Facts Series

Golden Rice

VIB

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Summary

Golden rice is the collective name of rice varieties that are genetically modified to counter vitamin A deficiency in developing countries. European scientists developed the first strain of Golden Rice towards the end of the 1990s.

Many people in developing countries battle against vitamin A deficiency due to an imbalanced diet including limited access to fresh fruit, vegetables and animal products. Persistent deficiency in this vital nutrient can result in blindness, illness and even death. Children are particularly vulnerable. Vitamin A deficiency is the leading cause of childhood blindness and increases the risk of death from common childhood infections.

Golden rice differs from standard rice in that it contains extra genes. These were added through genetic modification and ensure the production of provitamin A in the rice grains. Provitamin A colors the grains yellow-orange, hence the name 'Golden Rice'. Once absorbed into the body, provitamin A is converted into vitamin A. Provitamin A is found in many fruits and vegetables; it is also what makes carrots orange, for example.

The Golden Rice nutritional trait was subsequently crossed into popular local rice varieties, using conventional breeding methods. These new rice varieties are currently being assessed in field trials across Asia. Despite the developers' humanitarian motives behind Golden Rice, debate rages about these genetically modified (GM) crops, and as yet it remains unclear when Golden Rice shall come on the market.

This document discusses Golden Rice as a potential component of the broad strategy against vitamin A deficiency in developing countries. Efforts must continue to be made in combating global poverty and promoting a varied diet. But, for as long as vitamin A deficiency remains a public health problem in several countries, Golden Rice can be of added value.

Facts and figures

Vitamin A is a vital vitamin for the human body. We obtain vitamin A from animal products and provitamin A from certain fruits, vegetables and grains. Provitamin A is converted in our bodies into vitamin A.

An early symptom of vitamin A deficiency is night blindness. Persistent deficiency can result in blindness and a weakened immune system, which increases susceptibility to infections.

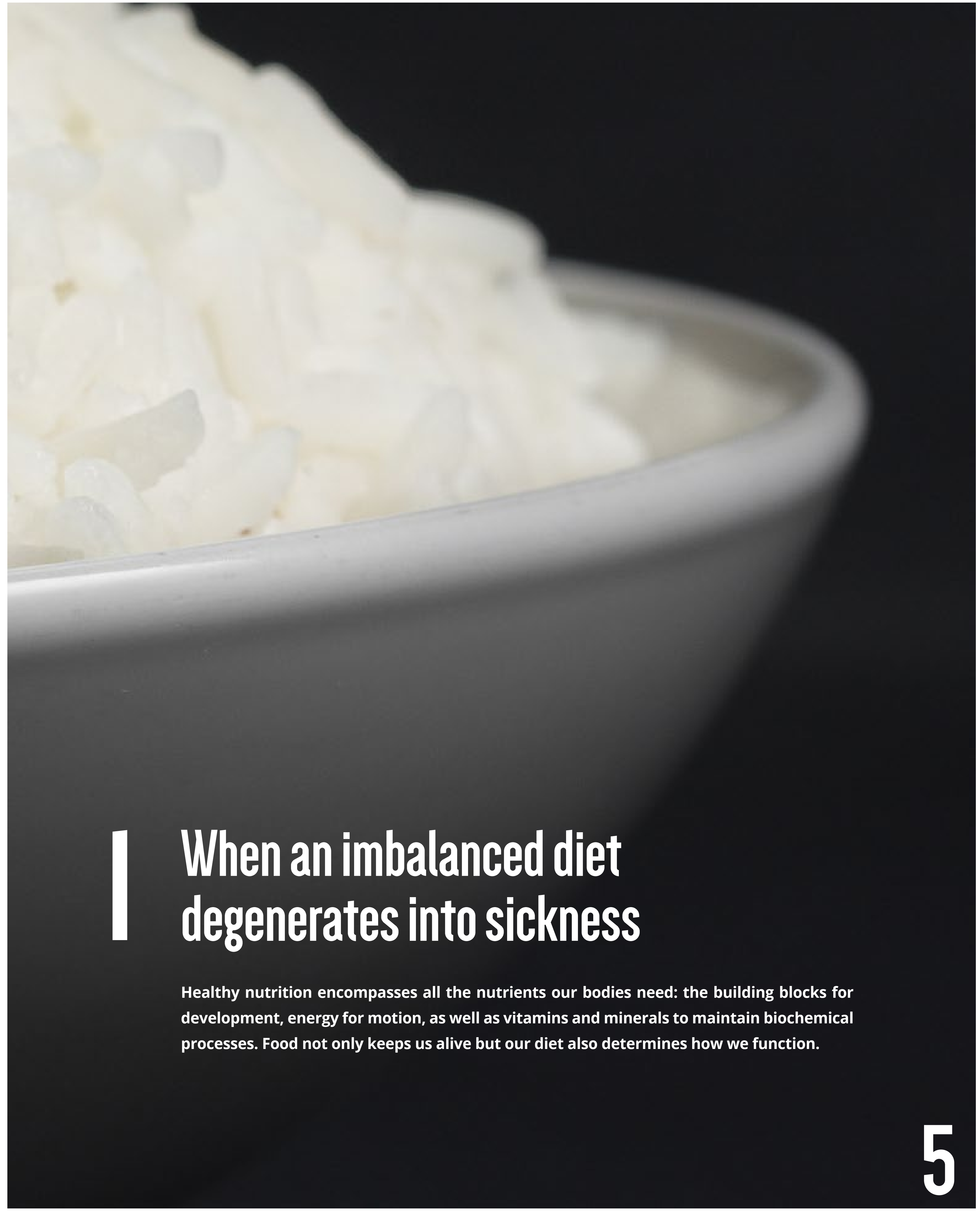
Each year between a quarter and half a million children become blind due to vitamin A deficiency. Half of these children die within a year from diarrhea or measles because their immune system is severely weakened.

Golden Rice contains extra genes; one from maize and one from bacterial origin together responsible for the production of provitamin A in the rice grain.

A bowl of 100 - 150 grams of boiled Golden Rice can provide children with 60% of their daily recommended intake of vitamin A.

Golden Rice is not a single rice variety. The Golden Rice nutritional trait has been crossed into various popular rice varieties from the Philippines, Bangladesh, India, Indonesia and Vietnam via conventional breeding and more will follow. This means farmers can cultivate Golden Rice plants that still contain the same traits as their customary rice varieties. In addition, the taste and cooking method of Golden Rice be the same as the white rice varieties.

The Golden Rice inventors donated the Golden Rice nutritional trait to assist resource-poor people in developing countries. This implies that there will be no charge for the nutritional trait and Golden Rice will cost the same as the equivalent white rice varieties.



I When an imbalanced diet degenerates into sickness

Healthy nutrition encompasses all the nutrients our bodies need: the building blocks for development, energy for motion, as well as vitamins and minerals to maintain biochemical processes. Food not only keeps us alive but our diet also determines how we function.

You are what you eat

A well-balanced, healthy diet is vital in providing our bodies with all the essential nutrients and energy to function properly. Those who deviate from a healthy diet soon notice the effects. An insufficient intake of certain nutrients can result in diseases, a weakened immune system or growth and developmental problems in children. For example, anemia arises from a lack of iron, whilst sight problems are the first sign of vitamin A deficiency. Specific deficiencies can even result in death. Conversely, an excess of energy through over-consumption of nutrients results in obesity, which brings with it an increased risk of cardiovascular diseases, joint problems and diabetes.

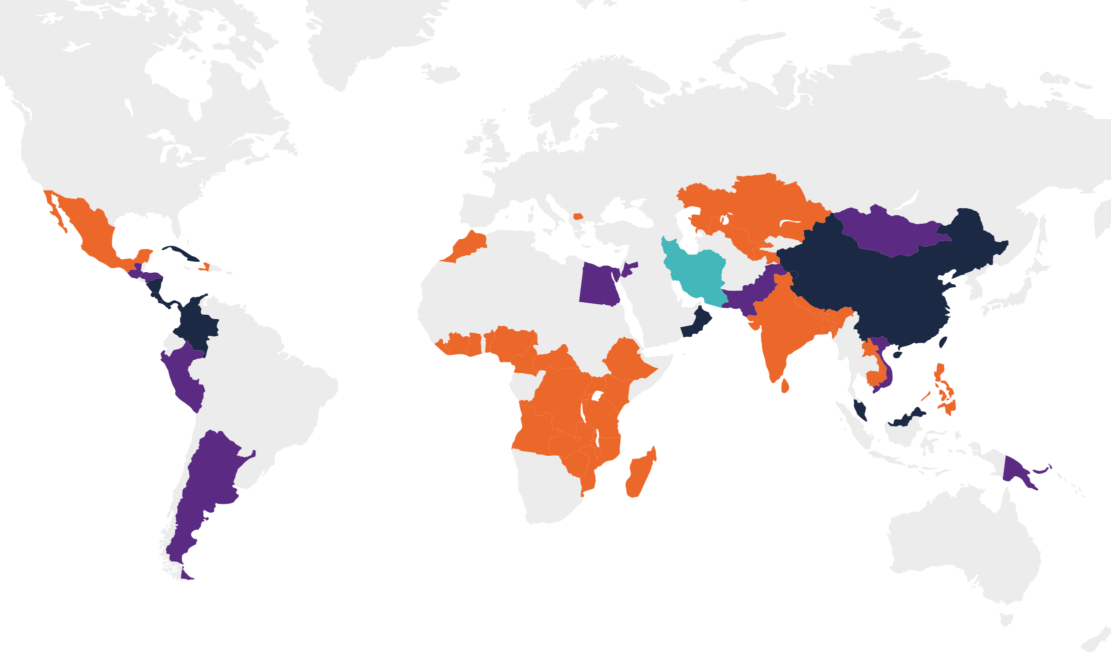
Each year more than 2.5 million children under five die as a result of an unbalanced diet.[1,2] The best way to fight nutritional deficiencies, is a varied diet rich in fruit, vegetables and grains, supplemented with animal products. Population groups that run the risk of nutritional deficiencies therefore benefit fully from the cultivation and consumption of a more diverse range of food crops, but for people who have an unbalanced diet as a result of poverty, this isn't a given. For example, in Bangladesh rice comprises 80% of the daily calorie intake for the rural population.[3] The fact that specific food crops are so dominantly present in certain areas has its reasons: they are adapted to the local conditions – made resistant to disease or drought – meaning that these crops offer increased harvest security. Traditions play a key role too: the cultivation of particular plants is often closely related to cultural identity.

Indispensable vitamin A

We need to absorb around fifty essential nutrients via our nutrition.[4] This includes water and carbohydrates, as well as amino acids, fatty acids, and micronutrients such as vitamins and minerals. If one of these nutrients is insufficiently absorbed, or not at all, our health will be undermined. This results in disrupted metabolism, which in turn results in sickness, poor health and potentially the impediment of children's development. One of these vital nutrients is beta-carotene, the pigment found in great quantities in carrots and responsible for their orange color. Also spinach, melons and maize are rich in this nutrient for example. Beta-carotene is the best known form of provitamin A, and is converted into vitamin A in our body.[5] Vitamin A deficiency can result in sight problems and even blindness. Animal products rich in vitamin A, such as eggs, liver, cheese and butter, are often unaffordable for poor families.

Vitamin A deficiency is a global health problem, primarily in developing countries in Africa and South-East Asia (see figure 1). Children and pregnant women are particularly at risk. The World Health Organization states that each year between 250,000 and 500,000 children become blind as a result of vitamin A deficiency. Half of those children die within a year.[2] Vitamin A deficiency also compromises the immune system, which means children die from common diseases including diarrhea, respiratory tract infections and measles. A research study that examined malnutrition among mothers and children, estimated that annually more than 100,000 children under five die due to vitamin A deficiency.[6-8] Populations of developing countries are primarily affected as this deficiency is the consequence of a poor diet and usually poverty-related.

Figure 1. Worldwide prevalence of vitamin A deficiency.
Map showing the prevalence of biochemical vitamin A deficiency in children under five, as indicated by a serum retinol concentration <0.70 µmol/l. Based on data collected by WHO between 1995 and 2005 in populations at risk of vitamin A deficiency.



Level of vitamin A deficiency
- *Severe (≥20%)*
- *Moderate (≥10% - <20%)*
- *Mild (≥2% - <10%)*
- *None (<2%)*
- *No data*

One of the humanitarian solutions comprises artificially developed nutrients in the form of pills. Since 1998, *Micronutrient Initiative*, an international non-profit organization, has donated around 500 million vitamin A capsules a year to UNICEF, to then be distributed in developing countries amongst children aged between six months and five years.[9] Another option is to enrich food (fortification) with certain micronutrients: grains enriched with iron, milk enriched with vitamin D and oil or sugar with vitamin A.[10] However, in both instances – supplements or fortified food - the high-risk groups depend on imports, distribution infrastructure and the benevolence of the industrialized world. Moreover, in light of continuing fatalities these strategies on their own do not appear to suffice.[7,11-13]

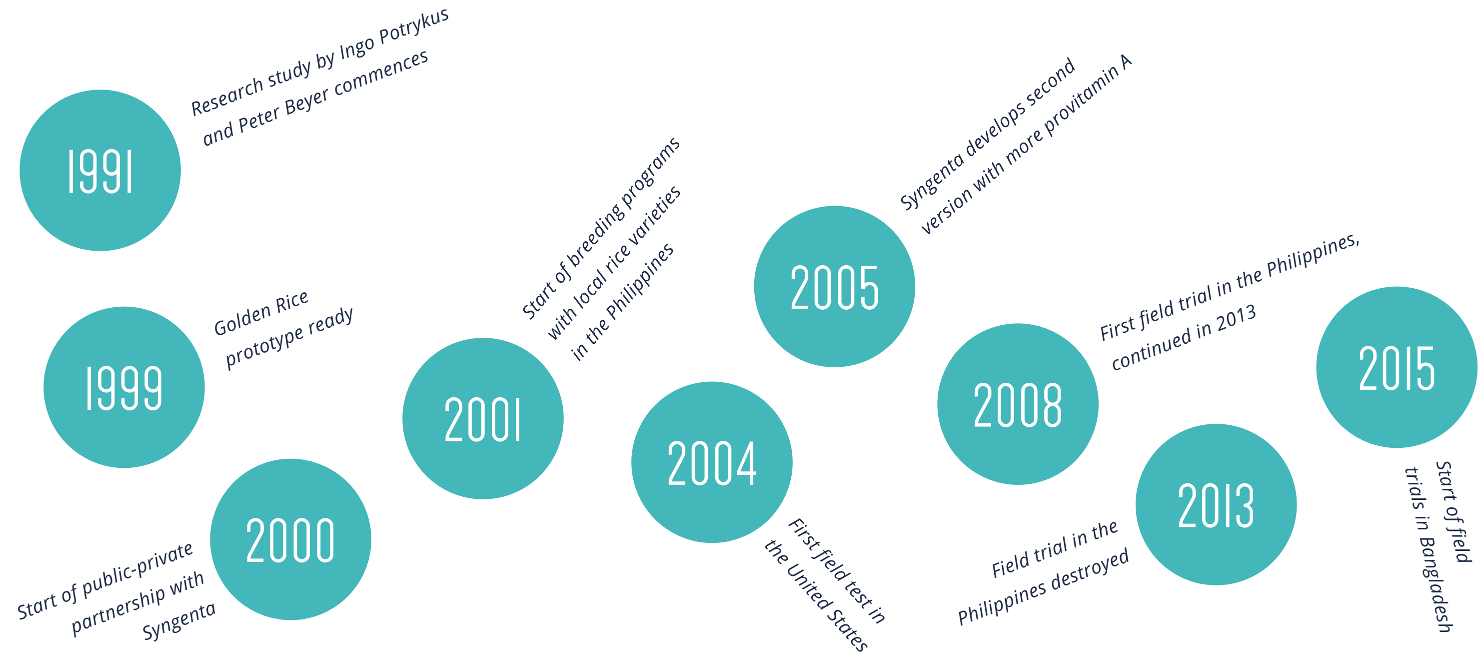
Orange sweet potato up for a prize

One alternative to the supplement programs is the development of plant varieties that produce the required nutrient in greater quantities.[14] We can find an example of this in Africa, where the orange-fleshed, provitamin A-rich, sweet potato is being promoted to replace its white-fleshed variant that doesn't contain provitamin A. The provitamin A trait could be introduced in more African sweet potato varieties via conventional breeding, by crossing the white-fleshed sweet potato varieties with natural (orange) variants that produce provitamin A.[15] Thanks to a sophisticated campaign the food crop successfully reached 2 million households in 10 African countries, and has improved the vitamin A status of millions of Africans.[16,17] The efforts of the African and American scientists responsible for this project were rewarded in June 2016 with the prestigious World Food Prize.[18]

Not all food crops though produce provitamin A in the edible parts. An example is rice: the rice plant does produce provitamin A in the leaf but not in the polished white rice grain.[19] Population groups with a rice-based diet are therefore at risk of vitamin A deficiency.

2 A humanitarian GM solution

According to the World Health Organization an estimated 19 million pregnant women and 190 million children are suffering from vitamin A deficiency.[20] Developing a rice variety that produces provitamin A in the grain can significantly contribute towards combating malnutrition.



Golden Rice in development

At the start of the 1990s two university scientists, Ingo Potrykus from the ETH institute in Zürich and Peter Beyer from the University of Freiburg, were well aware of the blindness caused by vitamin A deficiency. They undertook the initiative to develop rice that produces provitamin A in the grain. To this end the researchers gained support from the Rockefeller Foundation, the European Commission, national governments in Asia and finally from the Bill and Melinda Gates Foundation. Because no rice varieties exist that produce provitamin A in the grain, this trait couldn't be introduced via traditional breeding, such as was the case with the sweet potato. Yet genetic modification (see text box 'What is genetic modification?') offered an answer: adding two genes from the narcissus and one from the soil bacteria *Erwinia uredovora* to the DNA of rice enabled the production of provitamin A in rice grains.[21-23] More than one gene is needed because the production of provitamin A is a multistep process. For some of these steps no genes are active in white rice grains (see text box 'Genes for provitamin A production in rice grains').

It took eight years of laboratory work to develop such a rice plant. In 2000 this groundbreaking research was published in the Science journal.[22]

The first version of the rice rich in provitamin A produced just over 1.6 micrograms of provitamin A per gram of rice.[22] This proved a significant scientific breakthrough, as for the first time the entire production pathway of a nutrient had been introduced into a plant. The presence of provitamin A in the rice grains was even visible. Just as carrots are colored orange by their vast quantity of provitamin A, the GM rice grains are also yellow-orange in color (see figure 2). As such the rice was dubbed 'Golden Rice'. However, the concentration of provitamin A in initial Golden Rice was possibly too low to be effective in normally consumed amounts of rice. People would have to consume too much rice each day in order to reach the recommended daily intake of vitamin A. An improved version was developed several years later, whereby a maize gene was used instead of that of narcissus (see text box 'Genes for provitamin A production in rice grains'). The new Golden

WHAT IS GENETIC MODIFICATION?

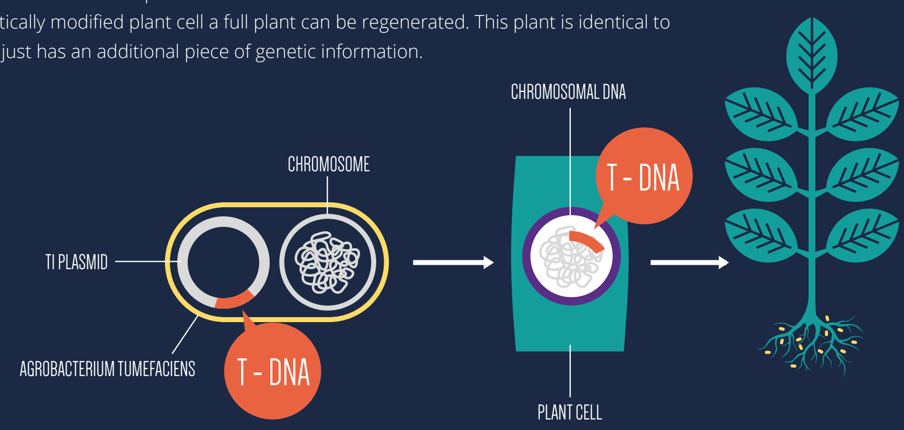
For thousands of years already, man has been looking for methods to obtain new traits in plants or to combine several traits of interest in a single crop. During the last 100 years different breeding techniques have been applied, such as selective crossing, hybrid technology and mutation breeding.[24] These methods all result in DNA modifications in the plant, albeit in an uncontrolled manner.

Around 1980 a technique was developed that allowed genetic information to be inserted into a plant's DNA. This method was dubbed genetic modification. The resulting products were labelled genetically modified crops or GM crops. Thanks to the novel techniques new traits needn't necessarily come from crossable plant species. So, for example, it became possible to provide a tomato with genetic information from peppers or maize.

In comparison with conventional breeding methods, GM technology is more precise, predictable and controllable. Moreover, with genetic modification traits can be added without losing existing variety traits. A GM Bintje potato stays a Bintje potato, but its GM version has an extra trait. With conventional breeding however, a mother and father plant are crossed, thus generating a new variety.

An oft-used method for the genetic modification of plants relies on the natural DNA transfer mechanism of the soil bacteria Agrobacterium tumefaciens. *This bacteria infects certain host plants and then inserts a section of its own genetic information into the plant's DNA. During the late 1970s this mechanism was unraveled by the research groups led by Jeff Schell and Marc Van Montagu at the University of Ghent.[25] In the bacteria they replaced the section of bacterial DNA (that the bacteria usually inserts into plant DNA) with the genetic information of an agriculturally interesting trait. After infecting the plant with the genetically modified bacteria, they observed that the bacteria inserted this information into the plant's DNA in the same way. Thus, the first genetically modified plant came about in Ghent in 1982.*

Schematic depiction of the gene transfer mechanism of *Agrobacterium tumefaciens*. Besides the chromosomal DNA the bacteria has a Ti plasmid (grey circle). The genetic information contained in the T-DNA (in red) is transferred by the bacteria to a plant cell where it is inserted into the chromosomal DNA of the plant. From this genetically modified plant cell a full plant can be regenerated. This plant is identical to the original plant but just has an additional piece of genetic information.



Rice produced up to 23 times more provitamin A compared to its initial counterpart, making it more useful in the fight against vitamin A deficiency.[23] To ascertain whether this would indeed work in practice, the GM rice was tested in nutritional experiments involving children aged between six and eight years in China.[26] This research showed that Golden Rice could provide just as much vitamin A as provitamin A capsules, and more than spinach. Based on this data it was calculated that a bowl of 100-150 grams of boiled Golden Rice (equivalent to 50 grams of dry rice) provides 60% of the recommended daily intake of vitamin A for children.[26] Considering that people in the Philippines eat around 330 grams of boiled rice a day, Golden Rice would provide enough vitamin A among population groups whose diet consists primarily of rice.[27]

The Golden Rice nutritional study with Chinese children earned criticism because the parents and children were insufficiently informed about all aspects pertaining to the experiment. For example, they were not aware the children were eating GM rice. Consequently, the scientific publication outlining the research study results was withdrawn in 2015.[28] However, there was no doubt about the safety of the study and the reliability of the results and conclusions. In addition, other research studies demonstrated that provitamin A from Golden Rice is efficiently absorbed when digested.[29-31]

Although the nutritional studies are encouraging, it should be noted that the use of Golden Rice is not the only, universal solution to the problem of vitamin A deficiency. An imbalanced diet, with the consequent deficiencies in certain micronutrients is caused by economic, social and cultural factors. Efforts in education, poverty alleviation, sustainable agricultural development and infrastructural improvements are vital in resolving global malnutrition.[30] As part of a broader strategy in Asian developing countries Golden Rice can have a supportive role in improving provitamin A intake.[33,34]

Figure 2. Golden Rice (left) and standard rice (right) © Courtesy of the Golden Rice Humanitarian Board www.goldenrice.org

GENES FOR PROVITAMIN A PRODUCTION IN RICE GRAINS

It takes four steps to achieve provitamin A production in rice grains. These start with the already present geranylgeranyl diphosphate, a precursor for provitamin A. The four steps are carried out by the enzymes phytoene synthase, phytoene desaturase, zeta-carotene desaturase and lycopene cyclase.[35] Inserting the first step into rice ran relatively smoothly. The gene for phytoene synthase was extracted from the DNA of the narcissus.[21] The GM rice plants that came about in this manner produced sufficient phytoene for the next steps in the production of provitamin A. However, the next steps were far more problematic, until it was discovered that steps two and three could be carried out by the desaturase enzyme of Erwinia uredovora*, a bacteria.[22] For the final step in the first version of Golden Rice the lycopene cyclase of narcissus was transferred into rice, but it soon became apparent that the enzyme naturally occurred in the rice grain and that two genes (synthase and desaturase) were sufficient to produce provitamin A in rice grains.[22,36] The improved, second version that was developed in 2005 contained the phytoene synthase of maize and the desaturase of* Erwinia uredovora*.[23]*

	REGULAR RICE GRAINS	GOLDEN RICE VERSION 1	GOLDEN RICE VERSION 2
STEP 1: *phytoene synthase*	Not functional in white rice grains	phytoene synthase of narcissus	phytoene synthase of maize
STEP 2: *phytoene desaturase*		bacterial desaturase performs both functions	bacterial desaturase performs both functions
STEP 3: *zeta-carotene desaturase*			
STEP 4: *lycopene cyclase*		lycopene cyclase of narcissus	

Simplified overview of the provitamin A pathway in Golden Rice.
The steps in the purple boxes were added by genetic modification

Cross-breeding into local rice varieties

Golden Rice is intended for the population in developing countries where rice is the staple food, mainly in South and South-East Asia. In the Philippines vitamin A deficiency affects around 4.4 million children aged between six months and five years. That amounts to 40% of the children within this age group. One in ten pregnant women in the Philippines suffers from vitamin A deficiency.[37] In 2001 the Golden Rice developers brought seeds to the International Rice Research Institute (IRRI) in the Philippines. IRRI researchers took on the task of crossing the provitamin A trait in local Philippine rice varieties.[19]

The cross-breeding into local crop varieties is an important step in the process of developing and marketing a GM crop. The introduction of the desired trait – and so the making of the GM plant – is just the start of it. This is followed by a great deal of conventional breeding work with which the GM trait is introduced into different rice varieties; each adapted to local needs and local cultivation and climatological conditions. It wouldn't suffice to merely introduce one Golden Rice variety onto the market. Vital is that sufficient crop diversity prevails and that varieties are adapted to cultural traditions and are suitable for local cultivation conditions. The Golden Rice trait is therefore crossed in as many varieties as possible. Once on the market conventional breeding work shall continue and new varieties with the trait can be continually added.

A similar initiative was also undertaken for rice varieties from India, Vietnam and Bangladesh.[19] In Bangladesh one in five children aged between six months and five years are affected by vitamin A deficiency. Of the estimated 190 million children globally suffering from vitamin A deficiency, 78 million reside in India.[37]

Field trials

The Golden Rice varieties are tested in greenhouses and in field trials. The first Golden Rice field trials took place in 2004 and 2005 in Louisiana in the United States.[38,39] In a test plot Golden Rice varieties grow alongside comparable, non-GM rice plants. This helps to research and compare agricultural traits, such as yield, seed quality and plant height of the rice varieties. Mapping those traits is important: after all, for the farmer it isn't just the nutritional value that counts but

Figure 3. Field trial with Golden Rice by IRRI in 2010. © This photo is part of the image collection of the International Rice Research Institute (www.irri.org)

also crop yield – so their profits. Moreover, it is assessed whether the cultivation of Golden Rice impacts the environment. The provitamin A trait is not expected to influence the impact of rice cultivation on the environment, as it is a trait that is prevalent in nature and which does not yield any selective benefit for wild crossable plants. Yet regulation surrounding GM stipulates extensive environmental risk analyses before a GM crop may be commercially cultivated (see VIB Facts Series issue 'Effect of genetically modified crops on the environment').[40]

In 2008 the IRRI initiated a field trial with different Golden Rice varieties in Los Baños, the Philippines. Extensive field trials at various locations in the Philippines were undertaken five years later by the IRRI together with the Philippine Rice Institute.[41] The data obtained from these trials are necessary in requesting cultivation approval in a country. In 2015 field trials started in Bangladesh.[42]

Research into the potential impact of Golden Rice

Research studies were undertaken to assess what Golden Rice can signify for India and the Philippines. In India vitamin A deficiency could drop by 60%, if Golden Rice were to be generally cultivated and eaten. This could lead to 40,000 fewer deaths per year.[37,43] Even with restricted cultivation thousands of lives could be saved each year. As vitamin A deficiency is linked to poverty, the anticipated positive effects of Golden Rice will be greatest amongst deprived families. These families usually live in very remote areas, where the opportunity to obtain vitamin A supplements is scarce. Moreover, Golden Rice would be a far more cost-efficient way in tackling health problems related to vitamin A deficiency. The costs in getting the GM rice to people who truly need it are far lower than those of other initiatives. Even considering the most pessimistic scenario, the cost of Golden Rice amounts to a tenth of what supplements cost society.[43]

Aside from the direct effects on public health there is also an economic aspect to the Golden Rice narrative. The health problems caused by vitamin A deficiency impact the economy. Through blindness and disease a portion of the population is unable to actively participate in everyday life. If Golden Rice can improve their health, the expectation is that the country's employment level and prosperity will rise. In China for example, the national income arising from Golden Rice cultivation would increase by an estimated 2%.[44]

3 From field trial to plate

In developing countries frequent use is made of local, publicly owned varieties of crops. These are crops that required no innovative technology to develop them and seeds that are handed down from generation to generation. For such crops, intellectual property rights are not an issue. The inventors of Golden Rice wanted this to be the same for Golden Rice: intellectual property rights will not restrict its use in developing countries. .

Figure 4 © Courtesy of the Golden Rice Humanitarian Board www.goldenrice.org

A web of patents

The development of a GM crop is one thing. Yet bringing the technology to the field where it's needed is a daunting undertaking; one that few scientists know little about. One particular aspect is managing technology that is patent-protected (see text box 'What is a patent?'). To create Golden Rice the scientists used patent-protected products and technology in their research. Depending on the country, the Golden Rice was consequently indirectly protected by up to as many as seventy different patents.[45] The scientists didn't pay too much attention to this initially as in many cases scientists are free to use patented technology. In other words: the research work that resulted in the development of Golden Rice could be carried out without committing patent infringement. However, that free use of technology ceases when the crop (in this instance Golden Rice) is made available to rice cultivators. So, the Golden Rice couldn't be marketed without the consent of the patent holders, seeing as it was in part the intellectual property of other market players. The risk was that the patent holders would collect fees on the utilization of Golden Rice or would even prohibit its use. This would severely restrict or even prevent access to seed for small farmers. Because the inventors wished the GM rice to reach people who needed it most at no additional cost, they applied for patents on the Golden Rice technology. This paradox reveals the flip side of the patent coin: by becoming the intellectual owner of an invention one gains advantage during negotiations.

The scientists required help in learning the ropes of the tangle of patents behind Golden Rice, and in adequately concluding the legislative side of the Golden Rice narrative. This assistance was given by the industrial sector, namely by Syngenta.[46] Syngenta is a Swiss company that specializes in crop protection and seeds. This public-private partnership succeeded in resolving the patent issue and in obtaining permission from all the indirectly involved patent holders to launch Golden Rice onto the market, compensation-free. In other words, free licenses on all protected components of the Golden Rice production process were achieved. Syngenta proposed that in return for commercial rights the Golden Rice technology could be provided to developing country farmers at no additional cost when intended for humanitarian purposes. This was possible because the scientists had applied for patents on the Golden Rice. Moreover, the following limitations were included for humanitarian use: the Golden Rice trait may only be introduced in varieties that are publicly available, the price of Golden Rice seed may not exceed that of non-GM rice, and the rice cultivator becomes the owner of the seeds.[47] This enables farmers to use saved seeds for the following season. These provisions were imposed for all developing countries on the list of FAO (the Food and Agriculture Organization of the United Nations) and India, and for farmers who earn less than 10,000 USD a year through their agricultural practices.[47] Moreover, in 2004 Syngenta declared no interest in developing Golden Rice on a commercial scale, but rather to continue supporting the humanitarian objectives behind it.[48]

WHAT IS A PATENT?

A patent is a form of intellectual property. When a particular innovative method, technology or product is developed the developer can apply for intellectual property rights on the invention. With some intellectual property rights, such as copyrights on a book or a CD, this occurs automatically. In order to obtain a patent the developer or inventor must submit a request to the mandated authority and explain in meticulous detail which invention they have conceived.

If the patent is granted – and that only occurs if the invention is new, innovative and usable within industry – the inventor becomes entitled to prohibit other parties to reproduce, use, import, sell or offer for sale the product. Whoever possesses intellectual property rights on an invention does not therefore possess the product in a material sense. The primary purpose of these rights is to offer the inventor the opportunity to regain their investment costs. When someone wishes to use protected technology or a protected product for commercial purposes they can reach an agreement with the patent holder and obtain a license whereby the product, technology or part of the technology can indeed be used in exchange for (financial) compensation.

This protection only applies in the countries where the patent is granted and usually lasts twenty years. If the intellectual property right were not in place, anyone and everyone would in theory be able to copy and commercialize the invention without having made any investment in the development thereof. The protection provided by the patent stimulates companies to keep investing in the search for new solutions and the development of new products.

A little known fact is that breeders of non-GM crops also protect their plants. They do so by requesting patents or plant breeders' rights. Both forms of intellectual property have much in common (see VIB Facts Series issue 'A late blight resistant potato for Europe').[49] Just as with a patent, the plant breeders' right gives the breeder the commercial rights to the newly developed variety, enabling the breeder to impede their competitors in launching that plant onto the market without their consent (usually this means without financial return). The significant difference with patents is that plant breeders' rights enable breeders to use each other's varieties without prior consent, and unpaid, for making new crossings. Despite acquiring the commercial rights to newly developed products or technology is important for stimulating innovation, seeking intellectual property on newly developed crops remains a laborious discussion. A balance must be sought: companies must be stimulated in making new investments, yet the right to food must at no time be affected.

Golden Rice Humanitarian Board

Via the partnership between the public sector and industry, the Golden Rice project also benefited from their industrial partner's experiences in product development. So as to guide and to provide assistance to the project a humanitarian organization was founded, the 'Golden Rice Humanitarian Board'.[35] This organization built up a network of public rice research institutes in Asia, including the IRRI. Public institutes in the Philippines, India, Bangladesh, Indonesia, Vietnam and China are also developing Golden Rice varieties by crossing provitamin A into local rice varieties. Those research institutes help propel the initiative of making Golden Rice available to local populations, in locally adapted and preferred rice varieties.

Not yet on the market

In 2016 Golden Rice is still not commercially cultivated. The field trials with various Golden Rice varieties in the Philippines (see page 13) nevertheless demonstrated that the rice grains contain sufficient provitamin A and that the seed quality is just as good as the conventional varieties. However, the plan to launch these varieties onto the market was abandoned. The tested varieties that were based on the same version of Golden Rice showed a lower yield compared to conventional rice.[35,48,50] This only became apparent when the crop was exposed to wind and rain in open field trials. To remedy this, new breeding programs were initiated in 2014 to develop new Golden Rice versions with a yield that is equivalent to popular rice varieties.[42] Indeed, when a GM crop is made there is not one but rather a large number of different versions that is made. Those versions differ from one another in the place where the extra genes have ended up in the DNA of the plant. That integration place can sometimes influence the already existing traits of the plant. The first-selected version thus didn't hit optimum performance in terms of yield, which necessitated looking at different versions. This resulted in a few years' delay in the development of the Golden Rice varieties.

Besides this setback, market authorization regulations comprise an enormous threshold for Golden Rice. This regulation is very stringent on GM food crops and stipulates a plethora of analyses and risk assessments before a GM food is permitted onto the market.[51] This regulation means the development of a crop via GM technology is expensive and time-consuming in comparison to crops that are developed via other breeding methods. The in-depth analysis of the safety and efficacy of new Golden Rice varieties is on-going. The point at which Golden Rice ends up with the farmers depends significantly on the regulation status in each individual country. The safety legislation that determines which tests are precisely needed before a GM crop is permitted onto the market can indeed differ from country to country.

Despite all the obstacles it seems realistic that the local Philippine population will gain access to Golden Rice before 2020.[52] Bangladesh is likewise placing the authorization of its cultivation high on the agenda.

4 Rice in the eye of the storm

Notwithstanding the successful nutritional studies of Golden Rice, anti GM groups continue to fight this humanitarian GM solution. The debate surrounding Golden Rice peaked in 2013 when a field trial in the Philippines was attacked and destroyed by activists. The scientific world strongly condemned this attack in a letter signed by more than 6700 scientists.[53] Many of the opponents' concerns about Golden Rice have existed for a while and do not merely affect Golden Rice.

The GM debate

That debate arises about new technology and the effects thereof is understandable. However, this needn't be a yes/no discussion. The GM technology is no miracle solution. It is just *one* of the techniques we have to make plants respond better to our needs and to advance agricultural sustainability.

GM crops are associated with large-scale agriculture, but can be applied small-scale as well: 90% of farmers who cultivate GM crops, work on a small scale.[54] GM crops are often presented as the property of powerful seed multinationals, whereas GM foods developed by independent research organizations – without industrial meddling – barely hit the news. An example of this is the GM papaya that is resistant to the ringspot virus and was deployed to save the papaya crop in Hawaii (see VIB Facts Series issue 'Virus resistant papaya in Hawaii').[55] Furthermore, British academic scientists are working on a GM wheat that survives frost to provide a solution to long-term periods of frost that threaten harvest.[56,57] Another example is the BintjePLUS project, an initiative by the University of Ghent, VIB and the Institute for Agricultural and Fisheries Research (ILVO) (see VIB Facts Series issue 'A late blight resistant potato for Europe).[49] The purpose of this project is to develop a Bintje potato that is resistant to potato blight. This disease is caused by a fungus-like organism currently being controlled by vast quantities of pesticides. Via genetic modification four natural resistance genes deriving from wild potato varieties are inserted, thus giving the BintjePLUS variety a broader, more long-term protection against potato blight. As a result, pesticide use during cultivation of such a potato is expected to drop to 80% lower than that of the current Bintje potato.

The safety of GM crops is also often raised by opponents. Fiddling with plant DNA is regarded instinctively by some as unnatural and unsafe. More insight into plant breeding can help alter this opinion (see VIB Facts Series issue 'The past, present and future of plant breeding').[24] After all, we have been interfering with the genetic makeup of our agricultural crops for thousands of years now. During conventional breeding drastic DNA reshuffling occurs, yielding new plant varieties. Another frequently applied technique is mutation breeding: seeds are exposed to chemicals or radiation so as to cause random mutations in the DNA. More than 3,200 crop varieties consumed today are the result of mutation breeding.[58] As opposed to the products of conventional and mutation breeding, GM crops are exhaustively tested on risks to humans and the environment before they come onto the market. The VIB Facts Series issues 'Food safety of genetically modified crops' and 'Effect of genetically modified crops on the environment' extensively cover these risk-analyses.[40,59]

While the cultivation of herbicide-tolerant crops (developed via GM technology or classic plant breeding) perpetuates pesticide use, the cultivation of insect-resistant GM crops actually requires *less* chemical crop protection products. Insect resistant crops are plants that have been genetically modified to produce their own insecticide (often Bt toxins). That insecticide is poisonous to the most important pest species of the crop. Thanks to the insect resistance fewer insecticides are sprayed: this benefits the farmer in terms of cost, and also benefits the environment. The cultivation of insect resistant GM cotton for example saves on millions of kilograms of insecticides each year.[60] A recent study collated data about pesticide use on American farms over 14 years and showed that the cultivation of insect resistant maize reduces insecticide use by 11%.[61] The BintjePLUS project (see page 20) likewise illustrates how biotechnology can significantly contribute to agriculture with fewer pesticides and an increased focus on organic pest control.

GM crops can benefit farmers and consumers, but cannot resolve all the problems present-day agriculture is battling against. GM technology is just one of the technologies available to us that can facilitate the sustainable feeding of people. Recently more than 120 Nobel prize laureates asked Greenpeace– one of the most influential opponents of Golden Rice – in an open letter to review their standpoint on GM crops.[62] In particular they appealed to the environmental organization to withdraw their opposition to Golden Rice.

BIOTECHNOLOGICAL KNOW-HOW ACCELERATES CONVENTIONAL CROP BREEDING

The boundary between conventional breeding and modern biotechnological techniques is becoming ever more blurred. Insights acquired through biotechnological research are steadily contributing to plant breeding. Cross-breeding programs can be made far more efficient by carrying out the selection at DNA level instead of on visible crop traits. Today, selection on the genetic level has become pretty standard in breeding work (based on DNA markers).[24]

Ten years ago a team of scientists discovered the Sub1 gene, which ensures that some rice varieties survive flooding. Millions of rice farmers in South and South-East Asia grow rice in regions prone to flooding. The majority of rice varieties die after three days of being flooded, yet plants with the Sub1 gene can survive flooding for two weeks.63 The IRRI used this DNA marker in cross-breeding programs to develop Sub1 rice varieties that in the meantime are being cultivated by nearly five million farmers.

Moreover, new methods are continually being developed, such as gene editing (for example with CRISPR/Cas).[24] Gene editing enables targeted and subtle changes to be made to DNA, and can do so without inserting DNA from other plant varieties. Those changes in the DNA occur with surgical precision and cannot be differentiated from spontaneously occurring genetic changes. This means the final product doesn't differ from a plant that has been obtained via conventional mutation breeding. As such, vagueness prevails over the possible regulation surrounding crops developed via gene editing. In scientific terms it would make sense to place these plants under the same risk-benefit analysis evaluation as plants obtained via conventional mutation breeding.

Figure 4. Golden Rice plants in a field trial by IRRI in 2010.
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BROWN RICE DOESN'T HIT THE MARK

Eating brown rice is frequently proposed as a simple solution to vitamin A deficiency. White rice is obtained by removing the outermost layer of the rice grain ('polishing') until the white, starchy part remains. The small amounts of provitamin A to be found in these outermost layers are thus lost. But in tropical and subtropical climates polishing is essential in storing rice, because the oil-rich outer layers soon perish. So eating a daily portion of brown rice isn't viable in regions where rice must be polished to be stored. In any case, brown rice only contains low quantities of provitamin A in comparison to other grains: just 0.1 micrograms per gram of rice, which amounts to 300 times less than in Golden Rice.[65]

Opposition to Golden Rice

Many of the frequently used arguments in the GM debate do not apply to Golden Rice. For example, in the launching of Golden Rice onto the market for humanitarian purposes, no commercial interests are involved. Indeed, the inventors had defined these conditions in the licensing agreement with Syngenta. Moreover, the extra crop trait – enrichment with a micronutrient – bears no impact on the environment. The likelihood of dispersal of the Golden Rice genes to other plants, similarly, isn't an issue. Provitamin A production is a trait that is omnipresent in nature, and yields no direct selective advance to crossable varieties. Furthermore, rice is self-pollinating, which means that the plant usually doesn't cross with other plants.

Still, opposition remains substantial. Opponents see Golden Rice as propaganda material for multi-nationals, promoting their capitalist interests. According to that argument, the introduction of technologies and crops that are owned by the companies in developing countries could make poor farmers depend on western industry. The developers of Golden Rice manifestly oppose this and regard Golden Rice as a humanitarian project. Golden Rice may cost only as much as white rice, and the farmers are at liberty to use the harvested rice as seed for sowing for the following growing season. The potential launching onto the market of Golden Rice for that matter needn't be viewed as a precedent in the introduction of GM crops in developing countries. Many developing countries have been planting GM crops for quite some time already. No less than 20 out of the 28 countries that currently cultivate GM crops are indeed developing countries.[54] An example is the commercial cultivation of GM eggplants in Bangladesh since 2013. [54]

Opponents of Golden Rice argue that GM technology isn't the solution and that vitamin A deficiency must be tackled in other ways. They argue for improved education and awareness surrounding nutrition, sustainable agriculture and infrastructural improvement, so that more people gain access to different fruits and vegetables, to in turn end global malnutrition. These advances are, of course, absolutely vital, but meanwhile food enriched with nutrients can help along the way in a sustainable manner. A good example is the orange-fleshed sweet potato that's rich in provitamin A (see page 7) that has been on the market in Mozambique since 2002 and in Uganda since 2007.[64] Similarly, Golden Rice can be seen as an addition to the available food range in Asia. Local trade can distribute the rice grains so that low-income and rural population groups are reached, as well as the people who live in remote areas. By planting the seeds after the harvest, Golden Rice can be a cheap, self-perpetuating source of vitamin A. Golden Rice can therefore be easily integrated into the existing agricultural systems and can contribute towards reducing vitamin A deficiency in an effective, affordable and sustainable manner.

5 Increasing nutrition security with biofortified food crops

Orange-fleshed sweet potatoes increase the intake of vitamin A in certain African countries, whilst Golden Rice can assist in countries where rice is the staple food. Meanwhile, other food crops that are enriched with vitamins or minerals are being developed.

Golden Rice and the orange-fleshed sweet potato are examples of *biofortification*: to increase the content of certain nutrients in food crops, such as iron, zinc and vitamins. Via biofortification the local population can continue to cultivate its preferred food crop, but now with a higher nutrient level. Through agriculture and food production people can become self-sufficient, and tackle nutritional issues by themselves. Biofortification can be achieved via conventional breeding, such as sweet potatoes, or via genetic modification, such as Golden Rice (see figure 5). For example, via breeding the amount of iron in Latin-American beans could be raised from 50 to 90 milligrams per kilogram.[66-68] Cross-breeding programs are also initiated to boost the provitamin A content in maize and cassava, iron in pearl millet, and zinc in rice and wheat.[64,69] When the micronutrient doesn't occur in any of the plant species varieties found in nature, GM technology offers a solution. For example, Ugandan and Australian scientists are working on a banana variety that was genetically modified to produce provitamin A.[70] In Uganda East-African upland bananas are a staple food and 'golden' bananas could reduce vitamin A deficiency. Just as with Golden Rice, this project is receiving financial support from the Gates Foundation. The effect of the provitamin A enriched bananas is currently being tested in the United States.

Hope for folic acid deficiency too

A deficiency in micronutrients such as folic acid (vitamin B9), iron and zinc can be problematic. Twenty percent of the Chinese population is de-

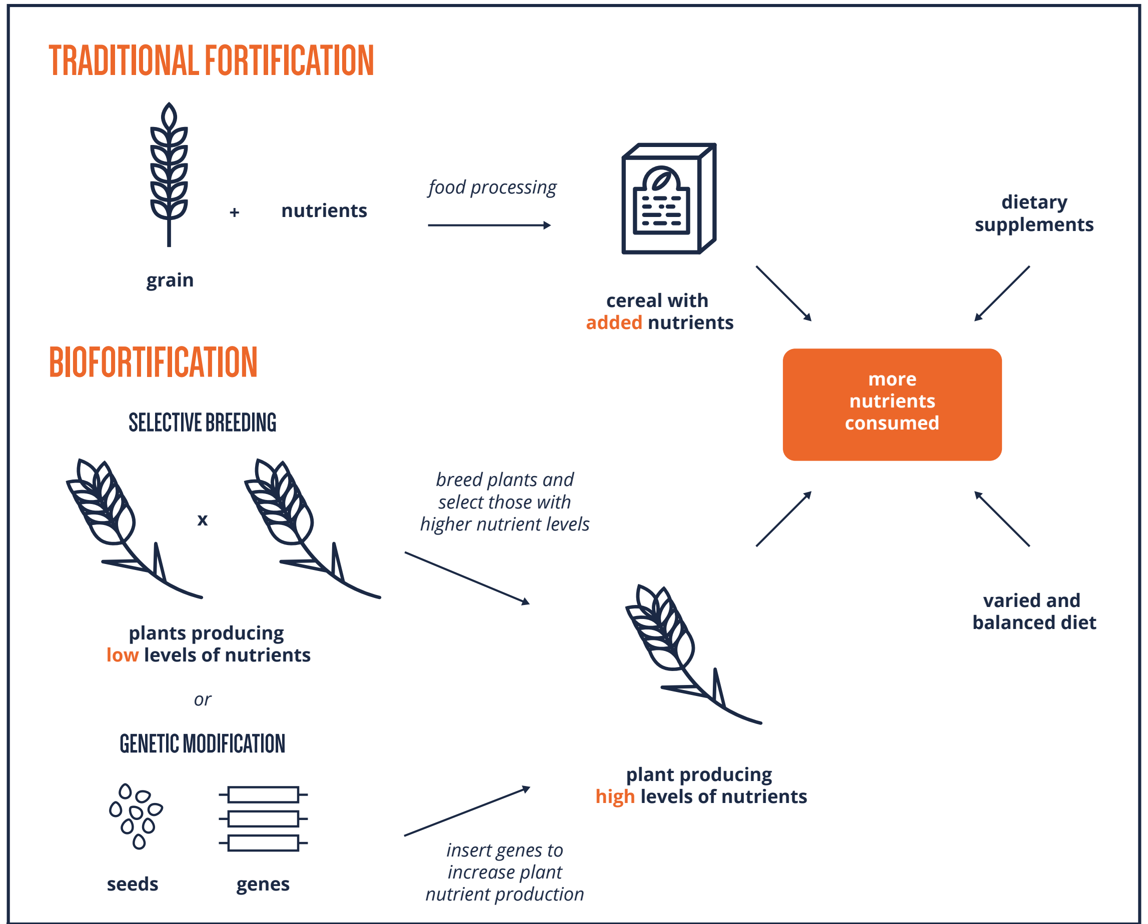

Figure 5. There are several ways to counter micronutrient deficiencies. Necessary vitamins and minerals can be obtained via a varied diet or via dietary supplements. Commonly consumed foods can be fortified by adding micronutrients, this is often the case with cereals. Biofortified crops are bred or engineered to produce higher levels of one or more micronutrients. Figure based on (Seim K.): Science in the News, Harvard University. http://sitn.hms.harvard.edu/flash/2015/good-as-gold-can-golden-rice-and-other-biofortified-crops-prevent-malnutrition/

ficient in folic acid. Harmful effects therefore arise during pregnancy: each year in China more than 18,000 babies are born with spinal deformities - spina bifida - known colloquially as an open back. Here too biotechnology can offer help. Two genes involved in folic acid production were added to the DNA of rice. The result was that the GM rice produced up to a hundred times more folic acid in comparison to the non-GM rice. Taking into account degradation during the cooking process and our body's ability to absorb folic acid, a portion of around 100 grams of folic acid producing GM rice would meet our daily folic acid needs.[71]

A technological solution alone will never provide the perfect all-in-one answer, but food crops – developed using GM technology or otherwise – in which a certain vital nutrient becomes more available, can be a part of a more all-encompassing solution. Biofortified food crops can provide a life-saving contribution to health problems arising from an insufficient diet.

6 Conclusion

Rice is the staple food of more than half of the world's population. Rice grains are rich in carbohydrates and comprise a good source of energy but lack many essential nutrients, such as vitamins and minerals. For people who barely eat more than a portion of rice a day, those deficiencies can result in serious health problems.

Tackling poverty, the lack of infrastructure and inadequate education are the greatest challenges. In attaining these goals the enrichment of staple food crops in developing countries can comprise a sustainable way of adding additional nutrients to people's diets. The development of Golden Rice is the first example of this. This rice contains provitamin A, a substance that the body converts into vitamin A.

Golden Rice offers great potential therefore in helping to combat vitamin A deficiency in developing countries. Development of the plant has already made significant progress and meanwhile many varieties exist. The field trials and analyses however demand a great deal of time, and regulation surrounding GM crops is stringent. Moreover, Golden Rice also faces opposition that primarily arises through misconceptions. All these different factors mean Golden Rice still hasn't found its way onto the market.

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