# The campaign for genetically modified rice is at the crossroads

## A critical look at Golden Rice after nearly 10 years of development

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# Contents:

# 1 Introduction

The idea for the Golden Rice project arose during an international conference in the Philippines in 1984. (Enserink 2008.) In 1999, an initial success was presented to the public. A team which included Ingo Potrykus from the Swiss Federal Institute of Technology in Zurich had succeeded in inducing genetically modified rice to generate carotenoids. (Ye et al. 2000.) The human body can use this provitamin A to synthesise essential vitamin A. Since grains of rice took on a yellow colour from the provitamin, this variety was quickly named Golden Rice. A cover story in Time Magazine in 2000 raised high expectations: *"This rice could save a million kids a year."* (Time Magazine 2000.) The article meant that this strain could theoretically be used to combat the vitamin A deficiency (VAD) that poses a problem in many developing countries. Children in particular suffer serious health disorders if they don't receive enough food with carotenoids. Vitamin A deficiency can be life-threatening. The World Health Organization (WHO) estimates that some 250,000 to 500,000 children go blind every year, and that half of them die within 12 months. (Enserink 2008.)

There are various international programmes that combat VAD using relatively simple measures: they distribute vitamin A pills or are committed to promoting the cultivation of vegetables with carotenoids such as green vegetables, tomatoes, and carrots, as well as fruits like mangos. Even if the problem has not been solved in all regions of the world, existing initiatives in the past 10 to 15 years have already achieved a lot. The Micronutrient Initiative (MI), for instance, working together with the United Nations, reports: *"MI's key contributions to global progress over the past 15 years include: providing support for supplies of vitamin A supplements that benefit over 200 million children annually in 70 countries."* (Micronutrient Initiative 2007.) In the end, combating VAD has less to do with new technological development than with setting clear political priorities. Even the Golden Rice Humanitarian Board, which steers communications and research around the vitamin A rice, admits that it will not solve all problems: *"Golden Rice is not a replacement for existing efforts to tackle the problem, but could substantially complement them in the future and make them more sustainable, especially in remote rural areas."* (Humanitarian Board.)

Although the first varieties of Golden Rice initially produced very low amounts of carotenoids, open field tests in 2004 showed better results. Syngenta in 2005 introduced a new variety of the rice (Paine 2005), which it promptly registered for patenting. Compared to the 1999 prototype, this new strain produces a higher amount of provitamin A. The argument posed by critics that the amount of carotenoids contained in the rice was much too low to effectively combat VAD seemed thus to be defeated. Nevertheless, even three years after the presentation of this new variety and nearly 10 years after the production of the first Golden Rice, many questions remain unanswered. This overview will look at several problematic aspects of this project regarding technical quality and development, possible risks and social ramifications. We are calling for a fundamental and new assessment of the project, comprehensively taking into consideration the risks associated with genetically modified (GM) plants and alternative solutions for combating vitamin A deficiency.

## 2 Lack of technical data

A sample of rice grains was sent to Germany by the Golden Rice team in 2001 in order to test their technical quality in trials with mice. In particular, the tests were to find out how much provitamin A was absorbed in the intestines and how much of that could actually be utilised by the body.

When rice grains were tested for their carotenoid content before the actual experiment began, scientists were surprised to learn that the rice contained less than one percent of the amount expected. After the rice was cooked, this share was reduced by another 50 percent[1]. As a result, the testing with mice was discontinued. If these findings, like so many other failures in research that have never been published, were to be verified, it would be certain that the quality of the rice at that time made it completely unsuitable for any real use. The specific findings of this trial with the first generation of genetically modified rice are today widely outdistanced. But fundamental technical questions in this connection still prevail:

- **How much carotene in rice degrades during storage?** No data has been published on this so far even though the Golden Rice Humanitarian Board confirms that there is a considerable need for clarity here. Officially, this was to be tested right after the first field trials in 2004: *"Because of their chemical nature – several conjugated double bonds – carotenoids are susceptible to light and oxidation. The effects of light and air after harvest can be studied now that the first field trials have begun. From these studies it will be possible to make recommendations as to how and how long to store Golden Rice without losing its beneficial nutritive effects."* (Humanitarian Board.) Even if rice is cultivated and eaten within a region, periods of storage can often be many weeks long. Decisive is what happens to carotenoid content during storage. The rate of carotenoid degradation is relatively easy to determine with standard technical methods. Systematic trials should have followed upon the test results at the German university in 2001 at the latest. It can be assumed that corresponding data is long since known to the managers of the Golden Rice project. Why haven't they published anything as yet (October 2008)?
- **How much provitamin A remains after cooking?** Rice can be boiled, steamed or even fried in many different ways. One publication stated that a 10 percent loss could be expected during the cooking of genetically modified first-generation rice. (Datta 2003.) However, this must be seen as a preliminary finding. To date there are still no data available on systematic trials with different cooking processes and how much carotenoid content is lost in each one. Research on the Golden Rice Humanitarian Board website to find an answer to this question brings up pages like Cooking with Golden Rice: *"Golden Rice will be cooked just like any other rice, from using plain water to highly refined sauces and spices, and it*

[1] This information was communicated verbally by scientists working on the experiment.

*will always taste good."* (Humanitarian Board.) Instead of finding specific trial results, the website visitor can download recipes for Paella a la Valencia, Jambalaya, Thai Fried Rice and Pilaf Rice with Whole Spices.

- **How well can genetically modified rice be utilised by the body?** Another unknown is the conversion rate of genetically modified rice. The conversion rate (or bio-availability) provides information on how well carotenoids in rice can be absorbed and utilised by the human body. Estimates for GM rice fluctuate between 1:1 and 1:12. This question could be roughly answered by conducting feeding trials with animals, such as those trials originally planned at the German university which were discontinued. To date, nothing has been published on feeding tests. Without citing specific data and circumstances, an article in Science Magazine from April 2008 mentioned that tests done with volunteers had shown conversion rates of 1:3 to 1:4. (Enserink 2008.) Nevertheless, the really limiting factor is not the absorption of carotene in the intestines but much more so the storage and preparation of rice. In an advisory publication, WHO notes about the absorption of conventional vitamin A and carotene supplements in food: *"Absorption of all forms is good (90%) but losses of vitamin A during processing, storage and food preparation may be high."* (WHO 2006, p. 118.)

Although trivial basic data about storage and food preparation are still not available (as of October 2008), environmental organisations in particular have been accused for years of delaying the market introduction of GM rice again and again because of exaggerated criticism and calls for higher safety standards. A perception broadly accepted by journalists and fomented by Golden Rice managers was expressed by the journalist Ulli Kulke in June 2008 in an article in Die Welt, for instance. At the centre of the article was Ingo Potrykus, who contributed to the development of GM rice: *"It has enough opponents surrounding it: environmental NGOs, governments, political parties, the Protestant church, trade organisations, part of the media and even farmers' lobbyists – all of them from countries in which no one suffers from vitamin A deficiency. But they are countries in which a closed circle of fear, populism, and vastly wealthy economic interests blocks the cultivation of plants like Golden Rice, so far with huge global success."* (Kulke 2008.) But the fact that even trivial technical data, enabling us to assess the quality of GM rice, is still missing after almost 10 years, is willingly suppressed in this kind of reporting.

Even placing questions directly does not garner much information. Replying to an email from 8 May 2008 posing specific questions, Jorge Mayer from the University of Freiburg, who acts as speaker for the Golden Rice Humanitarian Board, simply made a general announcement: *"The bioavailability studies should be published approx by the end of the year, depending on the publishing speed of the journal. (...) I can only say that so far, results are even better than we expected, but because this is being done by an independent scientific research group, we cannot talk about their results. But believe me, they are very eager to publish those results, as soon as they have been corroborated by the last, ongoing trial."*

This message is not only very vague, it is also contradictory. On one hand it states that making findings available depends only on how quickly a scientific magazine

can publish them, and on the other hand it says that trials have not been fully completed.

Another query on why trivial data on losses during storage and from cooking haven't yet been published remains unanswered. No matter when and how these data are finally published, a communication strategy that posts recipes on a website and withholds basic scientific data hardly seems reliable, particularly if opponents are being made responsible for delaying the project at the same time. This secretiveness would be understandable at best if a company wanted to protect sensitive business data. But the Golden Rice project is ostensibly being managed for purely humanitarian reasons. It is therefore incomprehensible why there is not complete transparency here.

# 3 Possible risks

A fierce international controversy is raging over Golden Rice and other genetically modified varieties of rice. Following soy and maize, rice is now in the crosslines of gene technology. This is of supreme importance for developing countries. Although the commercial cultivation of insect-resistant rice has not been allowed in China, and in Europe the debate continues on approving the import of rice from the United States that is resistant to sprayed herbicides, GM rice has reached the European market – in 2006, GM rice both from the United States and China was found in Europe. While the rice from China had reached the market directly without approval from the authorities, the rice from the USA came from a cultivation experiment years earlier. Evidently the GM rice had been mixed in with seed production and had proliferated unnoticed for a longer period of time. In Germany alone, the trade suffered damages of some 10 million EUR because of this contamination with American rice, which the German government admitted when asked. It is evident that even small mistakes can quickly have consequences in global markets. The manufacturers of genetically modified seed lose control over their products far too quickly.

Albeit, the Golden Rice Humanitarian Board believes the problem is under control, claiming on one hand that rice generally doesn't tend to outcross, and on the other hand saying that even if intermixture does take place, it would really have to be seen whether this had any consequences: *"While the chances of outcrossing to non-transgenic rice are very low (but not zero) the relevant issue is what effect the genes would have if outcrossing occurred."* (Humanitarian Board.)

At the International Biosafety Workshop in Beijing in September 2008, a rather different assessment was reached for the time being. Accordingly, different varieties of rice in fields initially barely cross with each other. However, there are plants outside of fields that are potential partners for crossing, such as strains of wild rice and weedy rice. It appears that genetic crossing through pollen flight occurs much more frequently then direct crossing between cultivated strains of rice in the field. According to findings from Chinese researchers, the plants that grow from crossing GM rice and weedy rice varieties exhibit surprising characteristics – their rate of reproduction seems be higher due to changes in flowering and seeding patterns. This gives them an advantage over other plants and they can assert themselves more strongly in the environment than normal members of the same species.

This would make weedy rice a problem again for rice cultivated in fields. The seeds from weedy rice simply drop and can't be harvested. If this weed crosses with normal rice in the fields, it can lead to huge losses in the harvest. For this reason, weedy rice has always been feared and consistently combated. But now that more and more people are migrating away from the country and into cities, and there is less manpower available for agricultural work, the weed is spreading out again. This development could be facilitated by the improved fitness (increased rate of reproduction) of the varieties that have crossed with GM rice. There is the threat that outcrossings with GM rice will significantly aggravate the spread of weedy rice. Chinese scientists now want to look into this

question more closely. If the dreaded scenario comes true, the cultivation of GM rice in China could become a time bomb.

Whether vitamin A rice also poses similar risks is unknown. To date there are no data available on risks to the environment posed by the fitness of plants crossed from Golden Rice and weedy rice, for instance. A read through the Humanitarian Board's website creates the impression that there are no risks, particularly because the existence of such a crossing has been denied from the very beginning.

Overall, the description of the risk assessment planned for GM rice is contradictory and by no means convincing. The Humanitarian Board here pursues a strangely zigzag route.

- Initially it states that it is committed to the highest safety standards: *"The Golden Rice Humanitarian Board is committed to the highest standards of safety assessment being conducted, and Golden Rice will only be made available for consumption after clearance by the relevant authorities according to national laws."* (Humanitarian Board)
- The claim is made that genetic modification is no more dangerous than conventional plant breeding: *"As concerns the genetic engineering step, conventional plant breeding involves the uncontrolled transfer and simultaneous random recombination of many thousands of genes from all parents involved. Therefore, safety concerns in respect of the deliberate and controlled transfer of no more than two genes, as in this case, is unwarranted."* (Humanitarian Board.)
- Altogether, the standards set for risk assessment are too high and too expensive, and they pose an insupportable burden for public institutions in particular: *"An unbearable financial burden: (...) 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."* (Humanitarian Board.)
- Ingo Potrykus takes these issues even further and calls for approval regulations to be generally loosened: *"One of my most important concerns is therefore to return the approval process to realistic terms and initiate an objective debate on opportunities and risks. If this doesn't happen, entering the market will be delayed even more and developing countries will continue to lose ground."* (Deichmann 2005.)

According to the Humanitarian Board, many of the objections are not scientifically grounded and assume unexpected consequences and scenarios that are hardly realistic. The Board believes that, in general, unpredictable negative results are not likely to happen. This opinion very quickly overlooks the fact that even the yellow colour of Golden Rice is an unexpected consequence. When the production of GM rice was first underway, it was thought grains would be coloured red like the carotene in tomatoes. The transmitted gene was supposed to cause the formation of lycopene (red) and not ß-carotene. (Ye 2000.) But an additional unexpected step in metabolism took place in the rice which caused it to take on a yellow ('golden') colour instead. (Beyer 2002.) Such unexpected consequences alone should be enough to warrant comprehensive safety assessment.

# 4 Trials with schoolchildren?

The approval trials carried out by the European Food Safety Authority (EFSA) have been highly criticised. The authority generally assumes that genetically modified plants are 'similar' to conventional plants. This approach is questionable because modern molecular biology shows that it is an illusion that 'targeted' gene transmission will have no side effects. The network of gene regulation is much more complicated than originally assumed. Genetic manipulation, in contrast to conventional breeding, doesn't use the normal system of gene regulation. Indeed, the gene regulation of plants has to be properly broken down first to force a plant to accept a new metabolism.

In addition, gene transmission is not targeted; it is a process of shotgun sequencing. More and more scientists see considerable deficiencies in this process of genetically modifying plants. A current research project financed by the German Ministry of Education and Research has publicly stated that: *"Until now, new genes have been integrated in the genome at random. It is not known beforehand whether the desired trait of the gene will be observed if it is in a random place or even whether other genes in the plant are negatively influenced."* (idw 2008.) Altogether one must assume that the concept of similarity as a basis for assessing risk is scientifically outdated.

It was seen in 2005 how justified the warning really is against the unexpected consequences of gene transmission. Bean genes were transmitted to peas, initially causing small changes in the protein; these changes made peas activate life-threatening reactions in the immune system. (Prescott 2005.) These effects would have been overseen in the EFSA's standard risk assessment procedures today. (Valenta 2008.)

Even though the EFSA still relies on the outdated idea of 'similarity', this could still make things difficult for Golden Rice because the metabolism of this rice plant has been massively tampered with and its components have clearly changed. The genetic change involved does not aim to affect the plant's agricultural characteristics but to have an effect on health. In such cases, EFSA guidelines call for much more comprehensive testing than for currently cultivated or imported GM maize. According to EFSA guidelines, Golden Rice should be evaluated as a new organism no longer similar to conventional rice. Extended risk assessment is envisioned in such cases. (EFSA 2008.) The guidelines for such testing must still be worked out in detail. One thing is certain – currently standard testing is not enough in this case.

The Golden Rice Humanitarian Board has officially pledged to apply the highest safety standards. However, the team does actually seem to absolutely accept health risks. Even though no data from previous trials have been published that would show the harmlessness of Golden Rice, scientists are already planning to carry out trials with children. In 2008, trials were to be done with schoolchildren aged six to eight in China; these were cancelled by Chinese authorities who received relevant information from Greenpeace. (Bisserbe 2008.) Trials to be conducted by Tufts University in the United States had already been approved by the National Institutes of Health (NIH), the United States health authority, but this rice would not have been taken through Chinese

approval trials for imports and food. These tests are now presumably being carried out somewhere else. Although information on the planned Chinese tests has disappeared from the NIH website, there is still a general announcement that tests are supposed to be conducted with altogether 72 children. (Clinical Trials 2008.)

As described under point 2, pretrials with adult volunteers have already been run at Tufts University in Boston. The findings of these studies haven't been published yet. (Enserink 2008.) Independent scientists who have not been involved with these trials have not had the opportunity to check standards and findings before tests are carried out with schoolchildren. In general it is problematic that rice is tested with human subjects without data from previous testing being available. At least the persons participating in trials in the United States were adults. They could make a conscious decision to participate. But it's very different if trials are run with schoolchildren. If initial testing is supposed to be carried out with schoolchildren in developing countries, without broad public debate and without publishing the findings of previous trials, then it is clear that the Golden Rice team is under a lot of pressure.

The open question is to what degree institutions like the Rockefeller Foundation and the Bill Gates Foundation, supporting the project with funding in the millions, actually share in this process. It can be feared that the Humanitarian Board will continue to push aside any criticism of its plans by drawing attention to the affliction suffered by millions of children. The website says: *"It took ten years – from 1980 to 1990 – to develop the necessary technology to introduce genes into rice. It took another nine years – from 1990 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 2004 – to develop Golden Rice. It is taking several more years to advance the first Golden Rice product through the regulatory approval process. Considering that Golden Rice could substantially reduce blindness (500,000 children per year) and deaths (2-3 million per year), the parsimony displayed by the responsible bodies after 20 years is hardly understandable."* (Humanitarian Board.)

# 5 A preliminary stocktaking

What began in 1999 with a surprising success in technology has now forced the hand of both advocates and critics of agricultural gene technology. Critics are aware of the drastic consequences of vitamin A deficiency for many people. They face the reproach that their criticism of the development of Golden Rice has led to delays and that they therefore share the responsibility for the fate of humans affected by VAD. Advocates have thus turned the introduction of GM rice rather into a test of conscience. But a closer look at the situation reveals that this argument has in the meantime turned back on itself.

Golden Rice was supposed to solve all problems at once – find acceptance for GM food, solve a real problem, simplify approval procedures, and muzzle opponents. Under the pressure of self-created expectations, the project seems to have partially slipped out of its managers' hands. Plans to conduct trials with schoolchildren in China at the present moment in the project's development are scientifically and ethically questionable and should lead to scientists and financiers fundamentally rethinking the whole project. If some kind of success is being sought in such a rush, the project seems to have far less to do with concern about humans affected by VAD than about implementing a certain technology.

If recipes for Golden Rice are posted on the Internet without at least some information being provided on how much carotene is in the rice after four weeks of storage and 20 minutes of cooking, then the project must face the suspicion that it is not about pursuing science to solve the problem of hunger but about making claims it cannot meet. If the project is to continue, scientists and financiers are best advised to make all data and information on its research absolutely transparent. Since the product is allegedly not being seen through for commercial interests, there is no reason to keep secrets. In addition, a broader and more participatory discussion process should be introduced in those regions of the world for which this product is intended, a debate in which critics and independent experts speak and in which the effort invested and the yield, risks and sustainability of the project are investigated from the bottom up. The managers of the project should take to heart the fact that, according to Science, specialists from WHO attribute more success to distributing vitamin tablets, fortifying normal food with vitamin A, and teaching people how to cultivate carrots and certain green vegetables, than to using gene technology. (Enserink 2008.)

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