REVIEW ARTICLE

The socioeconomics of genetically modified biofortified crops: a systematic review and meta-analysis

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Building upon the growing interest and research on genetically modified (GM) biofortification, its socioeconomic potential has been increasingly examined. We conducted two systematic reviews and meta-analyses to provide comprehensive evidence of consumers' willingness to pay (11 economic valuation studies, 64 estimates) and cost-effectiveness/benefits (five economic evaluation studies, 30 estimates). Worldwide, consumers were willing to pay 23.9% more for GM biofortified food crops. Aside from crop and design-related differences, information provision was deemed crucial. Positive information (nutrition and GM benefits) is associated with the highest consumer willingness to pay, compared with negative, objective, and conflicting GM information, especially when negative information was mentioned last. This health intervention would reduce the aggregated micronutrient deficiency burden in Asia (15.6 million disability-adjusted life years (DALYs)) by 12.5–51.4%, at a low cost of USD 7.9–27.8 per DALY in a pessimistic and optimistic scenario, respectively. Given that GM biofortified crops could tackle hidden hunger in a cost-effective and well-accepted way, its implementation is worth pursuing. A case study on folate biofortification further elaborates on the importance of socioeconomic research and the determinants of their market potential.

Keywords: willingness to pay; cost-effectiveness; golden rice; folate-biofortified rice; genetic modification

Introduction

Micronutrient malnutrition is still widespread in children and women from poor, developing regions. Currently, one out of three people in the world suffers from a chronic deficiency of one or, more often, multiple essential vitamins and minerals.[1,2] While this global affliction is often referred to as hidden hunger, due to an inferior quality of food consumption rather than a lack of food as such, its consequences are far from hidden. With a share of 7% of the annual global burden of disease,[3] micronutrient malnutrition is known to have far-reaching adverse consequences for both public health and economic development.

Of the large array of nutrition-sensitive interventions, agriculture–nutrition linkages are worth considering,[4,5] given that various plant-based foods provide most of the nutrients required for good health. Malnourished populations usually lack access to such micronutrient-rich foods, as they rely on few, less-expensive major staple crops, which are characterized by low micronutrient concentrations. As a consequence, agriculture is increasingly advocated as a means not only to reduce hunger through enhancing productivity but also to tackle hidden hunger through improving food quality.

Against this background, biofortification has been introduced as a sustainable, prorural, propoor strategy to improve micronutrient intake levels in target populations[6–8] and a valuable complement to supplementation and fortification.[9,10] Biofortification refers to all strategies that enhance

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the nutritional quality of food crops, either through traditional plant breeding (conventional biofortification), fertilizer application (agronomic biofortification), or intragenic/transgenic plant breeding (genetically modified (GM) biofortification). Since 2003, substantial progress has been made by the HarvestPlus program through testing or releasing various conventional biofortified crops in more than 50 priority countries.[11,12] While there is still unexplored potential,[13,14] this program already successfully targets vitamin A, iron, or zinc levels in seven key crops (cassava, corn, sweet potato, bean, pearl millet, rice, and wheat) and aims to introduce additional varieties in the near future.

Notwithstanding the growing evidence on the successes of conventional biofortification, as studies on breeding efforts and efficacy and effectiveness trials have shown,[8,10,15] biotechnology-based approaches are sometimes needed (e.g., when the nutrient is not naturally present in the target crop (e.g., vitamin A–enriched golden rice)[16] or is present only in marginal amounts, or when conventional methods are insufficient to obtain substantial enhancement (e.g., folate biofortification of rice[17,18])). Furthermore, they can increase micronutrient levels in the desired tissue, such as cereal endosperm, to avoid postmilling micronutrient losses through the outer layers.

Despite the various promising efforts in research and development for the use of biotechnology for developing micronutrient-rich crops[8,19,20] (e.g., effectiveness of golden rice[21] and the stability of folate-biofortified rice[22]), it is plagued by controversy while facing various political and regulatory hurdles,[23,24] which also impedes commercialization of the first GM biofortified crop. Aside from these forces, the success of their future commercialization will also hinge on its societal impacts. As a policy intervention, such consumer-oriented (second-generation) GM crops are expected to generate substantial health effects at a relatively low cost, in line with the high cost-effectiveness of conventional biofortified crops.[25]

Moreover, it will also be key to introduce such bioengineered biofortified crops under the right market conditions. To effectively support regions where the need to enhance micronutrient intake levels through such GM crops is highest, consumers should first embrace these crops. Besides technical prerequisites, particularly the bioavailability and stability of the targeted vitamins or minerals, it is the consumer who will ultimately determine the magnitude of the reduction of micronutrient malnutrition through GM biofortified crops. When looking at consumer studies on conventional biofortified crops,[26] positive reactions were generally reported by target populations, in terms of both sensory acceptance and willingness to pay (WTP). Whether or not nutrition traits are visible (e.g., vitamin A–enriched yellow corn), sensory attributes of conventional biofortified crops are often equally or—especially in case health information is provided—better evaluated than their regular counterparts. These positive findings are reflected in consumers' purchase behavior, as they were prepared to pay premiums between 6% and 50%.

Similar to conventional biofortified food research, socioeconomic studies on GM biofortified crops is growing to demonstrate proof of concept. Consequently, this paper presents a systematic review and meta-analysis on the socioeconomics of such GM crops with higher micronutrient levels. Therefore, the focus will be on (1) consumers' WTP (economic valuation) and (2) potential cost-effectiveness/cost–benefits (economic evaluation). Given that several studies are targeted toward (currently) hypothetical GM biofortified staple crops, this meta-analysis will estimate potential cross-product demands and ex-ante health effect sizes. In addition, (3) folate-biofortified rice will be reviewed as a case to provide an in-depth analysis of socioeconomic evidence, mainly focusing on the determinants of acceptance, WTP, health impact, and cost-effectiveness. A compilation of such evidence could lead to a better understanding of the potential value of GM biofortification, hence providing the scientific rationale for its future commercialization.

Methods

This systematic review and meta-analysis has to be situated in the field of agricultural economics. Therefore, we followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[27] that are applicable and relevant to this field, as well as the procedures in reviews on GM food valuations.[28,29]

Eligibility criteria

By searching the Institute for Scientific Information Web of Science and AgEcon databases, peer-reviewed socioeconomic studies that investigated (1) WTP as a measure of consumer preference (economic-valuation studies) and (2) cost-effectiveness or cost–benefits of GM biofortified crops (economic-evaluation studies) were eligible for systematic review and meta-analysis.

Additional and more specific inclusion and exclusion criteria were used to narrow the search down to the relevant studies. To be included in both the systematic review and meta-analysis for WTP, a study had to be written in English or French, target a specific micronutrient and GM crop, and report a WTP estimate (i.e., percentage premium or mean from which the former could be derived). A study was excluded if it determined consumer preference without economic-valuation methods (e.g., through sensory evaluation (nonexistent for nonapproved GM biofortified crops) or hedonic testing techniques[30,31]), or if it expressed WTP only as a percentage of a sample intended to purchase GM biofortified crops.[32,33] For cost-effectiveness and cost–benefits, only English or French studies analyzing a specific GM crop with a higher level of one or more specific micronutrients were retained. Thereby, a study must have reported an outcome measure based on the disability-adjusted life year (DALY) approach (e.g., cost to gain a DALY through the introduction of GM biofortified crops (cost-effectiveness), a benefit–cost ratio (BCR), or an internal rate of return (IRR) (cost–benefits)). As a consequence, burden and health-impact indicators (i.e., DALYs lost/gained and percent reduction in disease burden) could also be obtained. The DALY method is the standard measurement tool of the World Health Organization (WHO) for global burden of disease assessment and evaluation of the contribution of health interventions in alleviating disease burden.[34,35] More recently, it has been applied to measure the cost-effectiveness of conventional[25] or GE[36] biofortified crops (for a methodological description, see Ref. 37).

Four outcome variables were eligible for meta-analysis on both topics: percent WTP versus cost per DALY saved and percent IRR or BCR. The rationale behind this selection was the need for a common data parameter across, respectively, WTP and cost-effectiveness/cost–benefit studies that is easily amendable to an appropriate meta-analysis.

Study search and selection

The search for articles was carried out in October 2015 and later updated on November 21, 2015. The search syntax was developed using Web of Knowledge and consists of a combination of the following keywords: (biofortification or similar; GM (crop/food) or similar; golden rice) AND (acceptance, purchase intention, preferences, valuation, WTP, or similar) for WTP studies on one hand, AND (health impact or similar; cost-effectiveness, cost–benefit or similar) for cost-effectiveness/cost–benefit studies on the other. This broad syntax with regard to biofortified crops was used because socioeconomic studies are not only limited to the use of universal terminology (for a discussion, see WHO efforts on defining biofortification[38]) but also refer to specific terms like "golden rice." This reduced the likelihood that relevant studies were omitted at an early stage. All papers ready for scrutiny were transferred to Endnote (version X7, Thomson Reuters), and doubles were removed. Two researchers conducted the search. The first step was based on title search for existence of keywords that were important to the research question at hand. An abstract screening followed to gauge additional relevance of studies, and finally those deemed important were subjected to an in-depth critical full article review. At every search step, a cross-check was made by each researcher, who reviewed 30% of both included and excluded articles of the other researcher as a way to ensure that a potentially relevant or irrelevant study is not omitted or selected, respectively. In case a consensus could not be reached, an external opinion was sought.

Data extraction

To have a comprehensive understanding of the characteristics of the studies, data extraction sheets were developed to facilitate coding of information (Tables 1 and 2). Information extracted from economic-valuation studies included crop, micronutrient, breeding technique, United Nations (UN) subregion, country of study, year of data collection, setting, subjects, sample size, method of data collection, nature of study, and the main findings (split up according to information treatment). On the basis of what was observed is the systematic review and for the purpose of performing a meta-analysis, the percentage premium was extracted from the preference studies as a

Table 1. Systematic review of willingness-to-pay studies on GM biofortified crops: overview of key study characteristics and outcome indicators

Crop	Micronutrient	Breeding technique	UN subregion	Country	Year	Setting	Subjects	Sample size	Method of data collection	Nature of study	Main findings (% premium)[a]	Reference
Rice	Vitamin A	Transgenic	North America	USA	2001	Urban	Adults	574	Mail survey (CV)	Hypothetical	19.5% (P_{NU})	40
					2004	Urban	Adults	501	Mail survey (CV)	Hypothetical	38.0% (P_{NU})	41
			Southern Asia	India	2006	Urban	Adults	712	Mixed-method study[b]	Hypothetical	19.5% (C_{NP})	42
					2009	Urban	Students	154	In-person survey (CV)	Hypothetical	3.8% (No)	43
			Southeastern Asia	Philippines	2006	Urban	Students	60	Experiment (choice exp.)	Non-hypothetical	33.3% (No) 53.3% (P_{GM}), 6.7% (N_{GM}), 20.0% (C_{PN})	44
								100	Experiment (auction)	Non-hypothetical	66.7% (No) 120.0% (P_{GM}), 0.0% (N_{GM}), –20.0% (C_{PN})	44
											40.0% (No) 60.0% (P_{GM}), –13.3% (N_{GM}), –6.7% (C_{PN})	45
	Folate	Transgenic	Eastern Asia	China	2008	Urban and rural	Adults	944	In-person survey (CV)	Hypothetical	34% (P_{NU})	46
					2011	Urban and rural	Students[c]	119	Experiment (auction)	Non-hypothetical	25.8% (P_{NU}), 21.5% (P_{GM}), 7.3% (N_{GM}), 7.9% (C_{PN}), 20.6% (C_{NP}), 12.9% (O_{GM}), 11.3% (C_{PNO})	47[d]
							Adults[c]	132	Experiment (auction)	Non-hypothetical	40.0% (P_{NU}), 36.5% (P_{GM}), 12.7% (N_{GM}), 43.1% (C_{PN}), 14.0% (C_{NP}), 36.0% (O_{GM}), 21.3% (C_{PNO})	47[d]
Cassava	Vitamin A	Transgenic	South America	Brazil	2006	Rural	Adults	414	In-person survey (CV)	Hypothetical	64% (No)	48
									In-person survey (CR)		70% (No)	48
Potato	Vitamin C	Intragenic	North America	USA	2007	Urban	Adults	98	Experiment (auction)	Non-hypothetical	60.8% (No), 49.8% (P_{GM}), –12.3% (N_{GM}), 12.8% (C_{PN}), 2.2% (C_{PNO})	49
		Transgenic	North America	USA	2007	Urban	Adults	98	Experiment (auction)	Non-hypothetical	62.3% (No), 13.7% (P_{GM}), –21.9% (N_{GM}), 0.0% (C_{PN}), –20.4% (C_{PNO})	49
Broccoli	Vitamin C	Intragenic	North America	USA	2007	Urban	Adults	98	Experiment (auction)	Non-hypothetical	34.8% (No), 93.9% (P_{GM}), –11.6% (N_{GM}), 26.9% (C_{PN}), 12.6% (C_{PNO})	49
		Transgenic	North America	USA	2007	Urban	Adults	98	Experiment (auction)	Non-hypothetical	32.6% (No), 37.7% (P_{GM}), –12.4% (N_{GM}), 12.4% (C_{PN}), –5.8% (C_{PNO})	49
Tomato	Vitamin C	Intragenic	North America	USA	2007	Urban	Adults	98	Experiment (auction)	Non-hypothetical	40.3% (No), 77.2% (P_{GM}), –11.3% (N_{GM}), 17.6% (C_{PN}), 17.1% (C_{PNO})	49
		Transgenic	North America	USA	2007	Urban	Adults	98	Experiment (auction)	Non-hypothetical	24.5% (No), 27.5% (P_{GM}), –21.0% (N_{GM}), –3.4% (C_{PN}), –14.6% (C_{PNO})	49

Continued

Table 1. *Continued*

Crop	Micronutrient	Breeding technique	UN subregion	Country	Year	Setting	Subjects	Sample size	Method of data collection	Nature of study	Main findings (% premium)[a]	Reference
Apple	Vitamin C	Transgenic	Australia and New Zealand	New Zealand	2005	Urban	Adults	146	Experiment (auction)	Non-hypothetical	48.0% (No)	50

CR, contingent ranking; CV, contingent valuation; No, no information; P_{NU}, positive information (nutrition benefits); P_{GM}, positive information (GM benefits); N_{GM}, negative information (GM risks); O_{GM}, objective; C_{PN}, conflicting information ($P_{GM} + N_{GM}$); C_{NP}, conflicting information ($N_{GM} + P_{GM}$); C_{PNO}, conflicting information ($P_{GM}+N_{GM}+ O_{GM}$).

[a] Percent premium for GM biofortified food over the conventional counterpart. Average premiums are presented, unless information was given (information treatment code between brackets). Negative values refer to a discount. Positive information was mainly derived from statements of probiotech organizations/companies, while negative information was commonly based on antibiotech statements. For a representative example, see Ref. 49.

[b] In-person ($n = 602$) and online survey ($n = 110$); WTP elicited through random utility method.

[c] Women of childbearing age.

[d] Some of the values were derived from raw data of the study or other publications related to the same study.[51,52]

dependent variable. Together with the variables from the systematic review, these data constitute the metadata. In studies where a premium was not explicitly reported but rather means were stated, the following formula was used:

$$\text{WTP (\% premium)} = \frac{\bar{x}\,(\text{WTP}_{\text{biofortified}}) - \bar{x}\,(\text{WTP}_{\text{non-biofortified}})}{\bar{x}\,(\text{WTP}_{\text{non-biofortified}})} \times 100.$$

If the premium for the nonbiofortified crop was not available, researchers used the market price. In case regression models were used, percentage premiums were derived from the coefficients. Only a few studies reported point estimates and confidence intervals, which are important for a meta-analysis. As a consequence, it was necessary to use sample sizes that were universally reported as a measure of precision (weighting variable) to cater for variability that potentially exists in WTP estimates. This has also been expressed in another GM food review.[28] Multiple estimates included from single studies were nonoverlapping because their measurement was based on a categorization of methodological or contextual variables (e.g., information treatments, crop, nutrient, and data collection method).

With respect to cost-effectiveness and cost–benefits, the information sheet sought to obtain crop, micronutrient, UN subregion, country, burden, impact scenario, health impacts, cost-effectiveness, and cost–benefits. All cost-effectiveness indicators were expressed in USD per DALY gained. Cost–benefits were presented through BCRs or IRRs.

All socioeconomic findings related to the case study of folate-biofortified rice were derived from experts involved in the research consortium examining this crop.

Data analysis

First, in order to synthesize the data from the studies, two broad narrative overviews were made to describe characteristics of the studies used in the systematic reviews.

Second, for the meta-analysis on economic-valuation studies, mean WTP values (percentage premiums) and standard deviations were computed from the data, grouped by key study characteristics obtained from the systematic review. Comparisons within each characteristic were performed using analysis of variance tests for possible statistical differences. In addition, an overall metamean WTP summary was calculated using a random-effects (RE) model weighted by the sample size of each study. This controls for possible heteroscedasticity, due to the fact that—unlike the fixed-effects (FE) model—studies differed in a number of ways in which they were conducted (heterogeneity).[39] A specific analysis was run to illustrate the effect of information treatments on WTP.

Third, regarding the meta-analyses on cost-effectiveness and cost–benefits, average estimates based on study characteristics were computed in addition to simple overall means per economic-evaluation indicator (reported by at least two studies).

Results and discussion

Figure 1 depicts the process of the search strategy on economic valuation and evaluation. The

Table 2. Systematic review of cost-effectiveness and cost–benefit studies on GM biofortified crops: overview of key study characteristics and outcome indicators

					Burden (per year)		Health impacts (per year)			Cost-effectiveness (per year)	Cost–benefit		
Crop	Micronutrient	UN subregion	Country	Time horizon	Million DALYs lost	Impact scenario	% burden reduction	Million DALYs saved	Economic evaluation method	USD/DALY saved	IRR^{a} (%)	BCR	Reference
Mustard oil^{b}	Vitamin A	Southern Asia	India	20		Low		0.91	CEA/CBA	450.0^{a}	22		57
						High		1.69	CEA/CBA	403.0^{a}	43		57
Rice	Folate	Eastern Asia	China	30	0.31	Low	20	0.06	CEA	64.2			58
						High	60	0.19	CEA	21.4			58
			China, Shanxi	30	0.11	Low	20	0.02	CEA	120.3			59
						High	60	0.07	CEA	40.1			59
	Vitamin A	Eastern Asia	China	30	1.99	Low	17	0.33	CEA	18.1			58
						High	60	1.20	CEA	5.0			58
		Southern Asia	India	30	2.33	Low	8.8	0.20	CEA/CBA	19.4	29	26	60
											35	52	
											44	129	
						High	59.4	1.38	CEA/CBA	3.1	66	163	60
											77	327	
											93	816	
		Southeastern Asia	Philippines	16	0.27	Low	5.7	0.02	CBA		66		56
						High	31.5	0.08	CBA		133		56
	Multi-micronutrient	Eastern Asia	China	30	10.64	Low	11	1.19	CEA	9.6			58
						High	46	4.91	CEA	2.3			58

NOTE: All studies are hypothetical in nature (ex-ante economic evaluation studies), all biofortified crops are developed through transgenic breeding techniques or, in case of multivitamin-biofortified rice, through transgenic (vitamin A, folate) and conventional (zinc, iron) breeding techniques.

BCR, benefit–cost ratio; CBA, cost–benefit analysis; CEA, cost-effectiveness analysis; DALY, disability-adjusted life year; IRR, internal rate of return

[a] IRR represents the percentage yield per dollar spent per year. Therefore, each DALY saved is given a monetary value, either standardized (USD 500, USD 1000, or USD 2500 in India) or a national per capita income (USD 1030 in the Philippines).

[b] Derived from GM biofortified mustard seed.[61]

two searches resulted in an initial total of 7058 records, of which 3560 and 3498 studies refer to, respectively, economic-valuation and economic-evaluation search terms. After screening and full-text assessment, 11 and 5 articles, respectively, were included in the synthesis. We obtained 64 WTP estimates out of 11 consumer studies, each with a corresponding sample size, and we derived 30 estimates from the economic-evaluation studies. For each topic, key characteristics of each individual study will be summarized (Tables 1 and 2) before discussing the findings from the meta-analysis (Tables 3 and 4).

Willingness to pay for GM biofortified crops

Systematic review. The main characteristics of the selected studies on WTP for GM biofortified crops are summarized in Table 1 (64 estimates). Since 2001, when Lusk *et al.*[40] elicited consumer preferences for golden rice in the United States, 11 studies have reported WTP values for various GM biofortified crops.

Six food crops, of which three staple (rice,[40–47] cassava,[48] and potato[49]) and three nonstaple crops (broccoli,[49] tomato,[49] and apple[50]) were targeted. Except for the study of Colson *et al.*,[49] who also examined the use of intragenic breeding approaches (i.e., transferring genes from closely related species capable of sexual hybridization[53]), all studies looked at transgenic crops with a higher vitamin content, either vitamin A,[40–46] folate,[46,47] or vitamin C.[49,50] While, for nearly all products, there were estimates elicited in urban, developed settings, particularly in the United States, rice and cassava were also selected for examining reactions of consumers from developing countries, like India and the Philippines (golden rice),[40–45] China (folate-biofortified rice),[46,47] or Brazil (vitamin A–enriched cassava).[48] Except for a few studies using students as the target group, most of the WTP estimates refer to adults. Depending on the data-collection method and the nature of the study, the sample size ranged from 60 to 146 respondents for non-hypothetical experiments and from 154 to 944 respondents for hypothetical survey methods. While the former build upon experimental elicitation methods, such as choice experiments or experimental auctions (uniform, second, or

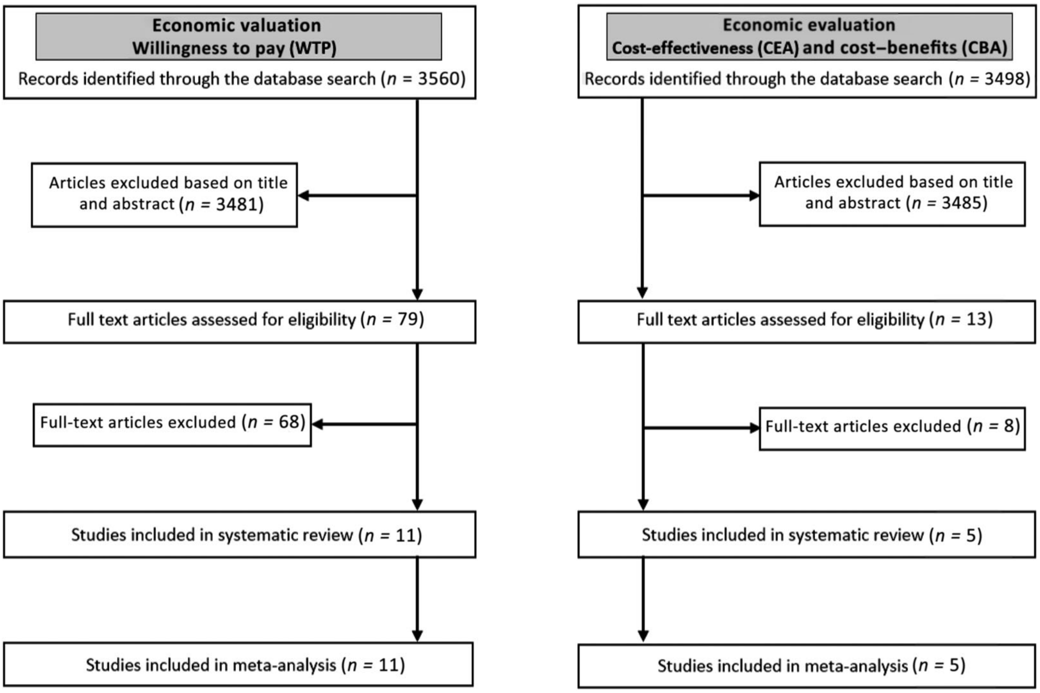

Figure 1. Flow diagram of study search, selection, and review.

random *n*th price), the latter employed contingent valuation/ranking techniques or random utility methods. Below, the key findings will be discussed for each crop, with particular attention to information effects (see Fig. 2).

Rice (vitamin A, folate). From the reviewed studies, two types of bioengineered rice were investigated, differentiated by the type of micronutrient. First, golden rice, currently the most advanced GM biofortified crop, was the subject of six studies.[40–43,45] Of these, two studies were carried out with urban consumers from North America.[40,41] Besides differences in year of data collection and sample size, the first study also incorporated a cheap talk script as a means to improve the validity of non-hypothetical survey estimates.[54] This might contribute to the variation in WTP between the studies (19.5–38.0%). The remaining four golden rice studies were all conducted in Asia: two in India[42,43] and two in the Philippines.[44,45] The design of the Indian studies was relatively similar, except for sample size and type of hypothetical valuation method. Depending on the targeted study, Indian consumers reported a low (3.8%)[43] to—when conflicting information about GM technology is shown—high (19.5%)[42] premium for this yellowish vitamin A–enriched rice variety. In the Philippines, two studies used a similar auction procedure, resulting in high premium levels of 40.0%[45] or 66.7%,[44] while one also conducted a choice experiment (33.3%).[44] When respondents were given specific positive information on GM technology, WTP values increased in all studies, from 53.3% up to a level of 120.0%. Much lower and even negative levels are reported for negative GM information, either alone (–13.3% to 6.7%) or after positive information (–26.7% to 20.0%). Second, the two studies on folate-biofortified rice examined consumers' WTP in Shanxi Province, a Chinese high-risk region for folate deficiency.[46,47] The 2008 survey[46] with 944 consumers reported an average price premium of 34.0%, while a more recent auction[47] with 251 subjects in 2011 revealed a similar premium in a non-hypothetical setting (33.2%), although valuations of the student sample (25.8%) were significantly lower than in the population-based sample (40.0%). The latter study also examined the role of GM information, using treatments based on positive, negative, or objective information or a combination. Adults exhibited a higher WTP for

Table 3. Meta-analysis on willingness-to-pay for GM biofortified crops

Variable	Sample size	No. of estimates (%)	Mean % premium (SD)	Reference
Crop			$P = 0.246$	
Rice	3647	31 (48.4)	24.7 (27.72)	40–47
Golden (vit. A)	2201	16 (51.6)	26.3 (37.31)	40–45
Folate	1446	15 (48.4)	23.0 (12.20)	46, 47
Cassava (vit. A)	828	2 (3.2)	67.0 (4.24)	48
Potato (vit. C)	196	10 (16.1)	14.7 (32.15)	49
Broccoli (vit. C)	196	10 (16.1)	22.1 (31.59)	49
Tomato (vit. C)	196	10 (16.1)	15.4 (29.75)	49
Apple (vit. C)	146	1 (1.6)	48.0 (0.00)	50
Micronutrient			$P = 0.372$	
Vitamin A	3029	18 (28.1)	30.8 (37.45)	40–45, 48
Folate	1446	15 (23.4)	23.0 (12.20)	46, 47
Vitamin C	734	31 (48.4)	18.4 (30.27)	49, 50
Breeding technique			$P = 0.513$	
Intragenic	294	15 (23.4)	27.4 (32.30)	49
Transgenic	4915	49 (76.6)	21.6 (28.9)	40–50
Country			$P = 0.246$	
Philippines	260	12 (18.8)	28.3 (42.75)	44, 45
China	1446	15 (23.4)	23.0 (12.20)	46, 47
India	866	2 (3.1)	11.7 (11.10)	42, 43
USA	1663	32 (50.0)	18.1 (29.51)	40, 41, 49
Brazil	828	2 (3.1)	67.0 (4.24)	48
New Zealand	146	1 (1.6)	48.0 (0.00)	50
Setting			$P = 0.099$	
Rural	828	2 (3.1)	67.0 (4.24)	48
Urban	2223	46 (71.9)	21.1 (33.01)	40, 41, 43–45, 49, 50
Rural and urban	2158	16 (25.0)	22.8 (11.82)	42, 46, 47

Variable	Sample size	No. of estimates (%)	Mean % premium (SD)	Reference
Subjects			$P = 0.937$	
Students	784	21 (32.8)	23.4 (33.03)	43–45, 47
Adults	4425	43 (67.2)	22.8 (28.18)	40–42, 46–50
Nature of study			$P = 0.236$	
Hypothetical	3713	7 (10.9)	35.5 (24.25)	40–43, 46, 48
Non-hypothetical	1496	57 (89.1)	21.4 (30.00)	44, 45, 47, 49, 50
Method of data collection			$P = 0.568$	
Experiment	1496	57 (89.1)	21.4 (30.00)	44, 45, 47, 49, 50
In-person survey	1926	4 (6.2)	42.9 (30.48)	42, 43, 46, 48
Mail survey	1075	2 (3.1)	28.8 (13.08)	40, 41
Mixed methods[a]	712	1 (1.6)	19.5 (0.00)	42
Type of information			$P = 0.000$	
Positive	2484	16 (25.0)	46.8 (28.86)	40, 41, 44, 45, 47, 49
Nutrition (P_{NU})	2270	5 (31.2)	31.5 (8.62)	40, 41, 46, 47
GM (P_{GM})	214	11 (68.8	53.7 (32.40)	44, 45, 47, 49
Negative GM (N_{GM})	215	11 (17.2)	−7.0 (11.76)	44, 45, 47, 49
Objective GM (O_{GM})	42	2 (3.1)	24.5 (16.33)	47
Conflicting GM	1155	22 (34.4)	7.7 (17.19)	42, 44, 45, 47, 49
Positive + negative (C_{PN})	227	11 (50.0)	8.2 (20.12)	44, 45, 47, 49
Negative + positive (C_{NP})	754	3 (13.6)	18.0 (3.54)	42, 47
Positive + negative + objective (C_{PNO})	174	8 (36.4)	3.0 (15.26)	47, 49
None	1313	13 (20.3)	44.7 (19.52)	43, 48, 50

Overall RE mean WTP % premium: 23.90 (SE 3.28)(CI 17.5–30.3)
Overall FE mean WTP % premium: 32.68 (SE 1.00)(CI 30.7–34.6)

Vit, vitamin; CI, confidence interval; P_{NU}, positive information (nutrition benefits); P_{GM}, positive information (GM benefits); N_{GM}, negative information (GM risks); O_{GM}, objective; C_{PN}, conflicting information ($P_{GM}+N_{GM}$); C_{NP}, conflicting information ($N_{GM}+P_{GM}$); C_{PNO}, conflicting information ($P_{GM}+N_{GM}+O_{GM}$); SD, standard deviation; SE, standard error; RE, random effect; FE, fixed effect.

[a] In-person ($n = 602$) and online survey ($n = 110$).

folate rice than students when providing positive information (36.5% vs. 21.5%), negative information (12.7% vs. 7.3%), objective information (36.0% vs. 12.9%), positive information followed by negative information (43.1% vs. 7.9%), and a combination of the three types (21.3% vs. 11.3%), but not when the negative treatment preceded the positive one (14.0% vs. 20.6%).

Cassava (vitamin A). In rural Brazil, Gonzalez *et al.*[48] administered a survey with 414 consumers to reveal their preferences for transgenic vitamin A–enriched cassava. Using two hypothetical valuation methods, Brazilian consumers were found to be prepared to pay 64.0% or 70.0% more for transgenic biofortified cassava.

Potato (vitamin C). An experimental auction study in North America focused on vitamin C–enriched potatoes—among two nonstaple crops—developed either through intragenic or transgenic breeding approaches.[49] In the no-information treatment, premiums for both potatoes are similar, 60.8% and 62.3%, respectively. However, when specific GM-related information is given, the intragenic biofortified potato elicits a substantial higher value than when a transgenic trait would be inserted: 49.8% versus 13.7% (positive), −12.3% versus −21.9% (negative), 12.8% versus 0.0% (positive + negative), 2.2% versus −20.4% (positive + negative + objective).

Nonstaple crops (broccoli, tomato, and apple). The study of Colson *et al.*[49] on intragenic and transgenic potatoes enriched with vitamin C was also used to determine WTP for two nonstaples, broccoli and tomato. Regardless of the breeding approach, consumers were willing to pay a premium for both products, when no information (32.6% and 34.8% for

Table 4. **Meta-analysis on cost-effectiveness and cost–benefits of GM biofortified crops, including current burden of disease and health impacts**

Variable	Burden mean (SD) million DALYS lost per year	Health impacts mean (SD)				Cost-effectiveness mean (SD)		Cost–benefit mean (SD)		Reference
		million DALYS saved per year		% reduction in burden per year		USD per DALY saved		IRR (%)		
		Low	High	Low	High	Low	High	Low	High	
Crop										
Mustard oil[a]		0.91 (0.00)	1.69 (0.00)			ICER: 450.00 (0.00)	ICER: 403.00 (0.00)	22.00 (0.00)	43.00 (0.00)	57
Rice	3.11 (4.32)	0.36 (0.48)	1.15 (1.97)	12.50 (5.89)	51.38 (12.62)	27.83 (24.64)	7.95 (9.04)	47.50 (26.16)	99.50 (47.38)	56, 58–60
Micronutrient										
Vitamin A	1.53 (1.10)	0.37 (0.39)	1.09 (0.70)	10.50 (5.84)	50.30 (16.28)	18.75 (0.92)[b]	4.05 (1.34)[b]	39.00 (23.64)	80.67 (46.76)	56, 58, 60
Folate	0.31 (0.00)	0.06 (0.00)	0.19 (0.00)	20.00 (0.00)	60.00 (0.00)	64.00 (0.00)	21.40 (0.00)			58, 59
Multi-micronutrient	10.64 (0.00)	1.19 (0.00)	4.91 (0.00)	11.00 (0.00)	46.00 (0.00)	9.60 (0.00)	2.30 (0.00)			58
Country										
India	2.33 (0.00)	0.56 (0.50)	1.54 (0.22)	8.80 (0.00)	59.40 (0.00)	19.40 (0.00)[b]	3.10 (0.00)[b]	25.50 (4.95)	54.50 (16.26)	57, 60
China	4.31 (5.54)	0.53(0.59)	2.10 (2.49)	16.00 (4.58)	55.33 (8.08)	30.63 (29.38)	9.57 (10.34)			58, 59
Shanxi	0.11 (0.00)	0.02 (0.00)	0.07 (0.00)	20.00 (0.00)	60 (0.00)	120.3 (0.00)	40.1 (0.00)			59
Philippines	0.27 (0.00)	0.02 (0.00)	0.08 (0.00)	5.70 (0.00)	31.50 (0.00)	–	–	66.00 (0.00)	133.00 (0.00)	56
Overall mean	3.11 (1.93)	0.45 (SE 0.20)	1.58 (SE 0.72)	12.50 (SE 2.63)	51.38 (SE 5.64)	27.83 (SE 12.32)[b]	7.95 (SE 4.52)[b]	39.20 (SE 7.61)	82.40 (SE 15.04)	

NOTE: If SD $= 0$, the metaresults are derived from single study findings. BCRs were only reported in Stein *et al.*[60] (see Table 3) and therefore not included in this meta-analysis.

DALY, disability-adjusted life year; ICER, incremental cost-effectiveness ratio; IRR, internal rate of return.

[a] Derived from GM biofortified mustard seed.[61]

[b] ICERs of vitamin A–enriched mustard oil in India were only included at crop level (for mustard oil), as other cost-effectiveness figures are based on data expressed in USD per DALY saved.

broccoli; 24.5% and 40.3% for tomato) or positive GM information (37.7% and 93.9% for broccoli; 37.7% and 77.2% for tomato) was given. While negative GM information led to a negative premium (discount) in all four cases, ranging from −11.3% to −21.0%, WTP values under the conflicting GM information (positive + negative) treatment were less positive for the transgenic traits (12.4% and 3.4% vs. 26.9% and 17.6% for intragenic traits), especially when objective GM information was included (−5.8% and −14.6% for transgenic traits vs. 12.6% and 17.1% for intragenic traits).

In New Zealand, Kassardjian *et al.*[50] discovered a relatively high premium (48.0%) for apples biofortified with vitamin C. As of today, this is the only economic valuation study on consumers' WTP for biofortified fruits.

Meta-analysis. Table 3 combines the WTP estimates based on study characteristics from the systematic review into a meta-analysis across all applicable studies. The overall (sample size) weighted mean premium for GM biofortified crops from the RE model is 23.9%, which is approximately 1.4-fold smaller than that from the FE model (32.68%), but a more realistic estimate justified by a significant heterogeneity test ($P = 0.000$; under the null hypothesis that all studies share a common effect size). In other words, consumers have exhibited positive preferences toward GM biofortified crops and are prepared to pay 24% more as compared with conventional crops. Below, mean WTP values are discussed with reference to product characteristics (crop, micronutrient, and technology), study characteristics (country, setting, subjects), methodology (nature of the study, method of data collection), and provided information.

Crop. For the type of crop valued, rice alone had nearly half the estimates (29 of 64). Across eight studies, consumers were prepared to pay an average premium of 24.1% for GM biofortified rice, with golden rice (26.3%) being valued slightly more highly than folate-biofortified rice (21.5%). Although consumer preferences for GM biofortified potato, broccoli, and tomato were derived from one study, with 10 estimates for each product, the average premiums differed (i.e., 14.7%, 22.1%, and 15.4%, respectively.) Furthermore, cassava and apple contributed the least number of estimates but obtained the highest value (premiums of 67.0% and 48.0%, respectively).

Micronutrient. Of the three micronutrients examined, seven studies on GM crops biofortified with vitamin A generated the highest mean WTP (30.5%, 18 estimates), followed by folate (21.5%, 13 estimates) and vitamin C (18.4%, 31 estimates), both from two studies each.

Technology. Although only one study also examined valuations of intragenic foods[49] (see Table 1 for a comparison at product level), the metaresults show

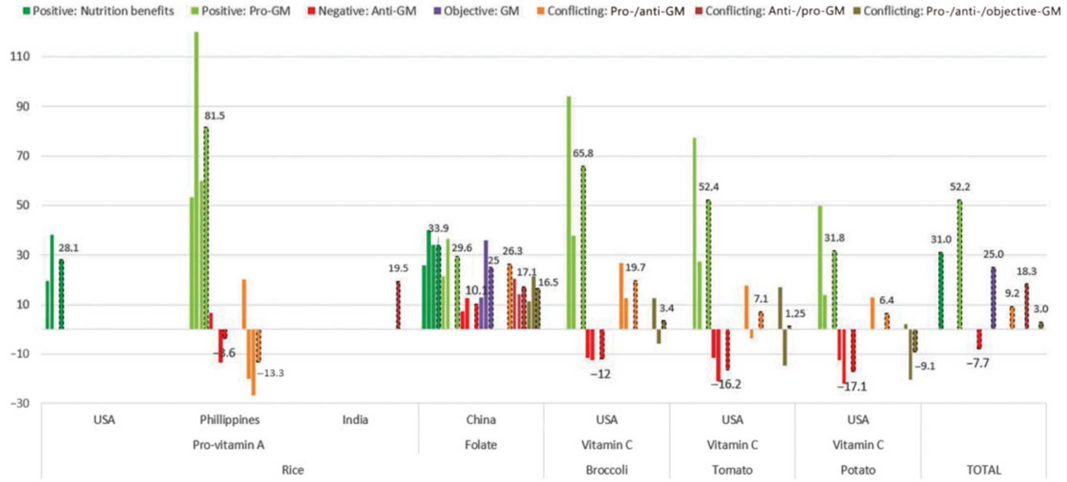

Figure 2. Willingness to pay for GM biofortified crops classified by information treatments, per country, micronutrient, and crop. Note: Bars with a dashed border refer to average mean values (percent premium) across studies, per information treatment. All other bars are based on single-study estimates (see Table 1).

that consumers were on average willing to pay a premium of 27.4% for intragenic biofortified broccoli, tomato, and potato together (15 estimates), which is 6.3% higher than the transgenic premium (21.1%, 47 estimates from 11 studies). As such, these results confirm the discrepancy of WTP values according to breeding technology.

Country. With 32 estimates from three studies, the United States is represented the most. Unexpectedly, the premiums for GM biofortified foods between people from developing or developed regions are not significantly different. Consumers in Brazil valued them the highest (67.0%), followed by those in New Zealand (48.0%), the Philippines (28.3%), China (21.5%), the United States (18.1%), and India (11.1%).

Setting. On the basis of 46 estimates from seven studies, the average premium of urban consumers was estimated at 21.1%, which resembles the 21.3% premium in both rural and urban settings (14 estimates from three studies). However, the average premium emanating from one study targeting rural consumers reached 67.0% (two estimates).

Subjects. Eight studies used adults in their sample of participants, resulting in 43 WTP estimates compared with 19 estimates derived from six studies for which only students were recruited. However, premium levels from both types of subjects did not differ (i.e., 22.4% and 22.8% for students and adults, respectively).

Nature of the study. Though insignificant, there is a difference in mean WTP between the five hypothetical and six non-hypothetical valuation studies: 35.5% (55 estimates) versus 21.0% (7 estimates). Given the lack of monetary incentives in the hypothetical setting, its lower premium is not a surprise and confirms findings in the economic-valuation literature (hypothetical bias).[55]

Method of data collection. Together, the experimental studies resulted in a mean premium of 21% (55 estimates). A low number of estimates were produced in the few studies that used survey techniques, like in-person survey (42.9%, four estimates), mail survey (28.8%, two estimates), or a combination of online and in-person surveys (19.5%, one estimate), which confirms the above-mentioned finding.

Information. The average premium a consumer is prepared to pay for GM biofortified crops is significantly different depending on the information that he or she receives. Besides nutrition-related information, all treatments refer to the risks and/or benefits of using GM technology (in food). In the studies that elicited WTP values when participants received a particular type of information, positive information—associated with 14 estimates—had the highest average WTP premium (48.8%). Thereby, values for GM biofortified foods that were associated with positive information about GM technology (57.3% 11 estimates) were surprisingly valued more highly than those associated with nutrition information (30.5%, three estimates). When negative information was given, however, consumers were on average willing to pay 7.0% less than for regular foods (11 estimates). Objective GM information alone, though only measured in one study, averaged a premium of 24.5% (two estimates). As far as conflicting GM information is concerned, 22 estimates resulted in an average of 7.7%. It is important to highlight the importance of the order of providing conflicting GM information. If positive information precedes negative statements on GM technology (8.2%, 11 estimates), values are substantially lower than in the reverse order (18.0%, three estimates), especially if objective information (3.0%, eight estimates) is added. While the only study that directly compared the order of conflicting GM information found a primacy effect,[47] by which information presented first is less effective than what is shown last, the metaresults lend support for the opposite, known as a recency effect. The seven studies that did not assess the effect of different types of information on WTP for bioengineered biofortified crops registered the second-highest WTP premium (44.7%, no information treatment, 13 estimates).

Figure 2 provides detailed insights into the role of information on consumers' WTP for GM biofortified crops. Notwithstanding the fact that a similar information treatment often generates different WTP values, whether the targeted product, micronutrient, or country is different or not, the metafindings generally confirm the size and direction of each of those information effects.

Cost-effectiveness and cost–benefits of GM biofortified crops

Systematic review. Table 2 provides an overview of the key findings of cost-effectiveness and cost–benefit analyses on GM biofortification, as well as its underlying health impact figures, per biofortified product and country. By targeting vitamin A deficiency in the Philippines, Zimmerman and Qaim[56] were the first to conduct an economic-evaluation study on GM biofortification, assessing the cost–benefits of golden rice in 2004.

Together, the selected studies generated a total of 14 cost-effectiveness analyses, either expressed in USD per DALY saved (10 values), incremental cost-effectiveness ratio (ICER, two values), or in USD per life saved (two values), and 16 cost–benefit analyses, of which 10 refer to the IRR and six to BCRs. Each analysis makes a distinction between a low, pessimistic and a high, optimistic impact scenario. The difference is mainly attributable to calculations or assumptions related to the efficacy (e.g., improved micronutrient content after postharvest processing and, in the case of vitamin A, bioavailability) and the potential market coverage (e.g., based on consumption levels and/or farmer adoption) of the targeted micronutrient intervention.

Furthermore, all studies measured the health impacts of GM biofortification, expressed in million DALYs saved per year (14 values). Except for the study of Chow *et al.*,[57] each study also reported figures on the current burden of the targeted micronutrient deficiency (six values) and, per impact scenario, the percent reduction in burden through introducing GM biofortification (12 values).

From the conducted review, nearly all economic-evaluation studies targeted GM-biofortified rice,[56,58–60] either enriched with folate[58,59] or vitamin A[56,58,60] or as a multi-biofortified GM crop with a high level of transgenic (vitamin A and folate) and conventional traits (iron and zinc).[58] Only one study[57] examined the potential of another product, namely golden mustard oil as a means to tackle the vitamin A burden. All analyses originated from Asia, particularly China,[58,59] India,[57,60] and the Philippines.[56] One of the Chinese studies[62] was particularly oriented toward Shanxi Province as a target region, given the extremely high prevalence of folate deficiency and neural-tube defects (NTDs) as its main adverse health outcome.[63] As none of the GM biofortified foods are approved for commercialization, these analyses have to be considered as ex-ante evaluation studies, in which the potential relative cost-effectiveness or cost–benefit is assessed over a time horizon from 16 to 30 years.

Assessments of the current burden of the specific micronutrient deficiencies in the study locations are inherent to economic evaluations of health interventions. Depending on the targeted vitamin and population, between 0.11 million (folate deficiency in Shanxi Province) and 10.64 million DALYs (multiple micronutrient deficiencies in China) are lost each year. Although such absolute figures are interesting from a public health perspective, the impacts of GM biofortification will be mainly discussed in terms of relative numbers (e.g., percent reduction of the burden or cost per DALY saved). In general, GM biofortified crops, regardless of the micronutrient they target, could lower the burden of micronutrient deficiencies to a substantial extent, from 5.7% to 60.0%, in a very cost-effective way (USD 120.3–3.1 per DALY saved).

Rice (folate, vitamin A, multiple micronutrients). Notwithstanding the relatively low burden of folate deficiency, partially because the analysis only targeted one of its functional outcomes (i.e., NTDs), introducing GM rice with a higher folate content into China[58] or Shanxi Province[59] leads to a 20–60% reduction of the burden, respectively, 0.06–0.19 and 0.02–0.07 million DALYs gained per year. Given the larger absolute benefits, a countrywide implementation leads to a higher cost-effectiveness (i.e., USD 21.4–64.2 per DALY saved, as compared to USD 40.1–120.3 per DALY saved in the regional analysis). Depending on the impact scenario and the study location, the implementation of golden rice would reduce the burden of vitamin A deficiency by 17–60% (China),[58] 8.8–59.4% (India),[60] and 5.7–31.5% (the Philippines).[56] In China and India, such an intervention would be considered highly cost-effective, as the cost per DALY through golden rice varies between USD 5.0 and 18.1 (or USD 54–358 per life saved), and USD 3.1–19.4, respectively. If vitamin A and folate were combined with zinc and iron into multi-biofortified rice, it would only cost USD 2.3–9.6 to save a DALY in China and reduce the burden of four micronutrient deficiencies at the same time (11–46%). When gene stacking would be possible, by which the different traits are inserted in one gene construct and transferred into a new stacked event, the cost-effectiveness ratio would even be higher (USD 1.9–7.9 for saving a DALY[58]). In any case, when compared with the World Bank's[64] threshold for highly cost-effective interventions (i.e., USD 273 per DALY saved in 2015), the estimated impacts of all GM biofortified rice varieties verify the costs of their introduction. With respect to cost–benefit analysis, the IRR of golden rice in India and the Philippines is substantially higher than the minimum required return for health-related interventions[60] (i.e., 10–12%), regardless of the impact scenario or the cost assigned to a DALY. In India, the (highly) positive BCRs lend further support for golden rice to be implemented.

Mustard oil (vitamin A). Chow *et al.*[57] used ICERs to calculate the additional cost of moving from vitamin supplementation to vitamin A–enriched mustard oil in India. Although the incremental cost of the latter is relatively large (USD 405–450 per DALY saved), GM biofortification would avert 0.9–1.7 million DALYs per year, which is far more than supplementation or fortification. The number of lives saved, as well as the IRR range (22–43%), further demonstrates that the impacts of golden mustard oil would be more or less similar as those of golden rice in India.

Meta-analysis. Table 4 summarizes the metafindings of three types of outcome indicators, namely burden of disease (million DALYs lost per year), health impacts (million DALYs saved per year, percent reduction of the burden), and economic-evaluation indicators (cost-effectiveness, in USD per DALY saved; cost–benefit, in percent IRR). Thereby, average values will be described for three study characteristics: crop, micronutrient, and country. BCR figures were only included in the golden rice study of Stein *et al.*[60] and, therefore, not discussed in the meta-analysis.

Across all categories and studies, GM biofortification could save each year, on average, between 0.5 and 1.6 million DALYs of all the targeted DALYs that are lost owing to micronutrient deficiencies (i.e., 15.6 million in total, or 3.1 million DALYs on average, based on the available absolute burden figures). This translates to an average reduction of the burden by 12.5% and 51.4%, depending on the impact scenario. As far as economic impacts are concerned, to save a DALY through GM biofortification, it would cost on average USD 27.8 (low impact) and USD 7.9 (high impact). Based on the high average IRR across studies, ranging from 39.2% to 82.4%, the potential of GM biofortification and rice in particular becomes clear.

Crop. The metaresults indicate that the average amount of DALYs saved through GM biofortified rice is somewhat lower than for oil from GM biofortified mustard, though the latter was only examined once. In terms of cost–benefits, however, IRRs of introducing micronutrient-enriched GM rice are more than twice as large as in the case of mustard oil. The relatively large costs of the latter (i.e., about 36 times higher than the cost of the relatively most expensive GM biofortified crop (e.g., multi-biofortified rice in China, USD 85.4 million)[58]) mainly account for this.

Micronutrient. Although the estimates for folate- and multi-biofortified rice varieties were built upon a single study in China,[58] it is no surprise that the most positive outcomes were reported for a health intervention that addresses multiple micronutrient deficiencies simultaneously. Comparison of single-biofortified foods shows that golden rice and mustard oil together are substantially more cost-effective (USD 18.8–4.1 per DALY gained) than folate-biofortified rice (USD 64.0–21.4 per DALY gained). Even so, the latter is also considered to be highly cost-effective and reduces its targeted deficiency to a larger extent (20.0–60.0% as compared with 10.5–50.3%), especially in the low-impact scenario. The differences between vitamin A and folate are mainly attributable to the effectiveness, as vitamin A–enriched foods generally address a larger problem—at least, according to the number of functional outcomes included in their calculations—at a relatively similar cost (e.g., USD 31.6 million and USD 48.9 million for, respectively, golden and folate-biofortified rice in China).[58]

Country. Country-specific differences in micronutrient deficiencies lead to substantial variation in burden of disease (0.11–10.64 million DALYS lost per year) and absolute reduction through GM biofortification (0.02–4.91 million DALYs saved per year), particularly between large (China, India) and smaller countries (Philippines) or regions (Shanxi Province). But relative outcome indicators, like the annual percent reduction in burden, cost-effectiveness ratio, and IRR, also vary between countries and impact scenarios.

Case study on folate-biofortified rice

In this case study, we present findings from various socioeconomic studies on the market potential of folate-biofortified rice. Following the aforementioned studies on WTP or cost-effectiveness, this section mainly elaborates on their determinants (at the individual level, rather than at the study level). All studies build upon a more generic framework to analyze the socioeconomic potential of GM crops with health benefits,[36] allowing for more in-depth information on other indicators, such as consumer acceptance of negative product attributes. Studies have been conducted in China and Shanxi Province (North China) and the Balrampur District of Uttar Pradesh (Northwest India). Their relevance is illustrated by their prevalence rates of folate deficiency and NTDs, which are among the world's highest.[65,66] Not surprisingly, the sample is often solely targeting women of childbearing age as one of the main beneficiaries of folate interventions.

Folate, folate deficiency, and folate-biofortified rice. Folate, which belongs to the group of water-soluble B vitamins, can be obtained through the diet,[67] with green and/or leafy vegetables, eggs, liver, and certain fruits as the most important dietary folate sources.[68] As an alternative option, one could also opt for its synthetic form, known as folic acid, either as a supplement or as a fortified, processed food. Despite these different options to increase folate intake levels, folate deficiency is still prevalent in various parts of the world and remains a major public health issue. Inadequate folate consumption has been associated with cardiovascular and coronary diseases, megaloblastic anemia, stroke, depressive disorder, schizophrenia, Alzheimer's disease, and—despite inconclusiveness regarding the direction of the effect—cancer.[67,69,70] Furthermore, periconceptional folate deficiency increases the onset of various pregnancy-related diseases and outcomes,[71] with most evidence for NTDs.[72,73]

In 2007, rice was for the first time successfully biofortified with folate using transgenic breeding techniques.[17] Through the overexpression of *Arabidopsis* transgenes in rice endosperm, folate levels of 100-fold above wild type could be obtained. Recently, folate concentrations were further increased, up to 150 times the initial levels, while folate stability was enhanced through complexation with folate-binding proteins, making long-term storage possible.[18]

Given the low folate concentrations in current rice varieties, as in other staple crops, like potatoes,[68] it is no surprise that the top rice-consuming countries (e.g., Cambodia, Bangladesh, Myanmar, Thailand, and China) are leading the charts when it comes to the prevalence of folate deficiency and NTDs.[18] Therefore, Southeast Asia is generally considered the key target area for implementing folate-biofortified rice.

Determinants of willingness to pay for folate-biofortified rice. Consumers' WTP for folate-biofortified rice in the Chinese Shanxi Province was elicited through a hypothetical consumer survey in 2008,[46] as well as non-hypothetical auctions with women of childbearing age in 2011.[47,51,52] Besides the discrepancy in valuations between both methods, by which higher premiums were obtained in the former, known as hypothetical bias,[55] these two studies revealed different insights in the potential market demand for this GM crop, regardless of their average WTP level (see also Table 1). First, the survey demonstrated a positive effect of objective GM food knowledge, acceptance of GM rice, and GM food-risk perceptions, whereas GM food price perceptions negatively affected WTP.[46] When looking at (subsistence) farmers, premiums increased when they had a low income or lived in rural areas, which underlines the appropriateness of biofortification in targeting poor, rural populations. As acceptance is considered a precursor of consumers' willingness to purchase a premium, this study also examined this concept and the role of negative attribute changes. In general, about 62.2% of the Shanxi consumers accepted this crop in 2008. Aside from indifferent consumers (26.6%), only 11.2% expressed their reluctance. When also taking into account consumers' GM food knowledge, risk and benefit perceptions, and the acquisition of and their trustworthiness in GM information, segmentation analysis identified three distinct consumer profiles: enthusiasts (14.2%), cautious consumers (44.6%), and opponents (41.2%).[74] Enthusiasts generally obtained a high score on all variables, hence the smaller size of this segment. However, as the cautious segment can be treated as less optimistic rather than reluctant, the profiling further confirms the positive reactions in this target region. However, this is under the condition that folate-biofortified rice does not alter conventional rice attributes. If key attributes, like taste or environmental impacts, would be negatively affected, the initial, potential coverage rate (62.2%) would be more than halved (−54%).[75] Surprisingly, the impact of changes in external appearance (−26.1%) and cultivation potential (19.6%) were considered less important.

Second, the experimental auction study[47] not only determined Shanxi consumers' WTP for folate-biofortified rice at different (GM) information levels (see also Table 1 and Fig. 2), but also confirmed the positive effects of objective GM knowledge and GM food acceptance[52] on consumers' intention to purchase (82.5% of the sample prepared to pay a premium) and, in line with the aforementioned survey,[46] their actual WTP values. Furthermore, a target-group effect was found, highlighting significantly lower WTP values for female students as compared with female adults, who broadly embraced GM technology. An additional comparative analysis of the information treatments[51] demonstrated that the average premium Shanxi women are prepared to pay for GM folate-biofortified rice (33.9%) is slightly but significantly lower than its conventional biofortified counterpart (36.5%). Premiums for both folate-biofortified rice types were relatively high, even if consumers could also opt for an alternative non-GE product based on folic acid supplements. Together with the low share of consumers who are opposed to buying biofortified rice (e.g., 17.5% when GM technology is involved), these results further underline the attractiveness of (GM) biofortified rice with a higher folate content in this high-risk region. In other words, regardless of potential negative perceptions of GM technology, the tangible health benefits associated with GM biofortified crops are dominating consumers' trade-off.

Determinants of cost-effectiveness of folate-biofortified rice. By applying the DALY framework to biofortification, its cost-effectiveness is determined by input parameters and assumptions that are associated with (1) the assessment of the current burden of targeted micronutrient deficiency, (2) the health benefits (reduced burden through folate-biofortified rice), and (3) the costs that are incurred for its development and implementation. As these are dependent on the specific case, its role will be discussed in view of two health-impact studies on folate-biofortified rice (not included in the meta-analysis) (i.e., one targeting all Chinese regions[63] and another comparing two high-risk regions in Asia (Shanxi Province versus Balrampur District))[76] and the two cost-effectiveness analyses on China[58] and its Shanxi Province[59] (see Table 2).

First, the application of the DALY formula to calculate the burden of folate deficiency is limited to different types of NTDs, as these are the only functional outcomes for which there is robust evidence on the attribution level and the prevalence rate. Aside from other DALY parameters, such as the discount rate for future costs and benefits (3%),[37] both factors directly influence the total number of DALYs that are currently lost and, thus, can be saved through folate biofortification. For this reason, the higher attribution level in Northern China (i.e., 85% as compared with 40% in Southern China) contributes to a relatively larger burden in the former region: 4.7 (north) versus 0.7 (south) DALYs lost per 10,000 persons per year[63] (for an overview of the folate-deficiency burden per province, see supplementary materials of Ref. 63). Because the NTD prevalence rate is also taken into account, both Shanxi Province (China) and Balrampur District (India) lose most DALYs owing to folate deficiency[76] (respectively 14.3 and 22.8–39.9 DALYs lost per 10,000 persons per year), which confirms their status as the most affected regions.

Second, calculating the health impacts of folate-biofortified rice requires input regarding the characteristics of the biofortified crop and the coverage rate of its introduction. Regarding the former, it is important to note that the added micronutrient content (1.4–2.9 μg/g rice) largely depends on the postharvest folate losses (50–75%) and its bioavailability (50%).[58] Together with the current folate intake patterns and rice consumption levels, folate intake levels after biofortification could be compared. In China, women of childbearing age could exceed the daily recommended nutrient intake level for folate when consuming folate-biofortified rice instead of a diet based on conventional rice.[58] As such, a folate-biofortified diet may prevent women from delivering a baby with an NTD caused by folate deficiency,[58] even in the NTD-prevalent regions of Northern China, where rice consumption levels are substantially lower than in the South.[63] Despite the fact that not all women are assumed to switch to a biofortified rice diet, known as the coverage rate, about 20–60% of the Chinese burden of folate deficiency (i.e., of folate-related NTDs) could be eliminated through this crop.[58,59] When using the aforementioned acceptance and WTP studies in Shanxi Province as an indicator of the potential coverage in high-risk regions, the health impacts would be even larger (i.e., 5.3–11.7 (Balrampur) and 8.4–32.7 DALYs gained (Shanxi)).[76]

Third, the high cost-effectiveness of folate-biofortified rice is also a function of the costs associated with its development and introduction. On a 30-year time horizon, the total costs are estimated at about 32.4 million USD[58] for China. Therefore, pre- and postimplementation costs are more or less equally distributed. While the former covers research and development (8 years, 5.7 million USD) as well as costs for inserting the folate trait into the local rice varieties and efforts to deregulate it (6 years, 9.5 million USD), the latter refers to social marketing (16 years, 15.0 million USD) and maintenance breeding costs (16 years, 2.1 million USD). Together with golden rice, which costs slightly less in India (21.4–27.9 million USD)[60] and the Philippines (15.7 million USD)[56] but more in China (49.9 million USD),[58] the examined GM biofortified crops are also worth pursuing from an economic perspective,[19] even when targeting only a high-risk region, like Shanxi Province.[59]

Conclusions

The process of applying transgenic breeding techniques to introduce or enhance micronutrient concentrations in food crops has moved on apace in the recent decade. With golden rice as the flagship, researchers are increasingly providing evidence on the market potential of GM-biofortified crops. The turn of the century, when golden rice was assumed to be ready for commercialization,[24] can be seen as the starting point of this field of socioeconomic research. Since the golden rice experiment of Lusk *et al.*[40] in 2001, 11 economic-valuation studies have elicited WTP for GM biofortified crops of consumers from various backgrounds. Not much later, research on the cost-effectiveness or cost–benefits of the introduction of those crops took a leap, with five studies targeting the Asian market. Through systematic review and meta-analysis of these studies, this paper examined 64 and 30 estimates that were obtained at the level of economic valuation and evaluation, respectively.

The findings reveal positive consumer reactions toward GM biofortified crops, with an average WTP premium of 23.9%. Notwithstanding the controversy around GM technology, its application to biofortification did not lead to values that deviated from those reported for conventional biofortified crops.[26] While variations can be observed for type of crop, micronutrient, and breeding technique, with higher values for rice, vitamin A, and intragenic breeding, nearly all premiums exceed the 10% level. Rice, as one of the world's most important staples, has often been targeted for crop modification, which is reflected in this socioeconomic review. Therefore, the higher premiums for vitamin A–enriched golden rice as compared with folate-biofortified rice may point to the importance of vitamin A deficiency and its earlier development[77] and, thus, longer history of consumer awareness than folate-biofortified rice.[17] Further, transferring genes within the same family of crops (intragenic breeding) is more acceptable to consumers than transgenic breeding, in line with recent findings on GM crops with improved agronomic traits in Europe.[78]

Unexpectedly, the type of country (developing versus developed) did not account for substantial differences in consumer valuations. Although no European WTP studies were conducted, which correspond with the objective of biofortification in addressing malnutrition in developing regions, consumer reactions in the United States and New Zealand further confirmed the broad attractiveness of tangible consumer benefits in GM food.

Besides methodological differences, where we found support for the general discrepancy between values derived from hypothetical and non-hypothetical study designs, it is the provision of information that also appears to be crucial. Positive information on GM technology (53.7%) or nutrition (31.5%) obtained the highest premium, followed by objective information (24.5%) and conflicting information, with higher values when negative information preceded positive information (18.0%) rather than vice versa (8.2%). This calls for further research on the role of information, what determines WTP at the consumer (rather than study) level (e.g., sociodemographics, knowledge, and attitude on GMOs), and how these crops should be delivered and marketed (e.g., labelling).

At the societal level, the health gains of GM biofortified crops largely outweigh the costs associated with their development and commercialization. Across all simulations, between 12.5% and 51.4% of the targeted burden of micronutrient deficiency could be reduced at a relatively low cost (i.e., between USD 7.9 and USD 27.8 per DALY saved). Given the low micronutrient concentrations in current staple crops, especially in rice,[68] GM biofortification has been shown to be a cost-effective means to tackle suboptimal micronutrient intake levels. Even under pessimistic assumptions, it should be considered an additional tool for alleviating the burden of hidden hunger, similar to conventional biofortification.[8,25]

The results also boost the evidence of vitamin A deficiency as a serious public health problem for which vitamin A biofortification can contribute to address its adverse health outcomes, including child mortality, but also may account for high valuations of foods enriched with vitamin A. The lack of evidence on the health contribution of delivering adequate folate, besides its ability to reduce NTDs, leads to a relatively lower burden of disease before and after introducing folate biofortification. Despite the (currently) limited scope, its application to rice is highly (cost-)effective to target NTD prevalence rates. The multi-biofortified approach for rice in China is an excellent illustration of how economies of scale can address the call for tackling various vitamin and mineral deficiencies at a very low cost (i.e., below USD 10 per DALY averted).

Owing to the growing but limited research that has been carried out with regard to the socioeconomics of GM biofortified foods, not all target regions were represented in our analysis. Especially when it comes to economic evaluation, all assessments dealt with GM-biofortified rice in Asia. While Asian rice-consuming countries, like India, are priority target markets, African socioeconomic studies are missing, urging for an extension of study locations. Moreover, at the level of biofortification, socioeconomic researchers often concentrate on few micronutrients and crops and lag behind biotech researchers, who have developed a wide array of biofortified crops, beyond the troika of key micronutrients (vitamin A, iron, zinc) and staples (wheat, rice, corn).[19] To anticipate and refine marketing strategies, efforts are clearly needed to bridge the gap between research and development and socioeconomic evidence.

Through reviewing various socioeconomic studies on folate-biofortified rice and its determinants, the case study further demonstrated the importance of the epidemiological data on the effect of folate deficiency and folate interventions when calculating its cost-effectiveness. Furthermore, the positive figures were mainly a consequence of the efficacy of the folate improvement in rice, the low recurrent costs, and the estimated coverage rate of its implementation. Regarding the latter, folate-enriched rice is generally accepted by its key beneficiaries, such as women of childbearing age and farmers from folate-deficient regions. To increase acceptance and hence intervention coverage, efforts should focus on information provision and improvement of objective GM food knowledge. From a developer's point of view, it is important to note that the promising acceptance rate (62.2%) and WTP value (21.5–36.5%) assume that all conventional rice attributes are unaffected. This may become an issue when inserting the folate trait in multi-biofortification as a highly cost-effective health strategy. The case study further highlights the need for combining micro-level analysis (e.g., acceptance, WTP studies) with macro-level simulations (e.g., cost-effectiveness) when aiming to evaluate the socioeconomic potential of GM biofortified crops. To date, such an approach has only been used for golden and folate-biofortified rice.

While the combined focus on economic-valuation and -evaluation studies is appropriate from a marketing and health policy perspective, many other research domains could contribute to evaluate and justify the potential of GM-biofortified crops. Research on stakeholder analysis,[79,80] regulatory and policy issues (e.g., intellectual property issues),[81,82] and trade impacts[83] is needed to identify and evaluate the most optimal way and platform to deliver biofortified foods. Moreover, building upon the challenges in terms of development (e.g., micronutrient stability, bioavailability, field trials), efficacy, and effectiveness studies will be needed to feed socioeconomic analysis and further underpin its importance.[8,10] Nevertheless, the significant consumer acceptance and its promising cost-effectiveness in developing countries, particularly in high-risk regions, show that—from a socioeconomic perspective—the time is right to launch and scale-up GM biofortification. In this perspective, the three reviews in this study provide food for thought for policy makers and health planners in priority target countries that seek a valuable, well-accepted nutrition intervention that is grounded at the heart of the food supply chain and that is complementary to the existing strategies. As such, biofortification can optimize agriculture–nutrition linkeages[84] and, especially when included in a holistic and inclusive health strategy,[7,85] contribute to brighten the future of nutrition.

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Conflicts of interest

The authors declare no conflicts of interest

References

1. Muthayya, S. *et al.* 2013. The global hidden hunger indices and maps: an advocacy tool for action. *PLoS One* **8:** e67860.
2. WHO. 2009. *Global Health Risks: Mortality and Burden of Disease Attributable to Selected Major Risks.* Geneva: World Health Organization.
3. Ezzati, M. *et al.* 2004. *Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors.* Geneva: World Health Organization.
4. Hirschi, K.D. 2009. Nutrient biofortification of food crops. *Annu. Rev. Nutr.* **29:** 401–421.
5. Welch, R.M. & R.D. Graham. 2005. Agriculture: the real nexus for enhancing bioavailable micronutrients in food crops. *J. Trace Elem. Med. Biol.* **18:** 299–307.

6. Mayer, J.E., W.H. Pfeiffer & P. Beyer. 2008. Biofortified crops to alleviate micronutrient malnutrition. *Curr. Opin. Plant Biol.* **11:** 166–170.
7. Johns, T. & P. Eyzaguirre. 2007. Biofortification, biodiversity and diet: a search for complementary applications against poverty and malnutrition. *Food Policy* **32:** 1–24.
8. Saltzman, A. *et al.* 2013. Biofortification: progress toward a more nourishing future. *Global Food Security* **2:** 9–17.
9. Kennedy, G., G. Nantel & P. Shetty. 2003. The scourge of "hidden hunger": global dimensions of micronutrient deficiencies. *Food Nutr. Agric.* **32:** 8–16.
10. Ruel, M.T. & H. Alderman. 2013. Nutrition-sensitive interventions and programmes: how can they help to accelerate progress in improving maternal and child nutrition? *Lancet* **382:** 536–551.
11. HarvestPlus. 2015. Nutritious staple food crops: who is growing what? Accessed October 19, 2015. https://www.spring-nutrition.org/publications/resource-review/updates/nutritious-staple-food-crops-who-growing-what.
12. HarvestPlus. 2014. Biofortification progress briefs. Washington, DC: International Food Policy Research Institute (IFPRI).
13. Welch, R.M. & R.D. Graham. 2004. Breeding for micronutrients in staple food crops from a human nutrition perspective. *J. Exp. Bot.* **55:** 353–364.
14. White, P.J. & M.R. Broadley. 2005. Biofortifying crops with essential mineral elements. *Trends Plant Sci.* **10:** 586–593.
15. Shimelis, H. & M. Laing. 2012. Timelines in conventional crop improvement: pre-breeding and breeding procedures. *Aust. J. Crop Sci.* **6:** 1542.
16. Paine, J.A. *et al.* 2005. Improving the nutritional value of Golden Rice through increased pro-vitamin A content. *Nat. Biotechnol.* **23:** 482–487.
17. Storozhenko, S. *et al.* 2007. Folate fortification of rice by metabolic engineering. *Nat. Biotechnol.* **25:** 1277–1279.
18. Blancquaert, D. *et al.* 2014. Present and future of folate biofortification of crop plants. *J. Exp. Bot.* **65:** 895–906.
19. De Steur, H. *et al.* 2015. Status and market potential of transgenic biofortified crops. *Nat. Biotechnol.* **33:** 25–29.
20. Martin, C. 2013. The interface between plant metabolic engineering and human health. *Curr. Opin. Biotechnol.* **24:** 344–353.
21. Tang, G. *et al.* 2009. Golden Rice is an effective source of vitamin A. *Am. J. Clin. Nutr.* **89:** 1776–1783.
22. Blancquaert, D. *et al.* 2015. Improving folate (vitamin B9) stability in biofortified rice through metabolic engineering. *Nat. Biotechnol.* **33:** 1076–1078.
23. Brooks, S. 2010. *Rice Biofortification: Lessons for Global Science and Development.* London: Earthscan.
24. Potrykus, I. 2012. “Golden Rice”, a GMO-product for public good, and the consequences of GE-regulation. *J. Plant Biochem. Biotechnol.* **21:** 68–75.
25. Meenakshi, J.V. *et al.* 2010. How cost-effective is biofortification in combating micronutrient malnutrition? An ex-ante assessment. *World Dev.* **38:** 64–75.
26. Birol, E. *et al.* 2015. Developing country consumers’ acceptance of biofortified foods: a synthesis. *Food Security* **7:** 555–568.
27. Moher, D. *et al.* 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann. Intern. Med.* **151:** 264–269.
28. Lusk, J.L. *et al.* 2005. A meta-analysis of genetically modified food valuation studies. *J. Agric. Resour. Econ.* **30:** 28–44.
29. Dannenberg, A. 2009. The dispersion and development of consumer preferences for genetically modified food—a meta-analysis. *Ecol. Econ.* **68:** 2182–2192.
30. Amin, L., N.A.A. Azlan & H. Hashim. 2013. Ethical perception of cross-species gene transfer in plant. *Afr. J. Biotechnol.* **10:** 12457–12468.
31. Hallman, W.K. A.O. Adelaja, B.J. Schilling & J. Lang. 2002. Public perceptions of genetically modified foods: Americans know not what they eat. Food Policy Institute, The State University of New Jersey/Rutgers University, New Brunswick, NJ. Report No. RR-0302-001.
32. Rozan, A., J.L. Lusk & M. Campardon. 2007. Consumer acceptance of a genetically modified organism of the second generation: the Golden Rice. *Rev. Econ. Polit.* **117:** 843–852.
33. Canavari, M. & R. Nayga, Jr. 2009. On consumers’ willingness to purchase nutritionally enhanced genetically modified food. *Appl. Econ.* **41:** 125–137.
34. Tan-Torres Edejer, T. *et al.* 2003. *Making Choices in Health: WHO Guide to Cost-Effectiveness Analysis.* Geneva: World Health Organization.
35. Evans, D.B. *et al.* 2005. Methods to assess the costs and health effects of interventions for improving health in developing countries. *BMJ* **331:** 1137–1140.
36. De Steur, H. *et al.* 2014. Conceptual framework for ex-ante evaluation at the micro/macro level of GM crops with health benefits. *Trends Food Sci. Technol.* **39:** 116–134.
37. Stein, A.J. *et al.* 2005. *Analyzing the Health Benefits of Biofortified Staple Crops by Means of the Disability-Adjusted Life Years Approach: A Handbook Focusing on Iron, Zinc and Vitamin A. HarvestPlus Technical Monograph 4.* Washington, DC: International Food Policy Research Institute.
38. WHO. 2015. TOP6. Proposed draft definition for biofortification. Joint FAO/WHO Food Standards Programme Codex Committee on Nutrition and Foods for Special Dietary Uses. Germany: World Health Organization.
39. Hunter, J.E. & F.L. Schmidt. 2004. *Methods of Meta-Analysis: Correcting Error and Bias in Research Findings.* Newbury Park, CA: Sage.
40. Lusk, J.L. 2003. Effects of cheap talk on consumer willingness-to-pay for golden rice. *Am. J. Agric. Econ.* **85:** 840–856.
41. Lusk, J.L. & A. Rozan. 2005. Consumer acceptance of biotechnology and the role of second generation technologies in the USA and Europe. *Trends Biotechnol.* **23:** 386–387.
42. Deodhar, S.Y., S. Ganesh & W.S. Chern. 2008. Emerging markets for GM foods: an Indian perspective on consumer understanding and the willingness to pay. *Int. J. Biotechnol.* **10:** 570–587.
43. Kajale, D.B. & T.C. Becker. 2015. Willingness to pay for golden rice in India: a contingent valuation method analysis. *J. Food Prod. Market.* **21:** 319–336.
44. Corrigan, J.R. *et al.* 2009. Comparing open-ended choice experiments and experimental auctions: an application to golden rice. *Am. J. Agric. Econ.* **91:** 837–853.

45. Depositario, D.P.T. *et al.* 2009. Effects of information on consumers' willingness to pay for golden rice. *Asian Econ. J.* **23:** 457–476.
46. De Steur, H. *et al.* 2010. Willingness-to-accept and purchase genetically modified rice with high folate content in Shanxi Province, China. *Appetite* **54:** 118–125.
47. De Steur, H. *et al.* 2013. The role of information on consumers' willingness-to-pay for GM rice with health benefits: an application to China. *Asian Econ. J.* **27:** 391–408.
48. Gonzalez, C., N. Johnson & M. Qaim. 2009. Consumer acceptance of second-generation GM foods: the case of biofortified cassava in the north-east of Brazil. *J. Agric. Econ.* **60:** 604–624.
49. Colson, G.J., W.E. Huffmann & M.C. Rousu. 2011. Improving the nutrient content of food through genetic modification: evidence from experimental auctions on consumer acceptance. *J. Agric. Resour. Econ.* **36:** 343–364.
50. Kassardjian, E., S. Robin & B. Ruffieux. 2012. L'hostilite aux OGM survit-elle a des produits attractifs? (Does consumer's aversion to GM food survive a yummy apple? With English summary). *Rev. Francaise d'Economie* **26:** 121–150.
51. De Steur, H. *et al.* 2014. Consumer preferences for micronutrient strategies in China. A comparison between folic acid supplementation and folate biofortification. *Public Health Nutr.* **17:** 1410–1420.
52. De Steur, H. *et al.* 2012. Determinants of willingness-to-pay for GM rice with health benefits in a high-risk region: evidence from experimental auctions for folate biofortified rice in China. *Food Qual. Prefer.* **25:** 87–94.
53. Rommens, C.M. *et al.* 2007. The intragenic approach as a new extension to traditional plant breeding. *Trends Plant Sci.* **12:** 397–403.
54. Morrison, M. & T.C. Brown. 2009. Testing the effectiveness of certainty scales, cheap talk, and dissonance-minimization in reducing hypothetical bias in contingent valuation studies. *Environ. Resour. Econ.* **44:** 307–326.
55. Murphy, J. *et al.* 2005. A meta-analysis of hypothetical bias in stated preference valuation. *Environ. Resour. Econ.* **30:** 313–325.
56. Zimmermann, R. & M. Qaim. 2004. Potential health benefits of Golden Rice: a Philippine case study. *Food Policy* **29:** 147–168.
57. Chow, J., E.Y. Klein & R. Laxminarayan. 2010. Cost-effectiveness of "golden mustard" for treating vitamin A deficiency in India. *PLoS One* **5:** e12046.
58. De Steur, H. *et al.* 2012. Potential impact and cost-effectiveness of multi-biofortified rice in China. *N. Biotechnol.* **29:** 432–442.
59. De Steur, H. *et al.* 2012. Ex-ante evaluation of biotechnology innovations: the case of folate biofortified rice in China. *Curr. Pharm. Biotechnol.* **13:** 2751–2760.
60. Stein, A.J., H.P.S. Sachdev & M. Qaim. 2006. Potential impact and cost-effectiveness of Golden Rice. *Nat. Biotechnol.* **24:** 1200–1201.
61. Shewmaker, C.K. *et al.* 1999. Seed-specific overexpression of phytoene synthase: increase in carotenoids and other metabolic effects. *Plant J.* **20:** 401–412.
62. Ren, A. *et al.* 2006. Awareness and use of folic acid, and blood folate concentrations among pregnant women in northern China—an area with a high prevalence of neural tube defects. *Reprod. Toxicol.* **22:** 431–436.
63. De Steur, H. *et al.* 2010. The health benefits of folate biofortified rice in China. *Nat. Biotechnol.* **28:** 554–556.
64. World Bank. 1993. *World Development Report 1993.* New York: Oxford University Press.
65. Cherian, A. *et al.* 2005. Incidence of neural tube defects in the least-developed area of India: a population-based study. *Lancet* **366:** 930–931.
66. Gu, X. *et al.* 2007. High prevalence of NTDs in Shanxi Province: a combined epidemiological approach. *Birth Defects Res. A Clin. Mol. Teratol.* **79:** 702–707.
67. Blancquaert, D. *et al.* 2010. Folates and folic acid: from fundamental research towards sustainable health. *Crit. Rev. Plant Sci.* **29:** 14–35.
68. USDA. 2015. USDA National Nutrient Database for Standard Reference, release 28. Washington, DC: Agricultural Research Service, USDA.
69. Fekete, K. *et al.* 2010. Perinatal folate supply: relevance in health outcome parameters. *Matern. Child Nutr.* **6:** 23–38.
70. Iyer, R. & S.K. Tomar. 2009. Folate: a functional food constituent. *J. Food Sci.* **74:** R114–R122.
71. Talaulikar, V.S. & S. Arulkumaran. 2011. Folic acid in obstetric practice: a review. *Obstet. Gynecol. Surv.* **66:** 240–247.
72. Calonge, N. *et al.* 2009. Folic acid for the prevention of neural tube defects: US Preventive Services Task Force recommendation statement. *Ann. Intern. Med.* **150:** 626–631.
73. De-Regil, L.M. *et al.* 2010. Effects and safety of periconceptional folate supplementation for preventing birth defects. *Cochrane Database Syst. Rev.* CD007950.
74. De Steur, H. *et al.* 2015. The potential market for GM rice with health benefits in a Chinese high-risk region. *J. Food Prod. Market.* **21:** 231–243.
75. De Steur, H. *et al.* 2013. How negative product attributes alter consumer perceptions of folate biofortified rice in a high risk region of China. *Int. J. Biotechnol.* **12:** 269–287.
76. De Steur, H. *et al.* 2015. Evaluating GM biofortified rice in areas with a high prevalence of folate deficiency. *Int. J. Biotechnol.* **13:** 257–279.
77. Ye, X. *et al.* 2000. Engineering the provitamin A (β-carotene) biosynthetic pathway into (carotenoid-free) rice endosperm. *Science* **287:** 303–305.
78. Delwaide, A.-C. *et al.* 2015. Revisiting GMOs: are there differences in European consumers' acceptance and valuation for cisgenically vs transgenically bred rice? *PLoS One* **10:** e0126060.
79. Pray, C.E. & J. Huang. 2007. Biofortification for China: political responses to food fortification and GM technology, interest groups, and possible strategies. *AgBioForum* **10:** 161–169.
80. De Steur, H. *et al.* 2015. Stakeholder reactions toward iodine biofortified foods. An application of protection motivation theory. *Appetite* **92:** 295–302.
81. Kowalski, S.P. & R.D. Kryder. 2002. Golden Rice: a case study in intellectual property management and international capacity building. Pierce law faculty scholarship series. Paper 7. Concord, NH: Franklin Pierce Law Center.
82. Potrykus, I. 2010. Lessons from the 'Humanitarian Golden Rice' project: regulation prevents development of public

good genetically engineered crop products. *N. Biotechnol.* **27:** 466–472.

83. Anderson, K., L.A. Jackson & C.P. Nielsen. 2005. Genetically modified rice adoption: implications for welfare and poverty alleviation. *J. Econ. Integr.* **20:** 771–788.

84. McDermott, J. *et al.* 2015. Agricultural research for nutrition outcomes—rethinking the agenda. *Food Security* **7:** 593–607.

85. Olney, D.K., R. Rawat & M.T. Ruel. 2012. Identifying potential programs and platforms to deliver multiple micronutrient interventions. *J. Nutr.* **142:** 178S–185S.