

The *Golden Rice* Project

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In the year 2000, more than 792 million people in 98 developing countries did not get enough food to lead a normal, healthy and active life, as estimated by FAO. More than 10 million children die of malnutrition every year, unnecessarily, and 90 percent of the fatalities are concentrated in only 42 developing countries. A vast majority of these deaths is linked to micronutrient deficiencies.^{1,2} The deficiencies with the highest impact on morbidity and mortality are in iron, zinc, iodine and vitamin A.

At its inception, the *Golden Rice* was conceived as a 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, 50 percent of which die within a year of becoming blind. VAD severely affects the immune system; hence it is also involved in many of these children's deaths in the guise of various infectious diseases. Recently, malaria deaths in children under five years of age have been linked to deficiencies in intake of protein, vitamin A and zinc.³ Various public and international programmes working on supplementation, fortification and diet diversification have achieved substantial improvements but have difficulty in attaining full coverage of the affected population and above all, sustainability. Biofortification—the fortification of crop tissues by means of their own biosynthetic capacity—involves conventional breeding of genetically improved staple crops, and offers an opportunity to obtain a more inclusive coverage, especially of the poorest sectors of society. Genetic improvement can be achieved in various ways, including conventional selection, introgression of traits from wild relatives, mutagenesis and genetic engineering.

VAD is prevalent among the poor who depend mainly on rice for their daily energy intake, because the rice endosperm—the starchy, edible part of the rice grains—does not contain any beta-carotene (provitamin A), which our body could then convert into vitamin A. 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, in extreme cases irreversible blindness, impaired epithelial integrity, exposing the affected individuals to infections, reduced immune response, impaired hematopoiesis 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, even though it is produced in the leaves of rice plants. No variability for this trait, suitable for breeding purposes, has been detected in the world's most important rice germplasm collections.

¹ Black RE, Morris SS and Bryce J. 2003. Where and why are 10 million children dying every year? *Lancet* 361:2226-2234.

² Jones G, Steketee RW, Black RE, Bhutta ZA, Morris SS, and the Bellagio Child Survival Group. 2003. How many child deaths can we prevent this year? *Lancet* 362:65-71.

³ Caulfield LE, Richard SA and Black RE. 2004. Undernutrition as an underlying cause of malaria morbidity and mortality in children less than five years old. *Amer. J Trop Med Hyg* 71 (Suppl 2): 55–63.

Scientific breakthrough

Golden Rice has been engineered to contain the genes necessary to make up the biochemical pathway for beta-carotene production in the grain.^{4,5,6} This breakthrough achievement was the result of many years of work by Ingo Potrykus and Peter Beyer, in Switzerland and Germany, respectively. The only thing required to turn on the pathway, which is silent in the grain, is to add two genes. These two genes were borrowed originally from daffodils and from *Erwinia uredovora*, a soil bacterium.⁷ Since the breakthrough in the year 1999, the gene construct was further refined to be expressed exclusively in the rice endosperm. In 2005, Syngenta scientists were capable of increasing the beta-carotene level obtained in the first-generation *Golden Rice* 23-fold, by replacing the daffodil with a homologous gene from maize.⁸ This level of beta-carotene should be enough to cover the recommended daily requirements of children and adults in rice-based societies.

The *Golden* trait is now finally being introduced into rice varieties used in target countries. The process has been delayed by the fact that only a *regulatory clean* event can be used as the starter seed for cross-breeding.⁹ Some regulatory requirements go beyond what is scientifically justifiable, making the process lengthy and expensive.

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. Thanks to strong support from the private sector and free licences for humanitarian use, the hurdle of extensive intellectual property rights attached to the technologies used in the production of *Golden Rice* could be overcome early during the process. The 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.

Once locally developed rice varieties containing the *Golden* trait have gone through regulatory approval—including all required biosafety testing—at the national level, seed will be made available to subsistence farmers, free of charge. 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, not requiring additional agronomic

⁴ Beyer P, Al-Babili S, Ye X, Lucca P, Schaub P, Welsch R and Potrykus I. 2002. *Golden Rice*: introducing the beta-carotene biosynthetic pathway into rice endosperm by genetic engineering to defeat vitamin A deficiency. *J Nutrition* 132: 506S-510S.

⁵ Al-Babili S and Beyer P. 2005. *Golden Rice* — Five years on the road — five years to go? *Trends in Plant Science* 10:565-573.

⁶ Schaub P, Al-Babili S and Beyer P. 2005. Why is *Golden Rice* golden (yellow) and not red. *Plant Physiology* 138:441-450.

⁷ Ye X, Al-Babili S, Klöti A, Zhang J, Lucca P, Beyer P and Potrykus I. 2000. Engineering provitamin A (beta-carotene) biosynthetic pathway into (carotenoid-free) rice endosperm. *Science* 287: 303-305.

⁸ Paine JA, Shipton CA, Chaggar S, Howells RM, Kennedy MJ, Vernon G, Wright SY, Hinchliffe E, Adams JL, Silverstone AL, Drake R. 2005. A new version of *Golden Rice* with increased provitamin A content. *Nature Biotechnology* 23:482-487.

⁹ Hoa TTC, Al-Babili S, Schaub P, Potrykus I and Beyer P. 2003. *Golden indica* and *japonica* rice lines amenable to deregulation. *Plant Physiol* 133: 161-169.

inputs. 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.

The progress achieved since the initial breakthrough would not have been possible without an innovative type of public-private partnership. Thanks to an agreement with Syngenta and other agbiotech industries, *Golden Rice* is royalty-free for humanitarian use, which, for the purpose of this project, is defined as ‘an annual farm income in the range of US\$10'000 per farmer, while a higher income would require a commercial licence from Syngenta.’ Royalty-free humanitarian sublicences are granted by the *Golden Rice* Humanitarian Board to public rice research institutions. These sublicense agreements ensure that the material is handled according to established biosafety guidelines and regulations, and that the target population—subsistence farmers and the urban poor—receives the biofortified rice with no surcharge for the *Golden* trait.

Golden Rice tailored for local consumption

Development of locally adapted *Golden Rice* varieties and applications to national authorities for field testing and for regulatory approval is in the hands of national and international public rice research institutions. To date, the *Golden Rice* Network includes eighteen national, developing-country institutions in Bangladesh, China, India, Indonesia, Nepal, South Africa, The Philippines, and Vietnam. 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.

The Humanitarian Board is an honorary body that benefits from the expertise of international authorities, including Dr Gurdev Khush, retired rice breeder from IRRI (rice breeding); Prof Robert Russell, Laboratory for Human Nutrition, Tufts University Boston (vitamin A malnutrition); Dr Howarth Bouis, Director of HarvestPlus, an initiative of the Consultative Group of International Agricultural Research (biofortification); Dr Gary Toenniessen, The Rockefeller Foundation (food security in developing countries); Dr Robert Bertram, USAID Washington (development in Third World agriculture); Dr Katharina Jenny, Swiss Development Cooperation (technology transfer and trans-sectorial issues); Dr Adrian Dubock, Syngenta (product development and intellectual property rights); Dr Robert Zeigler, Director General, Dr Ren Wang (Deputy Director General Research) and Dr William Padolina, all from the International Rice Research Institute (IRRI) in the Philippines (international cooperation in rice research); Dr S.R. Rao, Dept. of Biotechnology, India (national deployment strategies); Professor Ingo Potrykus (co-inventor), professor emeritus from the ETH Zurich, chairman (public relations and information); Prof Peter Beyer (co-inventor) Univ of Freiburg (scientific advancement in the areas of biofortification for provitamin A and other micronutrients); and the ex-officio members Dr Gerard Barry, IRRI (*Golden Rice* Network Coordinator) and Dr Jorge Mayer, Campus Technologies Freiburg (*Golden Rice* Project Manager).

Biofortified seeds — 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. Public sector investment to develop the basic technology has been relatively modest, amounting to about US\$2.4 million

between 1992 and 2000. To date, Syngenta has invested a similar amount. Product development, however, is time-consuming and requires substantial additional funding. Funds for product development are usually not provided by the public sector or academia, since the type work that this activity entails normally does not lead to scientific discovery. Costs increase even more dramatically when it comes to biosafety assessment, as required for regulatory approval purposes.

But 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 any additional investments. Consider the potential of a single *Golden Rice* seed: a single plant produces in the order of 1,000 seeds; within four generations—or less than two years—that one plant will have generated more than 10^{12} seeds, only limited by available land, of course. This would represent up to 28-thousand metric tons of rice, which would be sufficient to feed a 100-thousand poor people for one year. And if these people were eating *Golden Rice* they would be automatically supplemented with provitamin A, thus substantially improving their vitamin A status. This gained protection is cost-free and sustainable. All a farmer needs to benefit from the technology is contained in a seed!

Ignoring the benefits

It took ten years—from 1980 to 1990—to develop the necessary technology to introduce genes into rice. It took another eight years—from 1992 to 1999—to introduce the genes that reconstitute the pathway for provitamin A biosynthesis into the seed. And it took another five years—from 1999 to 2005—to develop *Golden Rice* in its present, high beta-carotene-producing form. It will take several more years to advance the first *Golden Rice* product through the regulatory process. Considering that *Golden Rice* could substantially reduce blindness (half a million children per year) and deaths (2-3 million per year), the reluctance displayed by the responsible bodies, especially in the face of the great success and safety record of genetically modified crops, is hard to understand. In the year 2005 ninety million hectares were planted with transgenic crops, 38 percent thereof in developing countries.¹⁰

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

The present regulatory practice in a number of countries is based on an overzealous interpretation of the precautionary principle, with little room left for risk management. The position at present is that even the slightest hypothetical risk must be thoroughly tested, and might lead to rejection of an application for registration. At the same time, potential benefits are disregarded. Ecologists of renown, 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 selective advantage to the crop. This shows a substantial level of irrationality applied to the present system of environmental risk assessment. Despite this fact, the first *Golden Rice* small-scale field trial worldwide took place only in 2004, in the USA, and not in South East Asia where

¹⁰ James C. 2005. Global Status of Commercialized Transgenic Crops: 2005. ISAAA Briefs No. 34. ISAAA: Ithaca, NY.

it should have taken place. The reason behind this is that developing countries have been put under severe pressure from EU countries and NGOs to adopt highly restrictive regulatory regimes based on a misinterpreted precautionary principle. Based on present-day scientific knowledge and experience, regulatory procedures could be substantially streamlined without detriment to health or environmental safety.

An unbearable financial burden

What are the regulatory requirements standing in the way of *Golden Rice* deployment? First of all, the application for regulatory approval must be for a carefully selected, *regulatory clean* transgenic event. Criteria are not necessarily based on scientific grounds; they include a number of requirements pertaining to the introduced genetic construct, eg the inserted DNA fragment should not have undergone multiple integrations or rearrangements, and there should be no read-through across the construct borders or any residual *ballast* DNA. This in turn requires the production of many hundreds of transgenic events using the same DNA construct, from which the regulatory clean event can then be selected. The carefully selected event is then carried through a lengthy biosafety assessment to prove or disprove any putative biosafety hazard. The consequence of this approach is that nearly ninety percent of all transgenic events, and often those with the highest levels of expression, must be discarded. This process required the production of many hundreds of similar events and the subsequent destruction of practically all but one event. This expensive process is beyond the reach of most public research institutions, in developing as well as in developed countries, and funding agencies are not prepared to take over such costs.

The biosafety assessment starts with event-independent studies, related to the introduced genes and their function, and is valid for all events produced using these genes. These studies are followed by animal and human exposure evaluation tests for the novel trait and its intended use. This phase of the study alone could take up to three years, because during the pre-field trial phase the materials have to be produced in dedicated plant growth chambers and greenhouses, which can be rather expensive and where production levels are low. These tests are followed by equivalence analyses of the proteins encoded by the introduced genes. For this purpose the proteins have to be purified from plant extracts, characterised biochemically, and their function confirmed. Further studies include a demonstration of lack of homology to known toxins and allergens, gastric degradation studies, heat stability, acute toxicity tests in rodent feeding experiments.

This all would seem reasonable if it were not for the fact that most people have been eating the genes introduced into *Golden Rice* and their products from a number of other food sources throughout their lives. At one point, critics even suggested to analyse whether known daffodil toxins were being produced in *Golden Rice* even though only one known, defined gene, out of tens of thousands of daffodil genes, had been introduced into the first *Golden Rice* version to reconstitute the beta-carotene biosynthetic pathway. Furthermore, this gene is homologous to genes from other organisms, where they perform the same function, and it has no relation whatsoever with any toxin or allergen production. These studies will take at least another two years of intensive work in a well-equipped biochemistry laboratory.

The event-dependent studies are even more cumbersome; they may include, depending on the country where registration is sought:

Molecular characterisation and genetic stability: data on single-copy effect; the marker gene used should be at the same position as the introduced, desired genes; simple integration of the gene construct; Mendelian inheritance, including phenotypic and biochemical evidence for stability over at least three generations; no potential gene disruption; no unknown open reading frames; no DNA transfer beyond borders; no antibiotic resistance gene or origin of replication; insert size should be limited to the minimum necessary; full sequence information on insert and flanking regions must be determined.

Expression profiling: gene expression levels at key growth stages and evidence of seed-specific expression must be provided.

Phenotypic analysis: field performance, typical agronomic traits, yield compared to isogenic lines; pest and disease status must be same as parent (unexpected improvements are not tolerated).

Compositional analysis: data from growing the event over two seasons at six locations in three replicates on proximates, macro and micronutrients, antinutrients, toxins, allergens; data must be generated on modified and isogenic backgrounds.

Environmental risk assessment: this type of analysis may take up to five years of work by an entire research team.

It is obvious that no scientist or scientific institution in the public domain has the potential, funding or motivation to perform such lengthy, expensive biosafety experiments.

It comes as no surprise then that virtually all transgenic events that have been carried through the regulatory process so far are in the private sector and are restricted to high-value crops, such as maize, soya bean, cotton and rapeseed. Humanitarian projects usually do not involve high-value crops in commercial terms, even though they would benefit millions of people.^{11,12} There is a lot 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 be capable of doing the trick. Scientific progress would become detached from product development and the population at large would not benefit from that progress.

No justification for extreme precaution

There are historic reasons for the present regulatory framework. In the 1970s, when gene technology was still incipient, taking a precautionary approach was sensible, and it was the scientists themselves—who at the time were not working with plants but with human-pathogenic micro-organisms—who established regulations based on the premise that the technology could lead to unpredictable genome alterations. More than 20 years of accumulated experience with transgenic plants and their widespread use on over ninety million hectares planted in 21 countries, accompanied by many hundreds of carefully conducted biosafety experiments by prestigious institutions, has led to the conclusion that there is no specific risk associated with the

¹¹ Zimmermann R and Qaim M. 2004. Potential health benefits of *Golden Rice*: A Philippine case study. *Food Policy* 29:147-168.

¹² Zimmermann R and Faruk A. 2006. Rice biotechnology and its potential to combat vitamin A deficiency: A case study of *Golden Rice* in Bangladesh. ZEF – Discussion Papers on Development Policy No. 104, Center for Development Research, Bonn, March 2006, pp. 31.

technology beyond that inherent to traditional plant breeding or natural evolution.¹³ And yet, we are still facing hard-to-justify calls for further moratoria.

The fact that regulation of transgenic crops has become stricter lately is counterintuitive. Some people claim that we have to do so to build up trust in the technology with the consumer. However, experience with this strategy over the last ten years has demonstrated that this approach did not work in Europe and in many developing countries. One reason is that in the general public's perception a highly stringent regulation must be associated with an inherently risky technology.

The guidelines pretend to apply a risk-based evaluation system based on objective empirical science. The present interpretation of the precautionary principle then turns the process into a subjective framework in which the assessment is based on pretend cultural and moral values guided by consumers' fear perceptions. Some EU countries have embedded overly stringent health and environment regulations into the current regulatory framework based on their interpretation of the precautionary principle. This has led to the introduction of safety standards that go beyond science-based requirements. These stringent regulations are then exported down supply chains via international treaties, international standardisation bodies and bilateral technical capacity building initiatives. Examples of this include the recently enacted EU biotech labeling and traceability regulations implemented by the EU obligations under the Cartagena Protocol on Biosafety, and the proposed EU REACH regulation, which is intended to serve as a template for global chemicals management.¹⁴

Ideally, we should be able to free the regulatory process from all scientifically unjustified ballast to end up with a set of rational regulatory guidelines. Such a move would require the involvement of institutions and governments which at the moment lack the will to do so or are under undue pressures—many times commercial in nature and putting aside human need—that do not allow them to proceed along these lines. Developing countries must make decisions under duress about the adoption of transgenic technologies, being caught in a conundrum between the urgent need to adopt the technology and possible commercial implications by doing so. In essence, the EU exports the high regulatory costs abroad, resulting in the buildup of de facto trade barriers.

Gene technology has been endorsed by international agencies, such as FAO and UNIDO, to help solve food security problems in developing countries, but yet we are threading at a very low pace. 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 projects", with safe financial returns for the private sector.

Every year more countries in the developing world refuse to accept the fuzzy arguments of opponents of green technology and a number of them have started embracing it based on hard scientific, health and economic facts. Positive, highly encouraging reports on increased harvests, reduced use of pesticides, a decrease in the number of people intoxicated from using those pesticides, and an increase in the number of beneficial insects in the fields are now coming from

¹³ For a discussion on the moral imperative of the use of genetically modified crops in developing countries see Nuffield Council on Bioethics, Follow-up Discussion Paper, January 2004, www.nuffieldbioethics.org.

¹⁴ Kogan L. 2004. The National Interest Journal, Number 77, Fall 2004; www.nationalinterest.org.

countries like South Africa and India. For *Golden Rice*, a World Bank report, presenting an ex-ante analysis on the potential socio-economic impact of the adoption of transgenic technology, is particularly encouraging in respect of health and welfare gains for adopting countries.¹⁵

Traditional genome meddling

One criticism frequently brought up in relation with genetic engineering is that the insertion of genes can lead to unpredictable genome alterations. In traditional plant breeding, agronomic traits are combined or eliminated by crossing, followed by selection. The sources for these traits are existing varieties, landraces or wild relatives. Since the dawn of agriculture, the search for many beneficial traits has relied on spontaneous, unpredictable mutations. During the breeding process many unpredictable genome alterations, such as recombinations, translocations, deletions, inversions and horizontal gene transfer, are combined into a new cultivar. 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 genome alterations. This statement is valid for all modern crop varieties, including those used in organic farming. Moreover, these unexpected changes are considered desirable, as witnessed by the use of rice mutants generated by radiation or chemicals.¹⁶ Nevertheless, while none of these [*genetically modified*] varieties has ever been assessed for biosafety, mankind has consumed them unharmed and the environment has not been affected by them either. The fact is that actually nobody could survive without eating these *genetically modified* crops.

By comparison, the creation of *Golden Rice*—which involves the insertion of two precisely defined genes into a genome that contains fifty-thousand-odd genes—is by several orders of magnitude more precise than traditional breeding. Why should this new strain, despite the fact that the modification is extremely small and exactly defined, be the subject of a comparatively over-the-top scrutiny?

Assuming responsibility

Green biotechnology has the potential to provide solutions to pest and disease control, improve photosynthetic efficiency, nutritional content, furnish plants with adaptation mechanisms for drought, cold and salt tolerance and many more things to come. More than 200 transgenic plants with many different beneficial, agronomic traits have been produced in developing countries but have trouble reaching the markets because of the problems outlines above.¹⁷ The benefits of *Golden Rice* are clear at face value, yet opponents of the technology are posing as saviours of humanity. Millions of children's deaths are not a risk; they are a reality we have to face in the eye. Will any of the opponents of the technology take the responsibility for this preventable tragedy that is being imposed upon innocents?

The Nuffield Council on Bioethics¹⁸ concluded 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.'

¹⁵ Anderson K, Jackson LA and Pohl Nielsen C. 2004. Genetically Modified Rice Adoption: Implications for Welfare and Poverty Alleviation. World Bank Policy Research Working Paper 3380, August 2004.

¹⁶ There are more than 500 rice varieties in the Mutant Variety Database held by FAO and the Intl Atomic Energy Agency. <http://www-mvd.iaea.org/MVD/default.htm> [consulted on 17 June 2006].

¹⁷ Cohen JI. 2005. Poorer countries turn to publicly developed GM crops. *Nature Biotechnology* 23:27-33.

¹⁸ The use of genetically modified crops in developing countries. Nuffield Council on Bioethics, January 2004.