Golden Rice: a long-running story at the watershed of the GM debate

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On 8 August 2013 a field trial of Golden Rice, one of several growing in the Philippines as part of the registration process, was destroyed by a 400-strong group of demonstrators. The Philippine Department of Agriculture (DoA) undertook to identify and prosecute those responsible for the physical damage and loss of data and the abuse of officials. The DoA said "[We have] always been at the forefront of promoting agricultural development and growth in the Bicol region. We support conventional, modern and organic farming as means of achieving food sufficiency and sustainability. We are committed to providing Filipinos

"Efforts to lift completely the shadow of death cast by vitamin A deficiency ... in some places still entail a struggle against intractable opposition. The victims who continue to suffer under the shadow are mainly the children.[1]"

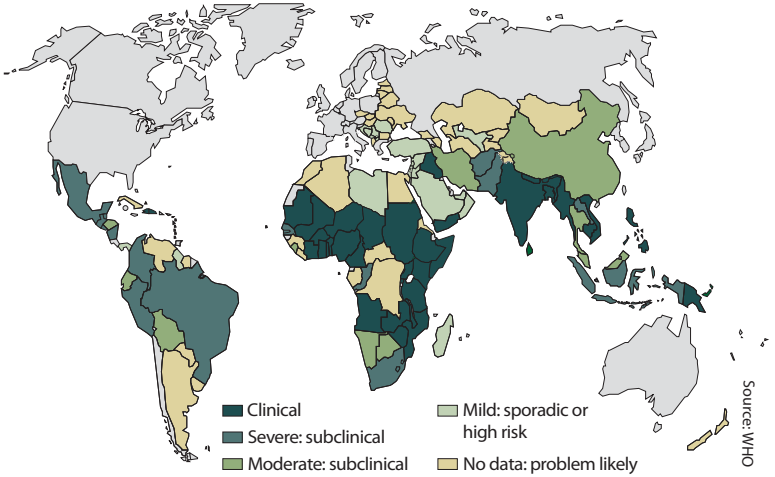
sufficient, safe, affordable and nutritious food. Thus, we are an active partner for rice research (including Golden Rice) and other projects which have complied with national biosafety regulations."

What started as a humanitarian project to help the disadvantaged in less developed nations had become the worldwide focus of an ideological conflict. How had this happened and who was responsible?

Vitamin A deficiency is a killer

Food must provide a source of macronutrients, carbohydrates, protein and fats. Also extremely important for human health are micronutrients including minerals (such as iron and zinc) and vitamins (such as vitamin A, C, D and the vitamin B 'complex').

Countries categorized by degree of public health importance of vitamin A deficiency



Global population mortality, 2010

Cause	Annual mortality (millions)
Vitamin A deficiency	1.9–2.8
HIV/AIDS	1.8
Tuberculosis	1.4
Malaria	0.7

In humans, vitamin A is essential for healthy skin and mucous membranes, a functional immune system, and good eye health and vision. Vitamin A deficiency is a significant health problem, widespread in the developing world, but which hardly occurs in the industrialised world.

What are available sources of vitamin A? In the diet, animal products such as milk, eggs, cheese and liver are rich sources. No plant contains vitamin A. Animals, including humans, make vitamin A from beta-carotene, a red-orange pigment found in plants, fruits and colourful vegetables.

It has taken about 200 years to understand fully the importance of vitamin A, and how it could prevent or cure many deadly diseases[1]. In comparison with the impact of other important public health problems, the mortality associated with vitamin A deficiency is stark[2, 3, 4, 5], with 2–3 million children dying annually as a result of vitamin A deficiency, despite existing interventions.

Long recognised as the leading cause of childhood blindness[6], only during the last 20 years has vitamin A deficiency come to be defined as "a nutritionally acquired immune deficiency syndrome"[1]. It mostly affects those whose bodies are under greatest physiological stress: children and mothers. Vitamin A

deficiency increases susceptibility to common childhood diseases such as measles, pneumonia, and diarrhea. Accordingly, 23–34 per cent of deaths among children under five years old, and up to 40 per cent of maternal deaths can be prevented with a universally available source of vitamin A[7,8,9,10].

Are vitamin A capsules the answer?

Since the 1990s vitamin A capsules have been provided to many at-risk populations. The vitamin A capsule programmes cost around US$1 billion a year[2] and have undoubtedly saved millions of lives. Nevertheless, they do not change the underlying vitamin A status of the targeted populations, nor are they sustainable because of the recurring cost. As the World Health Organization (WHO) stated recently[11] [vitamin A capsule supplementation programmes] "are only initial steps towards ensuring better overall nutrition and not long-term solutions ... Food fortification takes over where supplementation leaves off ... growing fruits and vegetables in home gardens complements dietary diversification and fortification and contributes to better lifelong health."

Notwithstanding WHO's comments, Semba[1] points out that it is almost impossible for young and poor children to avoid vitamin A deficiency through eating vegetables and fruit alone as a result of the low bioavailability of the beta-carotene within them. Adding vitamins or minerals to foods – 'food fortification' – also has its drawbacks. It requires industrial food processing, food packaging and distribution infrastructure. All add incremental cost and risk remote and marginalised or impoverished families not benefiting.

Biofortified food, a new way forward for the 21st century

Conversely, biofortification aims to increase the synthesis or accumulation of micronutrients by the staple food crop itself, so that all parts of the consuming population can benefit, in the most ideal case without incremental cost.

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Vitamin A deficiency is particularly problematic where the staple food is rice, as white rice is almost totally carbohydrate and contains no carotenoids. Rice provides around 80 per cent of the carbohydrate daily for half the world – about 3.5 billion people – and is the staple crop in most of Asia. Even in Africa, rice is becoming more and more important: imports are the fastest growing of all food crops, and efforts are underway to increase local production.

Almost 30 years ago, shortly after the dawn of genetic engineering of crops, Peter Jennings, already a famous rice breeder, suggested that rice with yellow endosperm instead of white would be useful to combat vitamin A deficiency. This idea eventually led, 15 years later, to the publication of a landmark paper[12].

The teams of Professors Ingo Potrykus and Peter Beyer working in Germany and Switzerland respectively had inserted three genes of interest into the rice genome of about 30,000 genes, activating the beta-carotene biosynthetic pathway in the endosperm[13].

Golden Rice is the first purposely created biofortified crop. As there was no naturally yellow rice to improve through breeding, only a genetic engineering approach had a chance of being successful. The colour of Golden Rice very obviously widens consumer choice, without words or special packaging.

A novel agreement to fulfill an altruistic vision: Golden Rice

In 2001 the inventors of Golden Rice completed a novel transaction[14,15]. Professors Potrykus and Beyer licensed their technology to Syngenta for commercial uses. In exchange Syngenta agreed to support the inventors'

humanitarian project, including technology improvements subsequently made by Syngenta scientists[16]. It was a field trial of this Golden Rice, which now includes a maize gene and one from a common soil bacterium to enhance beta-carotene levels, which was recently destroyed in the Philippines.

There has been much misinformation and misunderstanding about Golden Rice. The inventors, who are still closely involved with the strategic management of their project, aim to make the Golden Rice technology a public good, free of any cost or licence fees, available only in public-sector rice germplasm, and developed only by public-sector institutions. There will be no charge for the nutritional trait within the seed to smallholder farmers who sell locally (most rice is consumed close to where it is grown). No individual or organisation involved with the development of Golden Rice will benefit financially from its adoption.

In the Philippines, the International Rice Research Institute was the inventors' first licensee in 2001 and their breeding work is already largely complete. A regulatory data package is being developed for Golden Rice with funding principally from the Bill and Melinda Gates Foundation and involving work at the Danforth Centre, USA. The data will subsequently be provided free of charge to each country's regulatory agencies.

Golden Rice seed is available to public-sector rice-breeding institutions in less developed countries where rice is the staple and vitamin A deficiency endemic. Supply is subject only to national and international regulations, and simple and free agreements. Then using conventional breeding techniques the nutritional trait can be introduced into any locally adapted and pre-

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ferred variety of rice so that its agronomy, preparation and taste will be the same. Farmers will subsequently, initially using seed from their national seed supply system, be free to plant, harvest, save seed, and locally sell Golden Rice as they wish. There is no reason Golden Rice should cost any more than white rice to the farmer or consumer, and consumer benefit is expected from its health-promoting properties.

The commitment of the public, private and philanthropic sectors to the crucial humanitarian-driven invention and development of Golden Rice has been impressive[17]. Support has been forthcoming over the last 25 years from a variety of sources including the European Union, Switzerland, India, Philippines and Bangladesh, the Rockefeller Foundation, USAID, Syngenta Foundation and, since 2011, the Bill and Melinda Gates Foundation. But in comparison with investment targeting other public health problems, the costs have been tiny[18]. For example, in 2012 the audited financial statements of the International Rice Research Institute showed an annual spend of less than US$2.7 million on Golden Rice[19]. Estimates have calculated the value of conservative adoption of Golden Rice in Asia as adding between $4 and $18 billion to Asian GDP annually[20, 21].

Will it work and is it safe?

In adults[22] (in the USA) and most importantly children[2] (in China), careful and sophisticated research has shown that the beta-carotene in Golden Rice, following only a single meal, is very efficiently converted to vitamin A by the human body. Only a few tens of grams of dry Golden Rice, when cooked and consumed daily, is expected to combat vitamin A deficiency and save life and sight. The results show that Golden Rice "may be as useful as a source of pre-formed vitamin A from vitamin A capsules, eggs, or milk to overcome vitamin A in rice-consuming populations" [2].

In some countries, for example India, rice is seldom consumed without some oil or fat. In others, for example China, this is not always the case. The same research group has also investigated the effect of fat in the diet on the bioconversion of beta-carotene in Golden Rice to retinol. Preliminary analysis, which is subject to confirmation, shows little, if any, significant effect (Tang personal communication, in preparation for publication).

The only way in which Golden Rice differs from white rice is that the endosperm contains carotenoids, principally beta-carotene, and that genetic engineering techniques were used to create it.

At the levels found in food, beta-carotene is a safe source of vitamin A[23,24]. At these physiological doses consumption of beta-carotene over several years has no adverse health effects[25,26,27,28].

There is no evidence that genetic engineering techniques are harmful[29,30].

Golden Rice, only because it was created using genetic engineering techniques, has to complete exhaustive tests to prove its safety to humans and the environment before being registered on a country-by-country basis for use. After registration, its use as a food crop will be a decision for individual governments who will determine how quickly it is offered to that country's farmers and consumers for them to adopt.

The development process for Golden Rice is furthest advanced in the Philippines where millions of people suffer the effects of vitamin A deficiency, and where, incidentally, the government of the Republic has had significant nutrition improvement policies in place since the 1940s. It would be unsurprising if the Philippines became the first of many countries to adopt Golden Rice for the

benefit of local farmers and consumers. First registrations are expected within the next 12 months.

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Continuing research will clearly be necessary, after registration, to fully understand the benefits of Golden Rice to public health. Will regular Golden Rice consumption reduce the population's morbidity and mortality associated with vitamin A deficiency as expected, and as it was created to do? Of particular interest are neonates (babies under a month old). Vitamin A capsules are only recommended for children of six months and older[31], and very young children do not consume solid food. These children are the most vulnerable to vitamin A deficiency: neonate deaths in 2011 accounted for 43 per cent (increased from 36 per cent in 1990) of all deaths among under five-year-olds[32]. Can a good source of vitamin A, such as Golden Rice, when part of the staple diet, improve the mother's vitamin A status, benefiting her health, and simultaneously via the placenta and breast milk increase the baby's resistance to disease, and reduce neonate and child mortality?

Opposition

In 2001 Greenpeace, who have long opposed all genetically modified crops, said a breast-feeding woman would have to eat 18 kilograms of cooked Golden Rice daily to obtain any benefit. In 2012 Greenpeace were again extremely critical – not surprising in the light of their 2001 position – when research was published showing that only 100–150 grams of cooked Golden Rice could provide 60 per cent of the recommended daily allowance of vitamin A for a child aged six to eight years[2].

Criticism of this internationally very important research conducted in China is paradoxical since China, despite its rapid economic development, is still the home of hundreds of millions of very poor rice-consuming people, and where around 60 per cent of the rural population and 30 per cent of the urban population suffer from vitamin A deficiency, with 9 per cent of all children in the country severely affected[33].

To answer the question "who was responsible for the destruction of the Philippine field trial?", we await with interest the results of the Philippine Department of Agriculture's investigation and the court's decision.

Much is at stake here, as illustrated by the former lead anti-GMO campaigner for Friends of the Earth Jens Katzek, who reported last year that his colleagues, who are implacably opposed to genetically modified crops stated: "If we lose the Golden Rice battle, we lose the GMO war."

References

1 Semba R.D. (2012) The vitamin A story: lifting the shadow of death. *World Review of Nutrition and Dietetics*, 104, Series ed. Berthold Koletzko.
2 Tang G., Hu Y., Yin S.-A., *et al*. (2012). Golden Rice β-carotene is as good as beta-carotene in oil in providing vitamin A to children. *American Journal of Clinical Nutrition* 96, 658-664.
3 Avert (2012) http://www.avert.org/worldstats.htm accessed 7 June 2012.
4 WHO (2012) http://www.who.int/mediacentre/factsheets/fs104/en/ accessed 7 June 2012.
5 WHO (2012) http://www.who.int/mediacentre/factsheets/fs094/en/ accessed 7 June 2012.
6 Whitcher J.P., Srinivasan M., Upadhyay M.P. (2001) Corneal blindness: a global perspective. *Bulletin of the World Health Organization* 79, 214–221.
7 WHO (2005) Global prevalence of vitamin A deficiency in populations at risk 1995–2005. WHO Global Database on Vitamin A Deficiency.

8 Fawzi W.W., Chalmers T.C., Herrera M.G., Mosteller F. (1993) Vitamin A supplementation and child mortality. A meta-analysis. *Journal of the American Medical Association* 269:898-903.

9 Mayo-Wilson E., Imdad A., Herzer K., Yakoob M., Bhutta Z. (2011) Vitamin A supplements for preventing mortality, illness and blindness in children aged under 5: systematic review and meta-analysis. *British Medical Journal* 343, 19pp

10 West K.P. Jr *et al.* (1999) Double blind, cluster randomised trial of low dose supplementation with vitamin A or beta carotene on mortality related to pregnancy in Nepal. The NNIPS-2 Study Group. *British Medical Journal* 318, 570–575

11 WHO (2013) http://www.who.int/nutrition/topics/vad/en/ accessed 26 September 2013

12 Ye X-D., Al-Babili S., Kloti A., Zhang J., Lucca P., Beyer P., Potrykus I. (2000) Engineering the provitamin A beta-carotene biosynthetic pathway into (carotenoid-free) rice endosperm. *Science* 287:303–5.

13 http://www.goldenrice.org/Content2-How/how1_sci.php

14 Potrykus I. (2010) The private sector's role for public sector genetically engineered crop projects in: Potrykus, I. and Ammann, K., eds. (2010) *Transgenic Plants for Food Security in the Context of Development*, Statement of the Pontifical Academy of Sciences, Vol. 27, open source, pp 445–717, M. Taussig, New Biotechnology Elsevier, Amsterdam, http://www.sciencedirect.com/science/issue/43660-2010-999729994-2699796

15 Potrykus I. (2012) Unjustified regulation prevents use of GMO technology for public good. *Trends in Biotechnology* 31(3):131–133.

16 Paine J.A., Shipton C.A., Chaggar S. *et al.* (2005) Improving the nutritional value of Golden Rice through increased pro-vitamin A content. *Nature Biotech* 23:482–487.

17 http://www.goldenrice.org/

18 Dubock A. (2013) Nutritional enhancement by biofortification of staple crops in: *Successful Agricultural Innovation in Emerging Economies: New Genetic Technologies for Global Food Production* pp 199–220, eds. David J. Bennett and Richard C. Jennings. Cambridge University Press.

19 Stein A. (2013) http://ajstein.tumblr.com/post/60131379987/comment-on-golden-rice-and-gmos-the-best-solutions-to accessed 26 September 2013

20 Anderson K., Jackson L.A., Pohl Nielsen C. (2004) *Genetically Modified Rice Adoption: Implications for Welfare and Poverty Alleviation.* Centre for International Economic Studies. Discussion Paper 0413.

21 Anderson K., Pohl Nielsen C. (2004) *Golden Rice and the Looming GMO Trade Debate: Implications for the Poor.* CEPR Discussion Paper 4195.

22 Tang, G., Qin, J., Dolnikowski, G. G., Russell, R. M., and Grusak, M. A. (2009). Golden Rice is an effective source of vitamin A. *American Journal of Clinical Nutrition* 89:1776–1783.

23 www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm261245.htm accessed 27 September 2013
24 Grune T. *et al.* (2010) β-Carotene is an important vitamin A source for humans. *The Journal of Nutrition*. doi:10.3945/jn.109.119024.
25 Shekelle R.B., Lepper M., Liu S., Maliza C., Raynor W.J. Jr, Rossof A.H., Paul O., Shryock A.M., Stamler J. (1981) Dietary vitamin A and risk of cancer in the Western Electric study. *Lancet* 1185–1190
26 Grodstein F., Kang J.H., Glynn R.J., Cook N.R., Gaziano M. (2007) A randomized trial of beta carotene supplementation and cognitive function in men: The Physicians' Health Study II. *Archives of Internal Medicine* 167:2184–2190.
27 Kang J.H., Grodstein F. (2008) Plasma carotenoids and tocopherols and cognitive function: A prospective study. *Neurobiology of Aging* 8(29):1394–1403.
28 Kang J.H. *et al.* (2009) Vitamin E, vitamin C, beta-carotene, and cognitive function among women with or at risk of cardiovascular disease. *Circulation* 119:2772–2780.
29 Dubock A. (2009) Crop conundrum. *Nutrition Reviews* 67:17–20.
30 European Commission Directorate-General for Research and Innovation; Biotechnologies (2010). A Decade of EU-Funded GMO Research (2001–2010).
31 WHO (2011) *Guideline: Vitamin A Supplementation in Infants and Children 6–59 Months of Age.* Geneva, World Health Organization, 2011.
32 UNICEF (2010) *Levels and Trends in Child Mortality: Estimates Developed by the United Nations Inter-agency Group for Child Mortality Estimation.* New York, NY: United Nations Children's Fund (UNICEF).
33 Chinese State Council Information Office (2004) The nutritional health status of the Chinese people. Material for the press conference, October 12, 2004.

Further reading

Mayer J.E., Pfeiffer W.H., Beyer P. (2008) Biofortified crops to alleviate micronutrient malnutrition. *Current Opinion in Plant Biology* 11:166–170.
Moore P. (2010) *Confessions of a Greenpeace Dropout: The Making of a Sensible Environmentalist.* Beatty Publishing Inc. Chapter 16.

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