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Golden Rice: To Combat Vitamin A Deficiency for Public Health

Adrian Dubock

Abstract

Vitamin A deficiency (VAD) has been recognised as a significant public health problem continuously for more than 30 years, despite current interventions. The problem is particularly severe in populations where rice is the staple food and diversity of diet is limited, as white rice contains no micronutrients. Golden Rice is a public-sector product designed as an additional intervention for VAD. There will be no charge for the nutritional trait, which has been donated by its inventors for use in public-sector rice varieties to assist the resource poor, and no limitations on what small farmers can do with the crop—saving and replanting seed, selling seed and selling grain are all possible. Because Golden Rice had to be created by introducing two new genes—one from maize and the other from a very commonly ingested soil bacterium—it has taken a long time to get from the laboratory to the field. Now it has been formally registered as safe as food, feed, or in processed form by four industrialised countries, and applications are pending in developing countries. The data are summarised here, and criticisms addressed, for a public health professional audience: is it needed, will it work, is it safe and is it economic? Adoption of Golden Rice, the next step after in-country registration, requires strategic and tactical cooperation across professions, non-governmental organisations (NGOs) and government departments often not used to working together. Public health professionals need to play a prominent role.

Keywords: Golden Rice, VAD, biofortification, β -carotene, micronutrients, estimated average requirement (EAR), recommended daily allowance (RDA), novel proteins, allergenicity, substantial equivalence, hidden hunger

1. Introduction

Research was initiated in the early 1990s which led in 2000 to the publication of the technology behind what came to be known as Golden Rice [1, 2]. From the outset, the intention was to create a source of vitamin A in the endosperm of rice, as an additional intervention for vitamin A deficiency. Philanthropy and the public sector funded the research [1]. In 2001, the inventors, Professor Ingo Potrykus and Dr. (now Professor) Peter Beyer, assigned their patents to Syngenta for commercial exploitation as part of a transaction which obliged the company to assist the inventors' humanitarian and altruistic objectives [1, 3, 4]. At the same time, the nutritional technology was donated by its inventors for use in developing countries [3, 4]. The inventors licenced a network of Asian government-owned rice research institutes to deliver their objectives. Product development was initiated through the International Rice Research Institute (IRRI) and the network. The whole network,

including IRRI, worked to a common set of goals defined in licences each institution signed with the inventors. The terms included that there would be no charge for the nutritional technology and it would only be introduced to publicly owned rice varieties. Improvements were made to the technology by Syngenta scientists [5]. In 2005 and 2006, pursuant to Syngenta's legal obligations entered into with the inventors in 2001, Syngenta provided selected transformation events of the improvements to the Golden Rice Humanitarian Board. The Humanitarian Board, via Syngenta and IRRI, made these new versions available to the Golden Rice licensee network [4, 6]. In 2004 Syngenta ceased its commercial interest in Golden Rice [7]. From 2004 development was again only funded by philanthropy and the public sector; the national budgets of Bangladesh, China, India, Indonesia, Philippines and Vietnam; as well as the US National Institutes of Health together with the Rockefeller and Bill & Melinda Gates Foundations and USAID. Golden Rice is a not-for-profit project: no individual, nor organisation involved with its development, has any financial interest in the outcome.

To date the Golden Rice project has principally engaged plant scientists. Activist opposition to Golden Rice has been led principally by non-scientists, who have been very successful in developing a narrative about Golden Rice and gmo crops which serves the activist's purpose¹ but is fundamentally inaccurate [8]. Further background to the development of Golden Rice, including the political dimensions, is detailed elsewhere [6, 9, 10].

A few years ago, at Tufts University, USA, I gave a presentation about Golden Rice. The symposium was organised by the Friedman School of Nutrition Science and Policy whose strategic aims today include 'Reduce nutrition-related health inequities' and 'Promote food systems that increase agricultural sustainability while improving human health' [11]. I was dismayed to learn that the anti-gmo and anti-Golden Rice activists' narrative was widely accepted by the participants—all of whom were studying or working in nutrition and well aware of nutritional inequities in public health.

Without adoption, that is, regular growth and consumption of Golden Rice by populations in countries where rice is the staple and VAD is problematic, Golden Rice cannot deliver any public health and welfare benefits. Adoption requires cooperative working by different specialists, including medical, nutritional and public health specialists [12]. This chapter is designed to answer anticipated questions from such specialists, to facilitate adoption of Golden Rice as an additional intervention for vitamin A deficiency.

2. Rice, diet and deficiency

Rice is the most important staple crop [6]: more than half of the global population eats it every day. In some countries, 70–80% of an individual's calorie intake is from consumption of rice [13, 14].

For storage without becoming rancid, the husk and the aleurone layer of rice have to be removed. What remains after polishing—white rice, the endosperm—contains small amounts of fat and is an excellent source of carbohydrate for energy but contains no micronutrients. Yet humans require both macronutrients (carbohydrates, proteins, fats) and micronutrients (minerals and vitamins) for a healthy life. Like all plants, rice obtains its minerals from the soil. Vitamins are synthesised by plants and/or animals, including humans.

¹ For example: https://www.heartland.org/_template-assets/documents/12-3-18%20Analysis%20of%20Greenpeace%20Business%20Model.pdf

Human health is best served by a ‘balanced diet’ that is varied, containing both macronutrients and micronutrients, including animal products and, as sources of provitamin A, coloured fruits and vegetables. Micronutrient sources are insufficiently represented in the diets of many people in countries where rice is the staple. The reasons often include poverty: such dietary components are expensive compared to the cost of rice [15]. In countries where rice is the staple, the average consumption is 75.20 kg/capita/year. Of those countries where micronutrient deficiencies are common, consumption increases to 150 kg/capita/year [16]. In such populations micronutrient deficiencies, like poverty itself, often occur as part of an intergenerational cycle [17].

For the past 15 years, 800 million people—more than 10% of the global population—are hungry every day. These chronically hungry individuals lack sufficient calories in their daily diet [18–20]; indeed over the past 3 years, the trend is upward [20]. Even more alarming is that 2 billion people—almost 25% of global population—are micronutrient deficient; they suffer from ‘hidden hunger’, with important associated morbidity and mortality [17] and related economic impact [6, 17].

Figure 1 shows that over the 20-year period 1990–2010, the rate of reduction of chronic hunger (that is, macronutrient—carbohydrate, proteins and fats—dietary insufficiency) has been faster than the rate of reduction for hidden hunger (that is, dietary insufficiency of minerals and vitamins) [21]. Dr. Matin Qaim, member of the Golden Rice Humanitarian Board and one of the authors of the paper from which **Figure 1** is extracted, has commented: ‘In the future the hidden hunger [e.g. micronutrient deficiency] burden will be larger, [than chronic hunger – principally carbohydrate deficiency] unless targeted efforts to reduce micronutrient malnutrition are implemented at larger scale’ (pers comm: Dr. M Qaim).

Interventions for micronutrient deficiencies include *supplementation* (with pills, syrups or capsules containing micronutrients [22]) and *fortification* (adding micronutrients to processed food). Both interventions require some level of manufacturing and/or distribution infrastructure.

With the creation of Golden Rice in 1999 [2]—the first purposefully created biofortified crop—a new term was required: ‘biofortification’. The word was first used in 2002 [23] and first defined in 2004 [24]: “biofortification” is a word coined

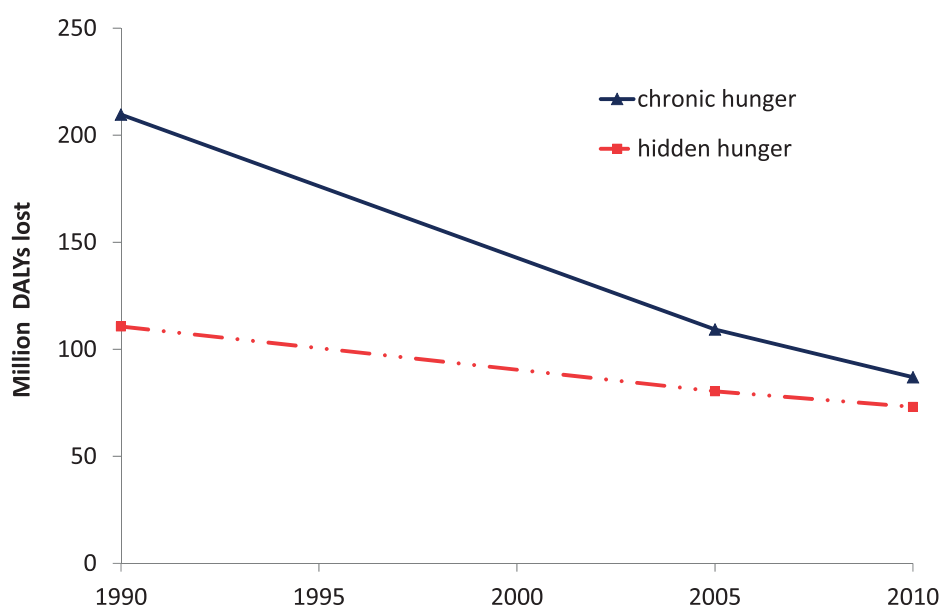


Figure 1. Disability-adjusted life years (DALYs) lost due to chronic hunger and hidden hunger between 1990 and 2010. Please refer to text for further explanation (**Figure 1** here is part of **Figure 2** from Ref. [21]).

to refer to increasing the bioavailable micronutrient content of food crops through genetic selection via plant breeding.’ In 2003 ‘Harvest Plus’ a not-for-profit public-sector programme started to biofortify staple crops by conventional plant breeding, to benefit the poor, and progress with biofortification through conventional plant breeding was rewarded by the World Food Prize in 2016 [25].

The intention of biofortification is to deliver public health benefits to populations which are micronutrient deficient, through consumption of the staple crop including the extra nutrition within the edible part of the crop. In this way minimal cultural change is required to food—production, processing or consumption—systems. For the most marginal members of the population, this biofortification approach overcomes the inherent access, cost and non-sustainability difficulties of supplementation and fortification. In 2017 the World Bank recommended that biofortified staple crops should be the norm rather than the exception: ‘conventionally’ bred biofortified crops and also genetically engineered crops—gmo crops—were both recommended with Golden Rice specifically mentioned [26].

For Golden Rice to deliver benefits, it has to be grown and consumed within target countries where VAD remains problematic despite significant progress with other interventions, notably vitamin A capsules, which have undoubtedly saved millions of lives and will save more, since they were introduced (accompanied by controversy) in the 1990s [15, 22]. And success or failure with Golden Rice will directly affect future adoption also of high zinc, high iron and high folate rice and their impact on public health for hundreds of millions of people. All these traits, introduced to the endosperm of rice, necessitated using gmo techniques [16, 27], and all cost no more than white rice to the grower or consumer. Eventually, as the end point of product development, it is planned to include all these nutritional traits together in multi-micronutrient-Golden Rice.

Adoption of Golden Rice requires public health professionals as well as agricultural and other professionals, to work together in each country [12]. Any scepticism created by the past 18 years of negative activist influence will prevent success, if not positively addressed by all involved. For billions of people, the stakes could not be higher.

3. The questions and answers

3.1 Is Golden Rice needed?

For more than a quarter of a century, vitamin A deficiency (VAD) has been recognised by the United Nations as a significant public health problem. Key milestones included the:

1990 United Nations (UN) World Summit for Children, where 50 heads of government and senior government officials committed their governments to the virtual elimination of VAD by the year 2000 [28].

1992 UN International Conference on Nutrition, which concluded that

- VAD control is the most cost-effective child health/survival strategy governments can pursue.
- All sectors of society should support the virtual elimination of VAD.
- Strategies should include promoting breast-feeding, dietary diversification, vitamin A supplementation and food fortification.
- Locally available food-based strategies are the first priority. Vitamin A capsule supplementation is only an interim measure [29].

2004 United Nations International Children's Emergency Fund (UNICEF) and the Micronutrient Initiative Report 'Vitamin and Mineral Deficiency', which concluded that 'controlling vitamin and mineral deficiency is an affordable opportunity to improve the lives of two billion people and strengthen the pulse of economic development' and that 'probably no other technology available today offers as large an opportunity to improve lives and accelerate development at such low cost' [30].

Nevertheless, vitamin A deficiency (VAD) remains a major public health problem, in more than half of all countries, especially in Africa and south-east Asia (Figure 2), hitting hardest young children and pregnant women [31] especially in countries where rice is the staple food. Food sources that are most valuable in terms of micronutrients—for vitamin A, animal products including milk, eggs, butter, liver and fish—are usually more expensive and 'beyond the reach of poor families' [15]. Food security staple crops such as rice are cheaper and therefore make up most of the diet.

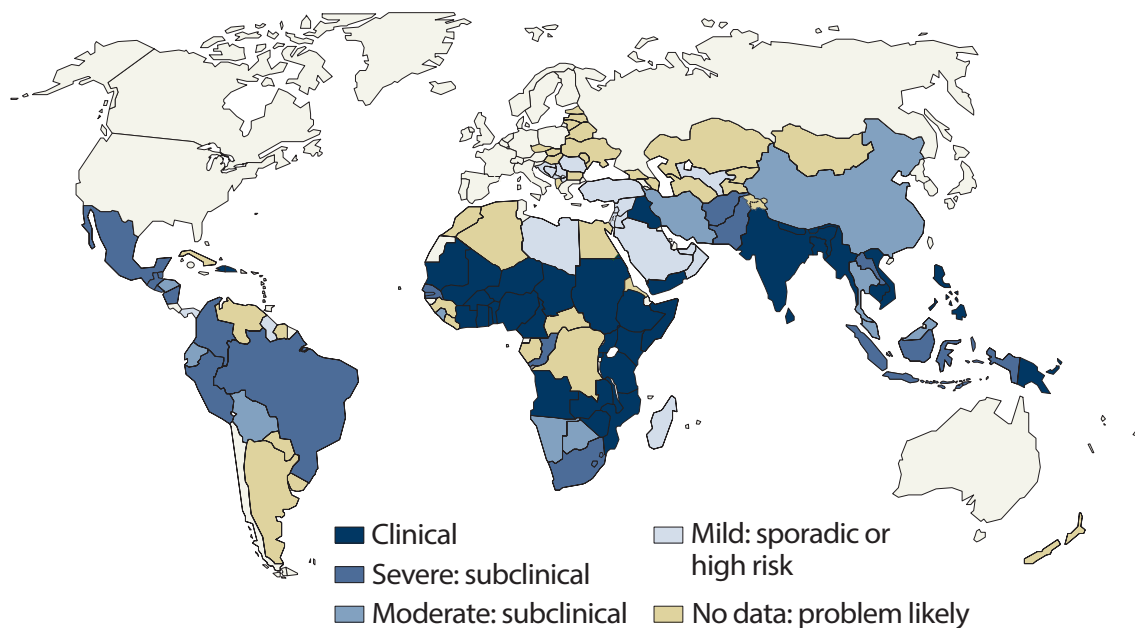


Figure 2. Public health importance for vitamin A deficiency, by country. Source [32] (the original WHO map has been redrawn and is provided here by courtesy of Banson, a publisher).

The problem of VAD is exacerbated by the limited bioavailability of vitamin A from fruit and vegetables [33]. It has been estimated that young children between ages 1 and 3 years would need to eat eight servings of dark green leafy vegetables per day in order to meet the recommended dietary allowance ('RDA') for vitamin A. These facts have resulted in the conclusion of 'the virtual impossibility for most poor, young children to meet their vitamin A requirements through vegetable and fruit intake alone' [15].

VAD is the principal cause of irreversible blindness in children [34]. Another morbidity of VAD is related to impairment of the immune system [15]: most children and mothers who die as a result of VAD do not become blind first but die of common childhood diseases. VAD is a *nutritionally acquired immune deficiency syndrome* [15]. Increased susceptibility to disease as a result of VAD results in the majority of the millions of preventable deaths annually, mainly of children less than 5 years old (<5 years) [22]. Meta-analyses have shown that 23–34% of global mortality of children <5 years can be prevented by a universally available source of vitamin A [22, 35, 36] and up to 50% for measles sufferers [31]. As the UN regularly

Global mortality (millions)	2010 ^a	2014 ^a	2016/2017
Vitamin A deficiency	1.9–2.8	1.4–2.1	1.3–1.9 (2016) ^b
HIV/AIDS	1.8	1.2	0.94 (2017) ^c
Tuberculosis (TB)	1.4	1.1	1.6 (2017) ^d
Malaria	0.7	0.6	0.45 (2016) ^e

^aSource: [6]

^bSource: 23–34%—see text—of 5.6 months <5 years children in 2016 [37]

^cSource: <http://www.unaids.org/en/resources/fact-sheet> [Accessed: January 10, 2019]

^dSource: <https://www.who.int/news-room/fact-sheets/detail/tuberculosis> [Accessed: January 10, 2019]

^eSource: <https://reliefweb.int/report/world/world-malaria-report-2017> [Accessed: January 10, 2019]

Table 1.

Annual mortality from different public health diseases (VAD deaths exclude significant maternal mortality).

measures and publishes global all-cause child mortality, the importance of VAD mortality can be stated compared with other public health mortality causes, also reported regularly by the UN (**Table 1**).

In 2016, 26 years after the first UN commitment to *virtually eliminate VAD by the year 2000* [28], and despite existing knowledge and interventions, 1.3–1.9 million, mostly children less than 5 years old, and many mothers, died from this preventable vitamin deficiency (**Table 1**).

3.2 Will Golden Rice work?

There is not one type of Golden Rice. The ‘genetic modification’ part of the process used to create Golden Rice occurred only once, in about 2004 [5]. The preferred ‘transformation event GR2E’ was selected in late 2013 [6, 9] and subsequently introduced by ‘conventional plant breeding’ into more than a dozen cultivars of the *Oryza sativa indica* rice variety agronomically adapted to and preferred by the farming and rice-consuming populations of India and Asia. These cultivars can be grown directly and harvested and the polished Golden Rice sold and consumed, or the Golden Rice seed can be used by rice breeders as ‘parents’ to introduce the trait into any locally adapted and preferred rice variety, of which there are over 20,000.

The agronomy of Golden Rice—how it grows, its resistance to pests and diseases, its water requirements and days to maturity and plant and grain morphologies—and yield are the same as the variety into which the nutritional trait has been introduced. An avoidable human error was made in an earlier selection of ‘a lead transformation event: GR2R’, which led to plants in open fields falling over when subject to wind and rain, and a small yield loss of about 2% was the result [9, 38]. GR2R was dropped from development in late 2013. The current lead transformation event, GR2E, was selected in the same year. GR2E has been, and will be, registered for use and has no problems associated with it [6].

In his wonderful book *The Vitamin A Story: Lifting the Shadow of Death* [15], the author Dr. Semba wrote (p. 159): ‘From a public health standpoint, for food fortification to be effective in reducing a population’s micronutrient deficiency, the food to be fortified must be a dietary staple eaten daily with little or no variation. Further, the fortified food should reach the entire population. Of course, the fortification process must be economically feasible and have minimal effect on the cost of the food treated. The micronutrient with which the staple is treated must be chemically stable and undetectable by persons consuming it. Finally, to enable observation and measurement of results, location or processing and distribution must be finite and constant’. The book was published in 2012, when biofortification was known, but

not sufficiently established to have any practical history. For whatever reason, Dr. Semba does not mention biofortification, nor Golden Rice, in his book.

Nevertheless, for Golden Rice ‘from a public health standpoint, for food fortification to be effective’, all the characteristics listed by Dr. Semba are satisfied, except when it comes to ‘undetectable by persons consuming it’. The Golden Rice colour is caused by the β -carotene content, a source of vitamin A for humans, which in Golden Rice is about 80–90% of all carotenoids [5]. It is the same β -carotene which colours mangos, papaya, squash and carrots, all of which consumers readily accept, and there is no taste associated with the β -carotene content. In Golden Rice, the intensity of the colour is proportional to the β -carotene content. The colour is obvious and cannot be ignored (**Figure 3**).



Figure 3.
Polished white and Golden Rice and (a different cultivar, after 2 months of postharvest storage) after cooking.

In 2009 MBA students at the Asian Institute of Management conducted qualitative attitudinal surveys of small farmers and consumers in four different representative island locations in the Philippines. Neither the colour nor the way it was created was considered a block to trying Golden Rice, so long as it was expected to assist their family’s health and was affordable. The solid colour of Golden Rice was recognisably distinct from the rather blotchy yellow colour of poorly stored white rice, which is sometimes offered cheaply by governments to assist poor people.

From several perspectives the colour of Golden Rice is positive. Consumers have a choice about whether to select it for cooking and whether to consume it or not. Such consumer choice is denied and therefore only made by governments or plant breeders, when the biofortified trait is ‘undetectable by persons consuming it’ [15], as in the case of invisible biofortificants such as iron or zinc introduced into biofortified grain crops or used in fortification of processed food. The colour of Golden Rice makes the consumers’ choice clear, even in populations with a variety of languages and dialects or where individuals are illiterate: each grain of Golden Rice is individually labelled, by its colour. No labelling is required on any packaging, and preference can be beneficially affected by communication of its lack of any adverse associations, and anticipated health benefits, from consumption.

Eighty percent—about 380 million tonnes—of global rice production is produced on small farms for family consumption, usually unprocessed except for polishing [38]. It is probably not stored for long, as rice is produced, usually, in two or three growth cycles annually, and storage facilities are limited. Data have shown that degradation of the β -carotene is minimal 2 months after harvest and samples of Golden Rice stored in ambient temperatures for 4.5 years remain noticeably yellow, indicating continued presence of β -carotene [39].

In early 2001, a year after the seminal paper describing the ‘proof of concept’ technology [2], Greenpeace made a press release: ‘Genetically modified “Golden Rice” containing provitamin A will not solve the problem of malnutrition in developing countries,... Greenpeace calculations show... , that an adult would have to eat

at least 3.7 kilos of dry weight rice, i.e. around 9 kilos of cooked rice, to satisfy their daily need of vitamin A from “Golden Rice” ...’ [40].

It is unclear how Greenpeace came to their conclusion. At the time, it was known that the bioavailability of carotenoids is influenced by nine different factors [41]. But no one knew how efficiently the β -carotene in Golden Rice was converted to circulating vitamin A, retinol, by human adults or children. And nutritionists agreed that animal models would not be helpful because animals metabolise carotenoids differently than humans. Research was needed to determine how efficiently the β -carotene in Golden Rice is converted to circulating retinol, in children in developing countries where rice is the staple, the population segment which suffers most from VAD.

A February 2002 grant application to the US governments National Institutes of Health (NIH) for a project, which is entitled ‘Retinol Equivalents of Plant Carotenoids in Chinese Children’, states ‘This project is to determine the vitamin A value (equivalence) of dietary provitamin A carotenes from spinach, Golden Rice, and pure β -carotene (β -c) in oil. These experiments will be conducted in children (ages 6–8) with/without adequate vitamin A nutrition.’

On February 10, 2004, Tufts University Institutional Review Board (IRB) approved the research Protocol for ‘Retinol Equivalents of Plant carotenoids in Chinese Children’ and noted that ‘The Zhejiang Academy of Medical Sciences [China] approval is on file’.

On March 11, 2008, the Tufts IRB reviewed and on May 10, 2008, approved the study ‘Vitamin A Value of Plant Carotenoids (Spinach and Golden Rice in Children)’ based on the Protocol ‘Retinol equivalents of plant carotenoids in Chinese children’. Both Protocols referenced ‘NIH grant proposal 1R01 DK060021’.

On March 30, 2008, with respect to ‘Retinol Equivalents of Plant carotenoids in Chinese Children’ and ‘NIH Grant 1R01 DK060021-01’: The Ethical Review Committee of Zhejiang Academy of Medical Sciences confirmed that they had ‘reviewed the proposed use of human subject identified on June 27, 2003’ and certified that ‘the approval notice is still valid’.

Although the Chinese children research was planned in 2003, various practical setbacks in the production² of the deuterium-labelled Golden Rice [9] meant that the field work in China was not completed until mid-June 2008 and, due to the complexity of analysis combined with limited analytical resources, publication not until 2012.

In the meantime, similar research was approved and conducted with adult volunteers in the USA. Data confirmed that 3.8 molecules of β -carotene derived by consumption of a single meal of Golden Rice converted to one molecule of circulating retinol [42]; this 3.8:1 bioconversion compared very favourably with conversion ratios established using other plant sources [33]. When the Chinese children research were published online on August 8, 2012, the authors reported a bioconversion ratio of 2.3:1.0, later adjusted to 2.1:1.0, and neither ratio significantly different, statistically, from the 2.0:1.0 of β -carotene in oil, another treatment in the same research. A third treatment, spinach, showed a 7.5:1.0 conversion. In each case the sophisticated research design measured the efficiency of conversion of β -carotene to circulating retinol following a single meal containing the β -carotene source. The publication noted that ‘In summary, the high bioconversion efficiency of Golden Rice β -carotene to vitamin A shows that this rice can be used as a source of vitamin A. Golden Rice may be as useful as a source of preformed vitamin A from vitamin A capsules, eggs or milk to overcome VAD in rice-consuming populations’ [4, 6].

These results were clearly very different from Greenpeace’s 2001 prediction. Instead of welcoming the excellent news of a potentially useful additional VAD intervention, Greenpeace, on August 29, 2012, issued a further press release in

² At Baylor College of Medicine, Children’s Nutrition Research Center, Houston, USA

China from their Netherlands HQ: ‘Greenpeace alarmed at US-backed GE food trial on Chinese children’..‘It is incredibly disturbing to think that an American research body used Chinese children as guinea pigs for genetically engineered food,... The relevance of this study is questionable,...Nor does high conversion rate solve all the technical, environmental and ethical issues around Golden Rice’ [6, 10]. Greenpeace claimed that the Chinese authorities agreed to halt the research before it started³ but were unable to substantiate their claim to an independent journalist. The press release created hysteria in China and, 4 years after the field research had been completed, caused the parents of the subject children consternation.

Tufts University IRB carried out an investigation and concluded that there were ‘no concerns related to the integrity of the study data, the accuracy of the research results or the safety of the research subjects. In fact, the study indicated that a single serving of the test product, Golden Rice, could provide greater than 50 percent of the recommended daily intake of vitamin A in these children, which could significantly improve health outcomes if adopted as a dietary regimen’ Tufts also noted that ‘the research itself was found not to have been conducted in full compliance with IRB policy or federal regulations’ [43].

Eventually following this Greenpeace Press release, Tang et al. (2012) was retracted by the American Society of Clinical Nutrition in 2015 for procedural reasons. The full details of this and other impediments to Golden Rice’s development are given elsewhere [6, 9, 10, 43].

Separately, the Chair of the Tufts IRB, a computer scientist, in complaint to the publisher of one critical review of the case [10], wrote: ‘There was no research ethics committee or IRB review and approval in effect for the study when it was conducted in 2008’ This gross error of fact, with reference to the NIH grant and related IRB authorisations quoted above, itself calls into question the professionalism or objectivity of the 2012 Tufts IRB review which led to the retraction. (The research sophistication and quality of the retracted paper can be reviewed online [44]).

Henry Miller, a physician, molecular biologist and the founding director of the US Food and Drug Administration (FDA), commented in 2015 on the retracted paper: ‘A 2012 article in the nutrition literature might have been the most momentous contribution to public health worldwide since Dr. Jonas Salk’s announcement of the polio vaccine. The operative phrase is might have been, because intimidation, politics and the dishonest, anti-science efforts of NGOs to impugn the research have delayed the translation of its findings to life-saving interventions for millions of children. Why do anti-genetic engineering activists want to save the whales but let children go blind and die?’ [45].

The data generated by the above-mentioned research allow determination of the proportion of the estimated average requirement (EAR) the β -carotene content of Golden Rice can provide to children and adults (**Table 2**). If Golden Rice was the sole source of β -carotene in the diet, 50% of the EAR is sufficient to combat VAD [46]. Many nutritionists consider that supply of 30–40% of the EAR will be sufficient to combat VAD because the biofortified staple crop is seldom the only source of β -carotene. (The recommended daily allowance—RDA—which implies maintenance of 3-months liver stores of vitamin A, is not required to combat VAD.) The calculations (**Table 2**) use the β -carotene levels observed in different Golden Rice cultivars (e.g. RC82, BR29, IR36, IR64) of Golden Rice GR2E 2 months after harvest, when degradation has stabilised. A 6% loss of β -carotene in cooking Golden Rice, or 25% loss of β -carotene when a Golden Rice meal is parboiled first, and then reheated, has not been taken into account.

³ <http://www.greenpeace.org/eastasia/news/blog/24-children-used-as-guinea-pigs-in-genetically/blog/41956/>

Amount of β -carotene in Golden Rice $\mu\text{g/g}$	Rice consumption per day (g of dry rice before cooking)	Percentage of EAR provided
β-carotene to circulating retinol bioconversion rate: 2.1:1 (e.g. children)		To a child^a
4.0	40	36%
4.0	100	91%
6.0	40	54%
6.0	100	136%
11.2	40	102%
11.2	100	254%
β-carotene to circulating retinol bioconversion rate: 3.8:1 (e.g. adults)		To an adult
4.0	40	20%
4.0	100	50%
6.0	40	30%
6.0	100	75%
11.2	40	56%
11.2	100	140%

^aFor 1- to 3-year-old child, 100% of EAR is 210 μg RAE/day. An EAR that does not ensure adequate stores but is enough for normal dark adaptation is set at 112 μg ~50% EAR [46]

Table 2.

The potential for Golden Rice to deliver the estimate average requirement of β -carotene, as a source of vitamin A, to 1–3-year-old children and adults.

3.3 Is Golden Rice safe?

Golden Rice differs from white rice only in that it contains β -carotene, that is, provitamin A, which the human body converts to vitamin A. Golden Rice contains no vitamin A itself. So the question about safety relates principally to β -carotene, which is anyway ubiquitous in a balanced human diet and the environment.

At the levels found in food, β -carotene is a safe source of vitamin A, and classed as ‘generally recognised as safe’ (GRAS), by the United States Food and Drug Administration (US FDA) [47, 48]. At these physiological doses, consumption of β -carotene over several years has no adverse health effects [49–52]. The human body only converts to vitamin A, in the form of circulating retinol, the amount of β -carotene necessary, with the rest being excreted or stored unchanged in body tissues (e.g. fat, liver, etc.). It is impossible to induce vitamin A toxicity by consuming β -carotene (pers. comm. Dr. R Russell).

In all β -carotene-containing crops, immediately after harvest the level of β -carotene reduces. For Golden Rice carotenoid degradation mechanisms have been thoroughly investigated⁴ and the products of degradation quantitated. Additionally, 102 plant food items from Philippine markets, together with orange- or yellow-coloured soft drinks, as well as non-gmo field grown, in all cases, orange maize cobs and yellow cassava storage roots from Zambia, and orange-fleshed sweet potato tubers from Uganda, were analysed for the cleavage products of β -carotene, apocarotenoids [53]. The potential risks arising from ‘aberrant plant carotenoid synthesis’ [54] in genetically modified plants, including Golden Rice, or from non-gmo crops biofortified with pro-vitamin A, have been thoroughly investigated, the authors

⁴ Golden Rice cv. Kaybonnet was investigated because it was available [5] and has high degradation potential. Kaybonnet is not a cultivar that will be used anywhere.

reporting that ‘Our analysis and quantification of β -carotene derived cleavage products across biofortified and non-biofortified crop plant tissues combined with the calculation of potential exposure document no reason for concern’ [53].

For the formal regulatory approvals for the use of a gmo crop in food, as animal feed or in food or feed processing, on a country by country basis, detailed data sets have to be submitted. For permission to grow a gmo crop in a country, additional data have to be generated⁵ and submitted showing environmental safety.⁶ The ‘food, feed and processing’ data package developed for Golden Rice GR2E is extensive (42 megabytes of data). It is available without cost to all Golden Rice licensee countries consistent with long-standing Golden Rice Humanitarian Board policy. Here are the key summaries of the regulatory data submission made in the Philippines:

“PROPOSAL FOR DIRECT USE AS FOOD AND FEED, OR FOR PROCESSING Provitamin A Biofortified GR2E Rice

Description of the Regulated Article for Direct Use

*Rice event GR2E (IR-ØØGR2E-5) was developed using recombinant-DNA techniques to express elevated levels of provitamin A (mainly β -carotene) in the rice endosperm, which is converted in the body to vitamin A. GR2E rice was produced by *Agrobacterium tumefaciens*-mediated transformation of embryogenic rice calli with plasmid pSYN12424 resulting in the introduction of the phytoene synthase (*psy1*) gene from *Zea mays* (*Zmpsy1*), the carotene desaturase I (*crt1*) gene from *Pantoea ananatis*,⁷ and the phosphomannose isomerase (*pmi*) gene from *Escherichia coli* as a selectable marker.*

GR2E rice is intended to complement existing efforts to mitigate vitamin A deficiency by supplying consumers in societies whose diet is primarily rice-based with a portion of the estimated average requirement for vitamin A.

Summary of Potential Effects on Human and Animal Health

The safety assessment of GR2E rice evaluated information on the history of safe use of rice as a crop, the source of donor genes introduced into GR2E rice, the molecular characterisation of the modified plant, the stability of the inserted genetic elements, characterisation of new proteins produced in the modified plant and their expression levels, the potential allergenicity and potential toxicity of the newly expressed proteins, and the nutrient composition of GR2E rice compared to conventional rice.

Molecular characterisation of the introduced DNA within event GR2E confirmed the presence at a single insertion site of one copy of the inserted DNA that was stably inherited over multiple generations as a single genetic locus per Mendelian rules of inheritance. Expression of the ZmPSY1 and CRTI proteins was limited to the rice endosperm with maximum concentrations in mature grain of approximately 0.245 and 0.03 ppm, respectively. The PMI protein was expressed in all rice tissues measured and accumulated to maximum concentrations of 1.89 and 0.796 ppm in mature grain and straw, respectively.

A tiered “weight-of-evidence” approach was followed in assessing the safety of the ZmPSY1, CRTI, and PMI proteins expressed in GR2E rice. The ZmPSY1 and CRTI proteins did not display significant amino acid sequence similarity with known allergens nor were there any primary sequence structural alerts for potential toxicity based on similarity searches against a database of known and putative protein toxins. Both ZmPSY1 and CRTI were rapidly and completely digested in the presence of simulated gastric fluid containing pepsin, and the enzymatic activity of both proteins was destroyed following treatment at temperatures well below those used during cooking.

⁵ Agronomic/phenotypic data and related studies for GR2E Golden Rice can be found at: http://www.agbios.org/?page_id=767

⁶ The regulations exist and have to be complied with. Nevertheless, many disagree that they are justified [6, 10, 59, 73–76].

⁷ This is the same organism as *Erwinia uredovora* [2, 5]. The name was changed.

Due to the non-food source of the crtI gene, acute oral toxicity testing of CRTI protein in mice was conducted as a further assurance of safety and demonstrated a lack of any observable adverse effects at a dose of 100 mg/kg body weight, which represents at least a 115,000-fold margin of exposure relative to any realistically conceivable human dietary intake from GR2E rice.

Based on its presence in a wide range of food and feedstuffs derived from genetically engineered maize lines, and on the extensive history of prior regulatory reviews in the Philippines, additional characterisation of the PMI protein was unnecessary. Previously submitted safety studies reviewed in the context of other genetically engineered plant events are directly applicable to the safety assessment of PMI protein expressed in GR2E rice.

The genetic modification resulting in GR2E rice was only intended to increase levels of provitamin A (primarily β -carotene) in the rice endosperm. To confirm the intended effect and the lack of any meaningful unintended consequences of the genetic modification, compositional parameters were compared between GR2E rice and control, unmodified, rice. Compositional analyses were performed on samples of rice grain and straw obtained from PSB Rc82 rice containing event GR2E and near-isogenic control PSB Rc82 rice that was grown at four separate sites in the Philippines during 2015 and again in 2016. The compositional assessment included analyses for proximates, fibre, and minerals in samples of straw, and analyses for proximates, minerals, vitamins, amino acids, fatty acids, vitamins, and key anti-nutrients in grain samples. Samples of processed bran derived from GR2E and control rice were also analysed for proximates, fibre, and minerals.

Among the 69 compositional components that were tested for in samples of GR2E and control PSB Rc82 rice grain, and 10 components that were assessed in derived bran and straw samples, the only statistically significant difference observed from the multi-year combined-site analysis was for stearic (C18:0) acid, a minor fatty acid component, measured in grain samples (not including the intended difference in provitamin A levels). Except for β -carotene and related carotenoids, the compositional parameters measured in samples of GR2E rice, including stearic acid, were within or similar to the range of natural variability of those components in conventional rice varieties with a history of safe consumption. Overall, no consistent patterns emerged to suggest that biologically meaningful changes in composition or nutritive value of the grain or straw had occurred as an unexpected, unintended consequence of the genetic modification.

Collectively, the studies performed for GR2E rice have not identified potential health and safety concerns, and support the conclusion that food and/or livestock animal feed derived from provitamin A biofortified GR2E rice is as safe and nutritious as food or feed derived from conventional rice varieties.”

Although it is hard to imagine that such golden grains of polished Golden Rice could be included in commercial shipments of white rice by accident, in the modern world, any such inclusion could be damaging to international trade. To prevent even such an unlikely situation, the Golden Rice regulatory data have been submitted to regulatory authorities in countries which import rice, where VAD is not a public health issue. As a result of these data submissions, Golden Rice GR2E has been confirmed as safe for use as food, in feed, and for processing by the government’s regulatory authorities in Australia, Canada, New Zealand and USA. The regulatory deliberations and decisions are publicly available: Australia and New Zealand,⁸ Canada⁹ and the USA.¹⁰

⁸ <http://www.foodstandards.gov.au/code/applications/Pages/A1138GMriceGR2E.aspx>

⁹ <https://www.canada.ca/en/health-canada/services/food-nutrition/genetically-modified-foods-other-novel-foods/approved-products/golden-rice-gr2e.html>

¹⁰ <https://www.accessdata.fda.gov/scripts/fdcc/?set=Biocon&id=IR-00GR2E-5>

Because in these industrialised countries rice forms only a tiny proportion of standard diets which already contain ample sources of vitamin A, the amounts of β -carotene in Golden Rice would have no significant additional nutritional benefit there. Comments to this effect by the US regulatory authorities were implied by anti-gmo crop opponents to be applicable also in developing countries where the dietary situation is completely different. Such implication has been rebutted by the US FDA [55]. The regulators in these industrialised countries concurred with Tufts University's statement issued after their investigation of the 'Chinese children' research: '... Golden Rice, ...could significantly improve health outcomes if adopted as a dietary regimen' [43].

Further regulatory submissions have been made, and registrations are expected, in countries where VAD is a public health problem [56]. In the Philippines the process is not yet complete; nevertheless various government departments have already expressed their support.¹¹

Gmo crops have been vilified by activist groups since the 1990s. 'Frankenstein foods' were used in a letter in the *New York Times* on June 16, 1992. *The Daily Mail*, a UK newspaper, headlined the same phrase in February 1998 and subsequently and extensively used 'Frankenfoods' [57]. The 'anti-gmo groups', in various guises, have been critical of Golden Rice, a gmo crop, since 2001 [6, 10, 40].

Notwithstanding this opposition, all independent scientific institutions globally have determined, for many years, that there is no inherent danger to crop plants, or the human use of crops plants, or the environment from transferring genes from one organism to another, to create gmo crops, also known as genetically engineered (GE) crops, including transfer of genes between species which cannot sexually reproduce to transfer the genes 'naturally' [6, 58, 59].

Norero [60] provides a list of more than 240 independent science institutions from all over the globe which have commented on the safety of the techniques of genetic modification. A particularly clear reference comes from the heart of the geography politically most opposed to gmo technology, the European Commission of the European Union:

'The main conclusion to be drawn from the efforts of more than 130 research projects, covering a period of more than 25 years of research and involving more than 500 independent research groups, is that biotechnology, and in particular GMOs, are not per se more risky than, for example, conventional plant breeding technologies' [61].

At the time of writing, 141 Nobel Laureates, of about 290 living, have signed an open letter dated June 29, 2016, addressed to the leaders of Greenpeace, the United Nations and governments around the world calling for the campaign against Golden Rice specifically, and crops and foods improved through biotechnology in general, to cease 'Opposition based on emotion and dogma contradicted by data must be stopped' [8]. The letter also has the support of more than 13,000 other scientists and citizens.

3.4 Is Golden Rice economic?

Golden Rice seed and regulatory data packages are available—without cost—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 [4]. The licences

¹¹ http://www.agbios.org:8085/wp-content/uploads/2018/07/Consolidated-Report-gr2e-rice_revised-1.pdf

ensure that the inventor's, Professors Potrykus and Beyer, objectives for their donated technology cannot be frustrated: only publicly owned rice varieties can be used, and the nutritional trait cannot be 'stacked' with any other gmo trait, unless the latter is also under the control of the public sector. There will be no charge to growers or consumers for the nutritional trait: Golden Rice will cost the same as white rice. Golden Rice homozygous seed, which breeds true generation to generation, will be provided by public-sector rice breeders. All small-holder family farmers—responsible for 80% of global rice production [38]—will eventually have access to it, with (except for commercial export—not a resource-poor farmer activity) no limitations on planting or replanting, harvest or sale of seed or grain.

Addressing micronutrient malnutrition, including VAD, is consistently ranked by the Copenhagen Consensus process, as the first, or at least within the top 5, most cost-effective investments with the potential to address the world's 30 most intractable problems [62–64]. Investing in alleviating malnutrition would repay \$45 for each dollar invested compared with \$36 from fighting malaria and \$10 from combatting HIV [65].

Compared with the World Bank standard, or the full cost of provision of vitamin A capsules, a common dietary supplement intervention for VAD since the early 1990s [15, 22], the cost of Golden Rice to save each disability-adjusted life year (DALY) is expected to be very low, perhaps US\$0.5 [9, 66, 67].

Costs (US\$ of 2006)	Highest efficiency	Lowest efficiency		
World Bank cost-effective standard ^a	\$200	\$200		
Providing vitamin A capsules ^a	\$134	\$599		
Vitamin A fortification of food ^a	\$84	\$98		
Golden Rice, India @ 12:1 ^a	\$3.10	\$19.4		
Golden Rice, Bangladesh 6:1 ^b & 12:1 ^c	\$4.0 ^b	\$54.0 ^c		
Golden Rice, above ^{a,b,c} adjusted 2.1:1 ^d	\$0.5	\$1.4	\$3.4	\$9.5

The earlier studies occurred before these bioconversion ratios had been elucidated

^aSource: [66]

^bSource: [67]

^cSource: [67]

^dSource: From the bioconversion efficiency 2.1:1 **Table 2**

Table 3.

Relative costs of saving one disability-adjusted life year using different sources of vitamin A and, for Golden Rice, different bioconversion ratios of β -carotene to circulating vitamin A.

Economists have calculated that conservative adoption of Golden Rice would benefit the gross domestic product (GDP) of Asian countries by US\$6.4 billion (value in US\$ of 2005) annually through increased productivity enabled by reduced vitamin A deficiency-induced sickness, and improved eyesight, and ~US\$17.4 billion (value in US\$ of 2005) if Golden Rice adoption encouraged adoption of other nutritional traits in rice [68]. Recently, HarvestPlus has exceeded target levels of iron and zinc in rice, which they were unable to achieve by conventional breeding, using gmo techniques [16]. Genetic modification has also been used to introduce folate into rice endosperm [27, 69]. The delay to the introduction of Golden Rice in India has been calculated to have cost Indian GDP US\$199 million per annum for the decade from 2002 [70, 71], in total about US\$1.7 billion (value in US\$ of 2014).

Goal #	Goal	Potential impact of biofortification
1	No poverty	Micronutrients in staple crops reduce effects
2	Zero hunger	Whole populations will be micronutrient sufficient
3	Good health	Provitamin A, Fe, Zn, Folate: less morbidity and mortality
4	Quality education	Pupils learn when adequately fed: Fe important
5	Gender equality	Biofortified staples available to whole population
7	Decent work and economic growth	Increased productivity from biofortified rice alone will add US\$17.4 (in US\$ of 2005) to Asian GDP

Table 4.
Biofortification and some Sustainable Development Goals 2015–2030.

Adoption of biofortified crops, including Golden Rice, will facilitate attainment of six of the most important Sustainable Development Goals 2015–2030 (**Table 4**). The standard costs used by the economists referenced in **Tables 3** and **4** [62–64, 66, 67] refer to the costs of supplementation with vitamin A capsules. As when using Golden Rice, the vitamin A source has zero cost to the grower or consumer; the cost benefit of Golden Rice will be very significantly better than using vitamin A capsules.

4. Conclusions

Vitamin A deficiency remains a huge public health problem despite existing interventions. Biofortification of staple foods is a new policy priority internationally. Golden Rice is safe. There is excellent human evidence that it will work. It is expected to be extremely cost-effective.

For successful adoption of Golden Rice as an additional intervention for vitamin A deficiency, the support of public health professionals is critical.

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Dr. Robert Russell chaired the ‘panel on micronutrients’ the output of which, published in 2001 [72], created the US Governments’ dietary reference intakes for 14 micronutrients, including vitamin A. Also, in 2001, he joined the Golden Rice Humanitarian Board. I am grateful for his nutritional advice and instruction over the intervening years and for checking my calculations in connection with **Table 2** and the surrounding text. I have known Dr. Guangwen Tang almost as long and thank her for providing, years ago, copies of the original documents which allowed me to construct with confidence the chronology of the IRB permissions 2003 and 2008 in the USA and China, all referring to the same NIH grant. Since 2015, the project has benefited from another specialist professional, Dr. Donald MacKenzie, who, aside from managing the GR2E regulatory data package generation, compilation and submissions, has also provided the web-links, which I have listed as footnotes in the ‘Safety’ section of this chapter. Thank you, Don, for your critically important work.

Conflict of interest

The author declares no conflict of interest.

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