E3LS Implications of Vitamin A Delivery Systems

Written by: Niklas Bobrovitz, Sibat Khwaja, and Daniela Navia

Supervisor: Dr. Gregor Wolbring

Part 1

Introduction

Micronutrient deficiency is a major cause of life threatening diseases and mortality through-out the world (1; 2). The UN World Summit on Children Micronutrient goal was:"Achieve sustainable elimination of iodine deficiency disorders by 2005 and vitamin A deficiency by 2010 (3). In poor, developing countries, micronutrient deficiency has been the major cause of impaired mental and physical functioning, mainly among children (1; 2). The four major micronutrients of concern in the developing world are iron, vitamin A, zinc and iodine(2). Our focus will be on Vitamin A deficiency. Roughly 400 million people worldwide are at risk of vitamin A deficiency. Of those 400 million affected, 100-200 million are children (1; 4). It can lead to progressive damage to the eye and eventually causes blindness. The WHO reports that 2/3 of deficient children die within two months of becoming blind(4).

Vitamin A deficiency is most prevalent among children located in Southeast Asia and Africa(5; 6), where staple foods are low in vitamin A (i.e. wheat, rice, maize…etc) and the poor cannot afford foods that would fulfill their Vitamin A requirements . Mammals must ingest provitamin-A Carotenoids from dark green vegetables, or yellow or orange fruits(7) and vegetables or fat soluble Vitamin A from animal products like eggs, butter and fish liver oils in order to synthesize Vitamin A in the body. Vitamin A is essential for protein metabolism, maintenance of epithelial cells, proper functioning of the immune system and retina, and for growth and reproduction (8). In order to reduce Vitamin A deficiency in developing countries, Beta-Carotene, the pro-vitamin A precursor, or Retinol, the animal version of Vitamin A, must be provided by some means to those who are deficient. There are currently 3 delivery systems for combating micronutrient deficiency; supplementation, increasing or diversifying dietary in-take and food fortification, which includes commercial or industrial fortification, as well as biofortification, microbial biofortification and home fortification(1; 9; 10). There is also a fourth and more recent delivery system, which can be labeled the synthetic biology approach (the approach the Guelph iGEM team takes). This paper will explore and highlight the major E3LS implications of the current and possible future delivery systems, for Beta-Carotene, a Provitamin A carotenoid. The goal of addressing the E3LS implications is to help advance towards realistic applications. These

implications must be considered and weighed in an effort to make the best choices for fighting deficiencies all over the world.

Part 2

Overview of the different approaches

Food fortification (11) is a food based strategy and includes commerical and industrial fortification, home fortification, biofortification and if implemented crops or animals; microbial biofortification and synthetic biology. In this context, fortification in general means to improve or strengthen the levels of nutrients in a target product. The several types of food fortification are distinct because different techniques and procedures are used to fortify the target foods.

Biofortification involves creating micronutrient-dense staple crops using traditional breeding techniques(7) and/or biotechnology. Cross breeding has been around for decades and has been used to fortify numerous crops. Using biotechnology to biofortify staple crops is more modern. The most popular example of this approach is the transgenic 'Golden Rice'(12; 13), which has been fortified with Beta-Carotene with the purpose to try to improve Vitamin A levels in people with deficiencies.

Microbial Biofortification involves using probiotic bacteria, which ferment to produce Beta-carotene, in the foods we eat or directly in the human intestine. The probiotic bacteria that are often selected for addition to food are lactic acid bacteria (LAB) because they are presumed to have beneficial effects on the host(14). An example of this would be mixing lactic acid bacteria (LAB) with animal feed so that animal meats and bi-products such as milk are enriched in Vitamin A.

Commercial and Industrial fortification

This approach involves fortifying commercially available products such as flour, cooking oils and butter with Beta-carotene or Retinol. This fortification process occurs during manufacturing.

Home Fortification

This approach consists of supplying deficient populations with home mixed vitamins and minerals in packages or tablets that can be added when cooking meals. This approach is basically a merger of supplements and fortification.

Supplementation

This has been the most widely used approach so far in fighting Vitamin A deficiency. There have been many successful campaigns using supplementation. Vitamin A supplements come in the form of tablets, syrup and capsules and can be provided in biannual large doses (micronutriets: dietary intake V supplement use). In most campaigns, the supplements have been handed out during national immunization days, like those dedicated to polio. However, National Micronutrient Days (NMDs), like those started in Africa in 1999, are becoming a more popular way to ensure supplements are received biannually(15).

Increasing and diversifying dietary intake

This approach involves creating larger and more diverse diets for the target population. This may require the population to increase their production of food which may be paired with educational campaigns to provide the information about which foods promote higher levels of vitamin A in the body. Another possibility is increasing the distribution of food to the region from another area.

Synthetic Biology Approach

Although techniques of synthetic biology are used in aspects of biofortification and microbial fortification, it is also an individual approach. This approach involves engineering a synthetic operon of beta-carotene metabolic genes in a plasmid, which may then be transferred to a diverse set of bacterial hosts. The biofortified probiotic hosts may be implemented in many ways to produce Beta-Carotene for humans. The probiotics may be place directly in the human intestine

or they may be associated with our foods. One possibility may be mixing the probiotics with animal feed so that animal meats and animal bi-products are enriched with vitamin A. (Guelph iGEM team)

Pros	Cons

Part III
The E3LS Implications of the Various Approaches (Pro V Con)

Economic argument **BIofortification**	once introduced, biofortified crop systems are highly sustainable and require minimal intervention (16)	
Environmental argument	Trace minerals can help plants resist disease and withstand other environmental stressors (16)	Currently there is a lack of adequate knowledge on the impact that GM crops have on local ecosystems (16) Monocultures reduce biodiversity
Ethics argument		Many people believe genetically modifying crops is wrong because nature shouldn't be altered
Legal argument		Who is responsible for regulation and quality control?
Social argument		farmers and consumers may not accept sensory changes of biofortified crops (16)
Other	biofortification is a well suited approach for developing countries since it utilizes the fact that the daily diet of low income micronutrient deficient populations, is large quantities of staple foods(16)	

Pros	Cons

Economic argument **Microbial biofortificaitoan**	- Additional benefits offered by LAB may lower subsequent health care service costs	Costs for delivering live bacteria and overseeing administering could be high
Environmental argument	- Vehicle for delivery exists in nature (Lactobacilli)	
Ethics argument		- difficult to establish clinical trials and to prove efficacy - may be seen as inappropriate for direct human application
Legal argument		-Who would be in charge of regulation and quality control? -no regulatory definitions for functional foods or prebiotics (17) - health claims can be difficult to obtain for probiotic products (14)
Social argument	- if Lactic acid bacteria used, there may be beneficial effects in addition to reducing VAD deficiency (14)	-People may feel uncomfortable ingesting live bacteria -intestinal health is not-well understood by consumers (17)
Other	- Lactic acid bacteria are generally recognized as safe ((18) -LAB have beneficial effects on the host in addition to reducing deficiency (14)	-difficult to demonstrate the efficiacy of prebiotics in humans (17)

Pros	Cons

Economic argument **Home fortification**	- Can be distributed as widely and cheaply as spices or condoms	- Not a sustained approach as the supply of additives must be replenished by a producer outside the target population
Environmental argument	- Not disturbing the natural state of plant or animal species	
Ethics argument	- The approach is not forced on any person, it is their choice to utilize the additives	- people may feel uncomfortable adding a substance to their food without knowing what it is
Legal argument		
Social argument	- Encourages self-reliance - People's behavior patterns are not effected	- No guarantee the targeted population will participate
Other		- Requires education program

Pros	Cons

Economic argument **Commercial/industrial fortification**		
Environmental argument	- Does not interfere with the natural state of plant or animal species	
Ethics argument		-may be viewed as unethical to place substances in people's food without their consent
Legal argument		- producers of the commercial goods must agree to the terms of fortification
Social argument	- large populations do have the ability to purchase commercial foods	-People who can't afford commercial foods won't benefit
Other		-some people are too far from markets to purchase commercial products

Pros	Cons

Economic argument **Supplementation**	Very inexpensive, 2-4 cents per dose of 200,000 (IU) (19)	costs of Vitamin A pills are magnified by infrastructure, logistics and distribution costs
Environmental argument		Multiple doses a year to the many populations in need mean a lot of transportation and therefore emissions produced
Ethics argument		May not reach all of those in need, who decides which populations will receive adequate amounts of supplements
Legal argument		
Social argument		Rely on Access to health care systems and markets
Other	could capitalize on mothers breastfeeding children. If mothers take supplements, they benefit and their breast milk is enriched with Vitamin A, this nourishes the unborn child and avoids potential for toxicity of high Vitamin A doses to infants Vitamin A and breastfeeding: a comparison of data from developed and developing countries. (20) supplements can have an immediate impact in individual cases (21)	High levels of a single micronutrient may not be as beneficial to health as does increasing or diversifying dietary intake (micronutrients: dietary intake V. supplement use, woodside, 2005) Only addresses one deficiency and may not be effective since adequate protein and fat stores, which is lacking among many of those deficient in Vitamin A, is needed for the proper absorption of Vitamin A (13) Vitamin A and retinol are teratogenic meaning high doses may cause birth defects so Vitamin A supplements in large doses can be harmful for pregnant women and for very young children

	Pros	Cons
Economic argument **Increasing and diversifying dietary intake**	May stimulate the local economy in low income countries (22) due to properties of disease prevention, funds could be re-allocated from health services to developmental activities (21)	Technology and services needed to increase yields are expensive for low income farmers
Environmental argument	increases biodiveristy	Weather services are difficult for farmers to obtain in poor countries Increase in pesticide and herbicide use in order to increase yields may have negative effect on environment

Ethics argument		
Legal argument		
Social argument	promotes community action and encourages self-reliance (21)	not only prevent micronutrient deficiency problems but also contribute to general malnutrition prevention. (21)
Other	Diverse diet can address multiple deficiencies Holds potential to cover a wide population (21)	requires complementary education programs to inform farmers which crops will best combat Vitamin A deficiencies healthy fruits not always available and depend on the season (13)

Pros	Cons

Economic argument **Synthetic Biology approach**		- Costs for quality assurance of health claims is very high (14)
Environmental argument	- Delivery vehicle (Lactobacilli) are naturally found in the human body and are generally regarded as safe (23)	
Ethics argument	- Lactic acid bacteria are generally known to be safe (23)	-clinical human trials may be difficult to establish and get ethics approval for
Legal argument	-	-Use of some technology depends on generosity of industrial patent holders (16) - health claims can be difficult to obtain for probiotic products (14)
Social argument	- Targeted populations wouldn't have to drastically alter their behavior	- Concept is unfamiliar to the general public and may meet resistance as a result
Other	- In some staple foods, conventional breeding cannot be used for fortification of Vitamin A in those cases transgenic approaches are superior (16) - If implemented in animal feed, probiotics would also benefit animal health	- Probiotic efficacy is difficult to measure (17) Depending on how the carrier of the operon is utilized, health care services may be required

Reference List

1. UNICEF The challenge: Vitamin A deficiency. (2008). UNICEF [On-line]. at: http://www.childinfo.org/vitamina.html

2. World Health Organization Vitamin and Mineral Nutrition Information System (VMNIS). (2008). World Health Organization [On-line]. at: http://www.who.int/vmnis/vitamina/data/database/countries/en/index.html

3. United Nations System Standing Committee on Nutrition SCN Working Group on Micronutrients. (2002). ACC/SCN's 29th Session in Berlin, Germany [On-line].

4. World Health Organization Vitamin A deficiency. (2008). World Health Organization [On-line]. at: http://www.who.int/nutrition/topics/vad/en/

5. Reddy, V. History of the International Vitamin A Consultative Group 1975–20001.,(2002) *The Journal of Nutrition, 132,* 2852S-2856S. [On-line] at: http://jn.nutrition.org/cgi/content/abstract/132/9/2852S

6. Ansstas, G., Thakore, J., & Gopalswamy, N. Vitamin A Deficiency. (2008). eMedicine from WebMD [On-line]. at: http://www.emedicine.com/med/TOPIC2381.HTM

7. Low, J., Arimond, M., Osman, N., Cunguara, B., Zano, F., & Tschirley, D. A Food-Based Approach Introducing Orange-Fleshed Sweet Potatoes Increased Vitamin A Intake and Serum Retinol Concentrations in Young Children in Rural Mozambique.,(2007) *Journal of Nutrition, 1320, 1327*. [On-line]

8. Potter, A. R. Reducing vitamin A deficiency.,(1997) *British Medical Journal*. [On-line] at: http://www.bmj.com/cgi/content/full/314/7077/317#R2

9. UNICEF. *Vitamin A Supplementation A Decade of progress*UNICEF (2007). [On-line].,.http://www.childinfo.org/files/Vitamin_A_Supplementation.pdf

10. UNICEF Vitamin & mineral deficiency a global progress report. (2004). UNICEF [On-line].

11. **World Health Organization and Food and Agricultural Organization of the United Nations**. *Guidelines on food fortification with micronutrients* Allen, L., de Benoist, B., Dary, O., & Hurrell R (2006). [On-line].,.http://www.who.int/nutrition/publications/guide_food_fortification_micronutrients.pdf

12. Nilva, E. Vitamin A Deficiency and Golden Rice--A Literature Review.,(2003) *Journal of Nutritional & Environmental Medicine, 13, 3*, 169-184. [On-line] at: http://www.ingentaconnect.com/content/routledg/cjne/2003/00000013/00000003/art00005

13. Van Wijk, J. Food insecurity: Prevalence, causes, and the potential of transgenic 'Golden Rice'.,(2002) *Phytochemistry Reviews, 1,* 141-151. [On-line]

14. Farnworth, E. R. The Evidence to Support Health Claims for Probiotics.,(2008) *The Journal of Nutrition, 138,* 1250S-1254S. [On-line]

15. Aguayo, V., Baker, S., Crespin X, Hamani H, & Mamadoul A Fortifying flour, salt, and cooking oil offers an effective and inexpensive way to get essential vitamins and minerals into food for low-income populations at risk of malnutrition.,(2005) *Food and nutrition bulletin, 26, 1*, 26-31. [On-line]

16. Nestel, P., Bois, H., Meenakshi, J., & Pfeiffer W Biofortification of Staple Food Crops.,(2006) *Journal of Nutrition, 136,* 1064-1067. [On-line] at: http://jn.nutrition.org/cgi/content/abstract/136/4/1064

17. Dwyer J Do Functional Components in Foods Have A Role in Helping to Solve Current Health Issues?,(2007) *Journal of Nutrition, 137,* 2489S-2492S. [On-line]

18. U.S.Food and Drug AdministrationCenter for Food Safety & Applied NutritionOffice of Food Additive Safety Partial List Of Microorganisms And Microbial-Derived Ingredients That Are Used In Foods. (2001). U.S.Food and Drug AdministrationCenter for Food Safety & Applied NutritionOffice of Food Additive Safety [On-line]. at: http://www.cfsan.fda.gov/~dms/opa-micr.html

19. Sommer A A deficiency disorders: Origins of the problem and approaches to its control. (2001). Biotech-info.net [On-line]. at: http://www.biotech-info.net/disorders.html

20. Newman V Vitamin A and breastfeeding: a comparison of data from developed and developing countries. (1993). Popline [On-line]. at: http://www.popline.org/docs/1070/102351.html

21. United Nation Food and Agriculture Organization. *Preventing micronutrient malnutrition a guide to food-based approaches - Why policy makers should give priority to food-based strategies*Food and Agriculture Organization of the United Nations and International Life Sciences Institute (1997). [On-line]. at: http://www.fao.org/DOCREP/x0245e/x0245e00.htm

22. Editorial A research menu More spending on agricultural science is needed to help resolve the world's food crisis.,(2008) *Nature, 453,* 1-2. [On-line] at: http://www.nature.com/nature/journal/v453/n7191/full/453001b.html

23. Walter, J., Hertel C, Tannock GW, Lis CM, Munro, K., & Hammes, W. Detection of Lactobacillus, Pediococcus, Leuconostoc, and Weissella species in human feces by using group-specific PCR primers and denaturing gradient gel electrophoresis.,(2001) *Appl Environ Microbiol, 67,* 2578-2585. [On-line]