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### **Vitamin A Deficiency and *Golden Rice***

In the year 2000, almost 800 million people in 98 developing countries did not get enough food to lead a normal, healthy and active life, as estimated by the UN's Food and Agriculture Organisation (FAO). Around eleven million children die of malnutrition every year; a vast majority of those deaths are linked to micronutrient deficiencies. Nutritional deficiencies with the highest impact on susceptibility to disease and mortality are related to the lack of iron, zinc, iodine and vitamin A. At its inception, the *Golden Rice* Project set out to alleviate the vitamin A deficiency (VAD) problem, because of its relevance and potential impact. Yearly, half a million people—mainly children—become blind as a consequence of VAD, fifty percent of whom die within a year of becoming blind. VAD severely affects the immune system; hence it is



Figure 1. The Golden Rice

also involved in many of these children's deaths in the guise of multiple diseases, like measles and malaria.<sup>1</sup> It has been calculated that simple measures, like breastfeeding, combined with vitamin A and zinc supplementation could save 25 percent of those affected children.<sup>2</sup>

Various public and international programs for supplementation, fortification and diet diversification have achieved substantial improvements but have difficulty in attaining full coverage of the affected population, and above all, sustain-

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ability. *Supplementation* is the provision of the needed micronutrients in the form of capsules, for example. *Fortification* is the addition of micronutrients to centrally processed foodstuff, like the addition of vitamin A to oil or butter. These activities require the involvement of ten thousands of people for the distribution and complicated logistics to reach the target population. Supplementation campaigns are very costly and should be carried out twice per year. Both approaches, fortification and supplementation, have difficulties reaching remote rural populations and an interruption in the flow of funds could jeopardise the whole program.

*Biofortification* is the fortification of crops by means of their own biosynthetic capacity. The acquisition of biofortified crops involves conventional breeding of genetically improved basic staple crops. This approach offers an opportunity to obtain a more inclusive coverage, especially of the poorest sectors of society who primarily depend on agriculture for livelihood. Genetic improvement of crops can be achieved in various ways, including crossing with wild relatives, mutagenesis and genetic engineering.

VAD is prevalent among the poor who depend mainly on starchy crops for their daily energy uptake, because most starchy crops, like rice and sorghum, do not contain any beta-carotene (provitamin A), which our body in turn can convert into vitamin A. Half of the world's population eats rice on a regular basis, again for half of those rice is the main energy source. Dependence on rice as the predominant food source, therefore, necessarily leads to VAD, most severely affecting children and pregnant women. For the 400 million rice-consuming poor, the medical consequences are severe: impaired vision, very often leading to irreversible blindness, impaired epithelial integrity, exposing the affected individuals to infections, reduced immune response, impaired blood cell production and skeletal growth, among other debilitating afflictions.

Rice containing beta-carotene could substantially reduce the problem. This can only be achieved using genetic engineering because there is no provitamin A in the endosperm, which is the starch storage tissue of the seed. There are a number of red and brown rice varieties, but these do not contain beta-carotene.



Figure 2. Children in Nepal.  
Photo J.Mayer

The unpolished rice grain contains other valuable nutrients, like vitamin B and essential fats. It is the latter that makes it usually necessary to polish the rice grain, as the fats may become rancid by oxidation after long storage, thus affecting the taste of the grain.

**Scientific breakthrough**

Rice, like all green plants, produces carotenoids in the leaves. Carotenoids are also often produced in the flowers, conferring some of the beautiful yellow, orange and red colours that we so much enjoy. Among the carotenoids produced in plants is beta-carotene, the best plant source of vitamin A. Animal sources deliver directly vitamin A, rather than the provitamin. Carotenoid production is often turned off in non-photosynthetic tissues, like in the rice grain. In *Golden Rice*, the biochemical pathway leading to the production of beta-carotene has been re-engineered to turn on its biosynthesis again.<sup>3</sup>

This feat was made possible by the advancements in green gene technology. The most successful methodology to introduce individual genes into the plant genome relies on *Agrobacterium*, a micro-organism that has been doing this for its own purposes for thousands of years. Scientists in the 1980s *tamed* this micro-

organism by eliminating the genes that *Agrobacterium* usually transfers to the plant host and replacing them with genes of interest to mankind. While some scientists were busy fine-tuning this methodology, others were elucidating the complex biosynthetic pathway of carotenoids.

*Golden Rice* is the result from the work carried out in laboratories of Profs Ingo Potrykus and Peter Beyer, at the Federal Institute of Technology, Switzerland, and the University of Freiburg, Germany, respectively. Newer developments with higher beta-carotene content were developed through collaboration with the Swiss company Syngenta. The target of this research was to produce enough beta-carotene in rice to cover the recommended daily requirements of children and adults alike.

The *Golden* trait could in principle be directly engineered into many different rice varieties, but because of the stringent biosafety regulation requirements, in the end only one *regulatory clean* event will be used as the starter seed for introgression in multiple breeding programmes.<sup>4</sup> Regulatory clean refers to the fact that regulators have imposed a number of criteria on transgenic plants, whereby a number of those are not based on scientific insights but rather on perception. This makes the generation of new transgenic plants of general interest to the public more expensive and cumbersome to achieve.

### Reaching out

*Golden Rice* will be made available to developing countries within the framework of a humanitarian project. This was, from the onset, a public research project designed to reduce malnutrition in developing countries. The hurdle of extensive intellectual property rights attached to the technologies, mainly in the form of patents, used in the production of *Golden Rice* was overcome thanks to strong support from the private sector in the form of free licences for humanitarian use. This arrangement opened the way to collaborations with public rice research institutions in developing countries, providing freedom to operate to develop locally adapted *Golden Rice* varieties.

The *Golden Rice* approach does not affect the diversity of traditional varieties used by farmers. The *Golden* trait can be crossed into any such variety by conventional means. What the farmer will sow and harvest will be original tra-

ditional varieties, with one little yet crucial difference: yellow grains containing the health-promoting beta-carotene.

Once the locally adapted *Golden* varieties are released to smallholders, the seed will become their property and they will also be able to use part of their harvest for the next sowing, without restrictions. *Golden Rice* is compatible with the use of traditional farming systems, it does not require more agronomic inputs than the parental variety. Therefore, no new dependencies will be created. Moreover, as concluded by many experts, the *Golden* trait does not pose any conceivable risk to the environment which would justify delaying its widespread use.

Moving *Golden Rice* from the laboratory to the field is not a trivial exercise. A group of international experts from reputed institutions provides strategic guidance to the project. At the next level, a network of national institutions participates in the development and distribution of locally adapted varieties. To date, the *Golden Rice* Network includes 16 national institutions in Bangladesh, China, India, Indonesia, Nepal, the Philippines, Vietnam and South Africa. The Network is under the strategic guidance of the *Golden Rice* Humanitarian Board and under the management of a network coordinator, based at the International Rice Research Institute (IRRI), in the Philippines.

### **A sustainable solution**

Biofortification—the genetically based complementation for missing micronutrients—of basic staple crops with the help of genetic engineering is presumably the most sustainable and cost-effective approach to reduce micronutrient malnutrition among poor populations in developing countries. *Golden Rice* is the first example of such an approach. If we put aside the research investment by Syngenta so far, investment in the public sector has been relatively modest so far (US\$2.4 million over nine years). Product development, however, is time-consuming and requires substantial additional funding. Funds for product development are normally not provided by the public sector, since the work involved is not the typical type of research work done by academics. In universities productivity of researchers is measured in terms of scientific productivity and not marketable products. The latter is a typical activity of industry.

While expenses increase even more dramatically when it comes to biosafety assessment—as required for deregulation purposes—once a novel, biofortified variety has been approved and handed over to farmers, the system can develop its full potential. From this point on, the technology is built into each and every seed and does not require additional investment. Let’s consider the potential of a single *Golden Rice* seed: a single plant will produce in the order of 1,000 seeds; within four generations—or less than two years—that one plant could generate up to 28-thousand metric tons of rice (see table), which would be sufficient to feed a hundred-thousand poor people for one year. A smallholder will typically have around one hectare of land and can produce two to five tonnes of rice on that land, requiring only about 100 Kg of seeds for planting. These people’s vitamin A needs would automatically be covered if they were eating *Golden Rice*, thus reducing VAD dramatically. This gained health protection is cost-free and sustainable. All a farmer needs to benefit from the technology is contained in a seed!

Generations	Seeds	Kg
0	1	0.000028
1	1,000	0.028
2	1,000,000	28
3	1,000,000,000	28,0000
4	1,000,000,000,000	28,000,000

### Ignoring the benefits

In the 1980s the technology to introduce genes into plants was developed. The concerted effort that led to *Golden Rice* took seven years, from 1992 to 1999. Thanks to further research the level of beta-carotene production was raised several-fold between 1999 and 2004 (see Figures 4a and b). We are hopeful that some countries affected by VAD will be able to release locally adapted *Golden Rice* varieties within a couple of years, pending regulatory approval. Considering that *Golden Rice* could substantially reduce blindness and deaths, it is not easily understandable that the project is not getting wider international support to accelerate the regulatory process.

Notwithstanding the fact that during the last 20 years a vast knowledge base on the production and commercialisation of genetically modified plants has accumulated, the next years will have to be spent on carrying out the required biosafety assessments to exclude any putative harm by *Golden Rice* to the environment and the consumer.

In our daily life we manage great risks, like driving cars or eating spoiled food. In the case of genetically modified plants, the present position is that even the slightest hypothetical risk can lead to the rejection of such a plant. At the same time, potential benefits are being disregarded, irrespectively of how great they are. Renowned ecologists, including opponents of the technology, have not been able to come up with a realistic hypothetical risk to any agricultural or wild environment stemming from the production and accumulation of beta-carotene in the endosperm of plants which produce high amounts of the same compound in other organs of the plant anyway, and thus will not provide any additional selection advantage to the crop.

The present interpretation of the precautionary principle would seem reasonable if it were not for the fact that most people have been eating these genes and their products from a number of other food sources throughout their lives. Moreover, the genetic information that has been introduced into *Golden Rice* is known right down to the last detail, and thus very accurate risk predictions can be made.

It is obvious that no scientist or scientific institution in the public domain has the potential, funding or motivation to perform the lengthy and expensive biosafety experiments presently required. It comes as no surprise then that virtually all genetically modified plants that have reached commercialization so far are in the private sector and restricted to high-value crops. Humanitarian projects do not fall into this category, even though they would benefit millions of people.<sup>5</sup>

There is plenty of goodwill in the public and in the private sectors worldwide to exploit the potential of green biotechnology for the benefit of the poor. However, without a realistic risk assessment approach, funds for public research will not suffice. Under such circumstances, scientific progress would become detached from product development and the population at large would not benefit from the great potential of the technology.



Figure 3. Women in one of Nepal's rice-fields. Photo J.Mayer

More than 20 years of experience using genetically modified plants worldwide, covering more than 90 million hectares in 2005, have not resulted in one single mishap related to damage to health or the environment. Thousands of carefully conducted biosafety experiments have been carried out by prestigious institutions, and all results lead to the conclusion that there is no specific risk associated with the technology, beyond that inherent to traditional plant breeding or natural evolution.

### The needs of developing countries

Developing countries are often caught in a conundrum between the urgent need to adopt gene technology and possible commercial repercussions affecting exports. In essence, the EU, where this technology is not urgently needed, exports the high regulatory and standardisation costs abroad, resulting in the build-up of *de facto* trade barriers, i.e. by stopping importation of agricultural produce because of alleged admixture of transgenic materials. Gene technology has been endorsed by international agencies, such as FAO, World Health Organisation (WHO) and the United Nations International Development Organisation (UNIDO), to help solve food security problems in developing countries, but still this promising technology lacks support from the general public in European countries, mainly because of unwillingness to digest the available information.

The highest price for the non-adoption of green gene technology is being paid by those voiceless persons who most need it. The great potential of gene technology to reduce hunger and malnutrition and to help protect the environment will only be attained once regulatory frameworks are based on scientific evidence and a proper risk-benefit analysis. Until then the technology will be restricted to *luxury products*, with safe financial returns for the private sector and mostly located in developed countries.

Slowly, more countries in the developing world have started embracing green biotechnology, based on hard scientific, health and economic impact analyses data. Positive, highly encouraging reports on increased harvests, reduced use of pesticides, a decrease in the number of people intoxicated from using pesticides and an increase in the number of beneficial insects in the fields are now coming from countries like South Africa and India. For *Golden Rice*, a recent World Bank report concluded that the potential welfare improvement derived from the adoption of *Golden Rice*—in the range of billions of dollars annually—could even dwarf the socioeconomic impact of the adoption of transgenic technology.<sup>6</sup>

### **It's all about genetic modification**

Green gene technology has the potential to support and complement traditional plant breeding. One criticism frequently brought up in relation with genetic engineering is that the insertion of new genes could lead to unpredictable genome alterations. In traditional plant breeding, agronomic traits are combined or eliminated by crossing, followed by selection. In this process, existing varieties and landraces are used as starting materials. Many traits selected by farmers since the inception of agriculture are based on spontaneous, unpredictable mutations. Traditional breeding includes the use of wild relatives of crop plants, which bring scores of unknown genes into the equation. The sexual crossing of plants, familiar to all of us, generates unpredictable genome alterations, such as gene recombinations, translocations, deletions, and inversions. This is even worse for varieties generated by radiation mutagenesis. There are around 2,500 registered varieties generated using this technology and many are used by organic farmers. The most widely used pasta noodle wheat was generated in this way.

These unpredictable, significant genome alterations accumulate at every breeding step and each new, traditionally bred variety is the result of an increasing array of such random events. This statement is valid for all modern crop varieties, including those used in organic farming. Nevertheless, while none of these *genetically modified* varieties has ever been assessed for biosafety, mankind has consumed them unabated, simply because it is familiarized with the procedures and their outcome. The fact is that actually nobody could survive without eating food from these *genetically modified* crops.

By comparison, the creation of *Golden Rice*—involving the insertion of two precisely defined genes into a genome that contains fifty-thousand-odd genes (Figure 4)—is by several orders of magnitude more precise than traditional breeding. Why should this small, defined modification be the subject of comparatively excessive scrutiny?

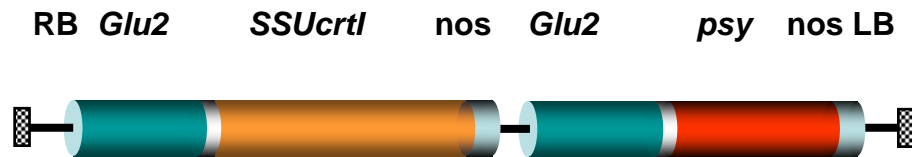


Figure 4a. The two genes *psy* and *crt1*, encoding the enzymes PSY (phytoene synthase) and CRT1 (carotene desaturase), and are needed to reconstitute the synthesis of  $\beta$ -carotene in rice grains. A promoter (starter sequence) *Glu2* (Glutelin) and a terminator sequence, *nos* (nopaline synthase terminator) are also needed to direct synthesis at the right time and tissue. RB and LB are the right and left borders of the gene construct. Redrawn after A. Paine et al. March 27, 2005, *Nature Biotechnology*

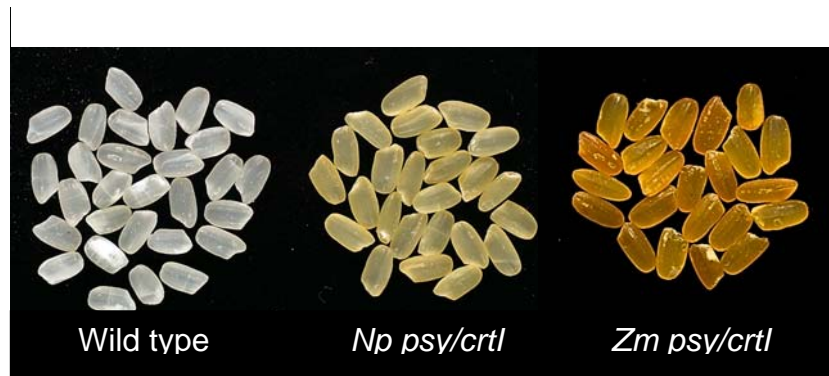


Figure 4b. Genes encoding PSY from different plant sources were tested. In the first Golden Rice a PSY gene from daffodil (*Narcissus pseudonarcissus*) was used. The second generation of Golden Rice uses a PSY gene from maize (*Zea mays*), which produces a much higher concentration of  $\beta$ -carotene. *Np psy/crtl* shows rice grains with a PSY gene from daffodil; *Zm psy/crtl* shows rice grains with a PSY gene from maize. After: A. Paine et al. March 27, 2005, *Nature Biotechnology*

### Ethical responsibility and the way ahead

Green biotechnology has the potential to provide solutions to pest and disease control, improve photosynthetic efficiency and nutritional content, furnish plants with adaptation mechanisms for heat, cold, drought and salinity tolerance and many more things to come. These applications of the technology could reduce or reverse some of the negative impacts of agriculture on health and the environment. On the same token, while the benefits of *Golden Rice* are obvious, opponents of the technology are pretending to save humanity by blocking its development, while blind and sick children in the developing world are confronted with the bitter reality, and not perceived risks. Who will assume the responsibility for this preventable tragedy being imposed upon the innocent?

The Nuffield Council on Bioethics<sup>7</sup> concluded in their 2004 report that '*[t]he European Union is ignoring a moral imperative to promote genetically modified crops for their great potential for helping the developing world*', and '*[w]e believe EU regulators have not paid enough attention to the impact of EU regulations on agriculture in developing countries.*'

The *Golden Rice* project has recently been awarded a grant by the Bill & Melinda Gates Foundation to further improve *Golden Rice* by adding genes that will promote the accumulation of iron, zinc, vitamin E and high-quality protein in rice grains. This project is being carried out by a consortium of seven institutions in a number of countries. Concurrently, other re-

search consortia are developing similar approaches for sorghum, cassava and bananas. These are all crops that provide the main caloric intake in developing countries where rice is not the main food source, and they all lack essential micronutrients. It is very encouraging to see that the *Golden Rice* approach has played a catalytic role in inspiring these activities, and it can only be hoped that people in need will soon have access to better nutrition thanks to these projects and the support of people with a vision and understanding.

### References

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