RESEARCH PAPER

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The politics of Golden Rice

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Genetic knowledge applicable to crop improvement has erupted over the past 60 years, and the techniques of introducing genes from one organism to another have enabled new varieties of crops not achievable by previously available methodologies of crop breeding. Research and particularly development of these GMO-crops to a point where they are useful for growers and consumers in most countries is subject to complex national and international rules arising out of the UN's Cartagena Protocol on Biosafety to the Convention on Biological Diversity, with 167 country signatories. (The USA and Canada are not signatories.) The Protocol was developed based on concerns initially expressed in the 1970's that such technology presented unusual risks to man and the environment. Those ideas have comprehensively and authoritatively been proven to be wrong. The Protocol has nevertheless spawned significant regulatory obstacles to the development of GMO-crop technology at great cost to global society and in conflict with many other UN objectives. The suspicion induced by the Protocol is also widely used, overtly or covertly, for political purposes. These points are illustrated by reference to the not-for-profit Golden Rice project.

Introduction

Within 20 years of Watson & Crick[1] describing the structure of DNA, scientists themselves initiated a debate as to what level of concern was appropriate in the way science conducted genetic research, and what level of regulation was appropriate. The Asilomar Conference Center in California hosted a 1974 meeting including global scientists, lawyers and (10% of the participants) the press.[2] The potential for recombinant DNA to make significant contributions to developments in medicine, agriculture and industry was well appreciated, but tempered with concerns for human health and the environment from newly created organisms with the potential for self-replication. Some scientists believed that there were dangers in scientists "assuming leadership in formulating policies that were matters of public concern. . .some. . .believed that the public debate itself was a great threat. . . and that the fallout of claim and counterclaim would bring debilitating restrictions or even prohibitions on molecular biological research."[2]

Almost a decade after Asilomar the first transgenic plant was created (in 1982), and within 2 years an established plant breeder, Peter Jennings, had the idea which directly led to Ingo Potrykus and Peter Beyer starting their decade of research to produce a rice which accumulated carotenoids, as a source of vitamin A when eaten by humans. Their first 'proof of concept' beta-carotene biofortified rice was produced in 1999.[3] The prototype Golden Rice contained 3 genes of interest introduced from other organisms, this was later reduced to 2, and then the plant source of one of the genes was changed from a daffodil to maize[4] which increased both the quantity of carotenoids and also the proportion of the most important carotenoid for vitamin A synthesis by the human body, beta-carotene. In 2001 the inventors donated the technology, including any future improved versions of it by them and their collaborators, to assist malnourished and resource poor people.[5]

In 2014 their vision has still not been realized. Undoubtedly the most significant factor in the delay is that the nutritional trait in Golden Rice, as rice varieties containing it are known, was initially created using genetic engineering techniques. In synonymous parlance, Golden Rice is a GMO-crop, where GMO means genetically modified organism, and particularly an organism where a gene from another species has been added to the genome. It is unclear how many years would have been saved if Golden Rice had been created without genetic engineering but the speed of introduction of an agronomically useful non-gmo trait is illustrative. The trait imparting submergence tolerance to rice was first described in 2006. An established Indian rice variety, Swarna, including the trait was by 2011 already the fifth and by 2012 the third of the 10 most demanded breeder seed in India for the monsoon planting season (AK Singh, pers. com. quoting draft Proceedings 46th and 47th Annual Rice Research Group Meeting, AICRIP, DRR, Rajendranagar, Hyderabad).

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For most currently common applications of recombinant DNA, including in pharmaceuticals (such as insulin and many drugs) and food processing (such as enzymes routinely used in the manufacture of bread, cheese, wine, and beer) at the Asilomar meeting "The issue [of concern about the technology] and it's resolution were complete before an entrenched, intransigent and chronic opposition developed."[2]

What is different about the application of recombinant DNA technology to crop plants and which has caused the Golden Rice delay? A one word answer is "regulation," as explained by many authors including prominently by one of the inventors of Golden Rice.[6-9]

Regulation of GMO crops includes – usually on a nation by nation basis–review by that nation's government appointed officials of data about that crop including molecular structure of the altered genome, any allergenicity potential by comparison with databases of know allergens, and its comparison with established standard data for the genomes of the same crop, and any other data the officials think necessary to establish that the crop poses no risks to the environment or human health if it were to be cultivated and consumed on a large scale. Comparison of the data for the GMO-crop with the non-gmo version is designed to demonstrate only the intended effect of the transformation for which the novel genes were introduced to that genome. Such comparison is challenging as the standard data set for any crop is usually very limited 'spot data' without a range of values, although crop plants exist in many varieties and life stages, all of which may have very different values for all the analytic variables. Only when regulatory clearance has been applied for by an applicant, and the regulators have judged it safe, will the GMO-crop be cleared for planting by farmers, and consumption by consumers, in that country.

Obtaining regulatory clearance (called deregulation in the US) is undoubtedly time consuming and expensive, but regulation is but one aspect of what may be better described as 'societal suspicion' of genetic engineering of crop plants. The sum of all the societal suspicion, and its effects, relating to Golden Rice can be regarded as the 'Politics of Golden Rice.'

United Nations: The Convention on Biodiversity and its Cartagena Protocol on Biosafety

The concerns about the impact of the new field of genetic research on human health and the environment initially expressed by the scientists and discussed in the 1970's eventually resulted in the United Nations Conference on Environment and Development ("The Earth Summit") in Rio de Janeiro in June 1992. This was the first UN meeting where parties other than Governments participated[10] and 'civil society'–now called NGO's (non-governmental organisations)—participated much more diligently than industry or academe.

Annex 1 of the Report of the UN Conference on Environment and Development,[11] which immediately followed the Rio meeting of June 1992, "Reaffirm[s] the Declaration of the United Nations Conference on the Human Environment, adopted at Stockholm on 16 June 1972, [eg 2 years before the Asilomar conference] and seek[s] to build upon it" and lists 27 Principles. Principle 15 states: "In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation."

The "Earth Summit" meeting resulted in the 30 page Convention on Biological Diversity ('CBD') which came into effect in late 1993. Its intent was to provide "a comprehensive and holistic approach to the conservation of biological diversity, the sustainable use of natural resources and the fair and equitable sharing of benefits deriving from the use of genetic resources." The CBD recognized the obligation to protect the world's genetic resources. It also recognized that human development was the overriding priority of non-industrialised countries.[12] It appears that this sensible approach was insufficient for some.

The Cartagena Protocol on Biosafety ('CPB' or Cartagena Protocol) was developed as an addendum to the CBD, published in 2000[13] and came into force in 2003. The Principle which only made number 15 of Annex 1's 27 Principles, the 'precautionary approach' is nevertheless used to qualify the first Objective of the Cartagena Protocol which addresses "biosafety, focusing specifically on transboundary movement of any living modified organism resulting from modern biotechnology that may have adverse effect on the conservation and sustainable use of biological diversity." This is unfortunate: "The [precautionary] principle has long been a major impediment to good sense in public policy. It is either so obvious as to be otiose ("if there is cause for concern, be careful"), or so vague as to be meaningless. But in its most common application—"where an activity raises threats of harm to the environment or human health, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically"—it has been an invaluable tool for those who want to stop any new scientific development that they dislike."[14]

The Cartagena Protocol was subsequently reinforced by the UN Environmental Programme spending more than $100 million on training developing countries on risk assessment associated with "transboundary movement of living modified organisms" e.g. GMO-crops. Nothing was spent on benefits assessment of GMO-crops.

GMO-crops have been found by numerous independent scientific authorities globally to be no more hazardous to man or the environment than crops produced by other methods. With almost the same access to scientific experience as the authors of the Cartagena Protocol all independent scientific authorities in the world, starting in 1999 have concluded that GMO-crops are safe (**Table 1**).[15]

Similarly, the European Commission's very substantial scientific evaluation of GMO- crops was published in 2010: "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."[16]

Table 1. List of impartial institutions that have concluded genetically modified crops are safe to man and the environment and the technology poses no inherent risk

Institution	Country	Year
Nuffield Council on Bioethics	UK	1999
Organization of Economic Co-operation and Development	International	2000
European Research Directorate	European Commission	2001
French Academy of Science	France	2002
French Academy of Medicine	France	2002
Director General, World Health Organization	International	2002
International Council for Science	International	2003
Royal Society	UK	2003
United Nations, Food and Agriculture Organization	International	2004
British Medical Association	UK	2004
Union of German Academies of Science & Humanities	Germany	2004
European Commission	EU	2010
Plus: the American, Brazilian, Chinese, Indian and Mexican Academies of Science!		

And this is now based on actual empirical evidence of almost 2 decades of commercial usage of gmo crops, and multiple evaluations, rather than theoretical concerns of the 1970's, upon which the CBD and the Cartagena Protocol are based.

Additionally there are many publications concerning the benefits of GMO-crops, including by the UN's Food and Agriculture Organisation.[17,18]

The Cartagena Protocol Foundations of the Opposition to GMO-Crops, Initially Considered Rock, Are Actually Sand

Many observers have tried to explain the opposition to genetically engineered crops and Golden Rice,[eg19] when overwhelmingly science does not explain it: there remains not one substantiated case of harm to human health or the environment from the use of genetic engineering in connection with crop breeding. And biologically this is not surprising, at the molecular level there is no difference between conventional breeding, including techniques of inducing random genome changes using chemicals and radiation as mutagens[17,20] common since the 1940's, and recombinant DNA technology use in genetic engineering. Natural molecular evolution of genetic variants, and genetic engineering, involve the same 3 processes: small local changes in nucleotide sequence, internal reshuffling of genomic DNA segments, and acquisition of small segments of DNA from another type of organism by horizontal gene transfer.[21]

Understanding the fundamental reasons for opposition to genetically engineered crops is difficult as each time evidence based logic prevails in favor of the anti-GMO-crop position; another often unrelated objection is raised.

The media do not help either. Usually pursuing an agenda to entertain rather than educate, they conventionally adopt the posture of "False Equivalency" described as assuming the correct position between 2 opposing views is the midpoint between them independent of the weight of evidence.[22] The media are more inclined to this behavior with respect to GMO-crops than with, for example the different views of creationists and evolutionists. In these ways the debate appears to be endless, even though on the weight of scientific evidence the argument is over.

Underpinning most if not all of the arguments against genetic engineering of crops are the suspicions raised by the CBD and especially the Cartagena Protocol. The Cartagena Protocol's foundations initially considered rock, are actually sand. The public consciousness 'knows' that there is 'no smoke without fire': why would these crops justify such onerous oversight if there was no need for it? And these suspicions have been harnessed, and emphasized by different interest groups to support their particular positions.

House #1 (built on the sand foundations)

Initially, when the first GMO-crops became commercially available in 1996, not all scientists were convinced by the reassurances of their peers, nor the regulatory decisions of their governments. Some set up experiments to investigate potential environmental or other hazard. For a public sensitized by a series of food scares in Europe, including BSE and salmonella in eggs where reassurance from politicians had proved to be false, the press found it interesting to highlight the published results of Ewen and Pusztai[23] on potatoes and Losey et al.[24] on Monarch butterflies. Both groups concluded there were adverse effects of genetic modification. However, in both cases the experimental design did not support the conclusions reached by the authors, nor did it allow the research to be repeated by others. The quality of the science in both cases was discredited, and found to be of no validity for practically relevant understanding.[25,26,27,28]

House #2 (built on the sand foundations)

Food safety, playing God, anti-capitalist, anti-globalisation, a romantic view of small scale agriculture, anti-government and in the case of Europe anti-America, were commonly held views of many, and GMO-crops and the business model supporting their commercialisation were both a useful single issue proxy for opposition to all of them.

So activist groups including Friends of the Earth and Greenpeace, and many other acolytes were not slow to appreciate the campaigning value of the sentiment of the public for raising donations. Individuals campaigning on a similar basis for donations to support their political ideology included prominently Mae-Wan Ho and Vandana Shiva.[29,30,31]

The fear of genetically modified-crops emanating from Houses 1 and 2 became the accepted wisdom of many people who were so uneducated about biology ("don't give me tomatoes with genes") and agriculture ("agriculture is about lifescape and landscape") that they were unable to discern the truth. (On being informed that one of the new genes in genetically modified Golden Rice now came from maize, not as initially daffodil, a practicing medical clinician commented that it must be much easier growing rice alongside maize than alongside daffodils to produce Golden Rice. The message that the genetic modification involved occurs only once, in a laboratory, in the development of a gmo crop, is not well understood.) And governments and companies were not trusted. So 'moral leadership' from anyone not associated with government or companies was welcomed: NGO's – organisations or individuals – found useful acceptance.[32]

Activist organisations try a variety of tactics, usually in the same order, in each country where they are active:

i. Address the population through the media and media stunts
ii. Attempt to intimidate government by appeals to "popular support," and especially involve "environmental concerns" and intimidate Ministers into action
iii. Write papers in "peer reviewed" journals, which are sham science, and where the "peer reviewers" share their ideology
iv. Utilize legal challenges to due process – especially regulatory process–of research or use. Science matters less to most courts, than process.

The phrase 'Frankenstein foods' first use is credited to a letter in the New York Times on June 16 1992. Subsequently the British newspaper 'The Daily Mail' used the same phrase in a headline in February 1998,[33] and thereafter extensively used the shortened form 'Frankenfoods.' Governments in Europe were taken by surprise by the use of the label, and the vehemence of the opposition to GMO-crops. Without a consistent, science based set of principles, and mindful of short electoral cycles, European governments had soon boxed themselves into a position where they increasingly knew that the science did not support any technology-specific opposition to GMO-crops, but were unable to publicly voice any support for them. Already published in 2005 Lord Taverne wrote a book entitled "The March of Unreason."[34] The lack of scientific justification for effectively European political rejection of GMO-crops was endorsed by the 2008 World Trade Organization decision in support of the US contention that it was no more than an illegal trade impediment.[35]

By 2011 despite all representatives of the respective European Community governments privately admitting that there was no scientific justification for opposition to GMO-crops many did not vote positively for them (**Figure 1**).[36]

Only in 2014 has it been agreed in the European Commission that individual EU countries shall be free to choose to approve, or not, for planting within their territory GMO-crops judged safe by the European Food Safety Authority. But this agreement to a 2-step process still has to be voted on by the European Parliament.[37]

House #3 (built on the sand foundations)

The scientific evidence that GMO-crops were as safe (some said safer) to man than crops produced by other methods continued to mount so that no rational individual or organization with even a slight scientific understanding could morally ignore it.

And evidence also was mounting that in many respects GMO-crops provided significant economic and environmental benefits

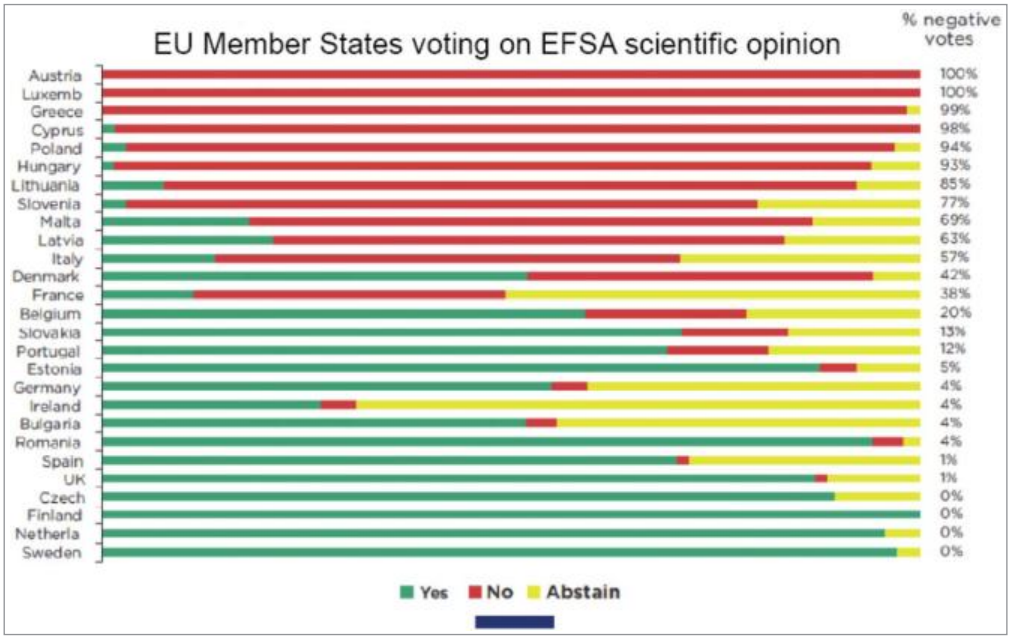

Figure 1. Most policy-makers follow public opinion, rather than science. Adapted from Ref.[68]

too, by for example reducing the amount of tractor fuel required for tillage, by increasing yields, by reducing the need for machinery to handle pesticides, by making insect control agricultural-scale neutral, by allowing improvements to the micronutrient content of some crop plants where 'conventional' plant breeding was not possible, whereas for the past 40 years all yield improvements had been around macronutrient (principally carbohydrate) yield.[38]

But House #3 became occupied by those which, despite understanding the above, cynically ignored the facts and continued to fuel the fears for commercial, or other, gain. Who are these occupiers? Some of them are the same NGO's who started living in House #2, but found it convenient to move because the fundraising campaign strategy of 'anti-gmo' was so powerfully useful. Friends of the Earth is prominent, and others, but the most trenchantly opposed to GMO-crops for many years has been Greenpeace. In his book "Confessions of a Greenpeace Dropout – the making of a sensible environmentalist" Greenpeace co-founder Patrick Moore writes:

"There is also a growing trend among environmental activists to take on campaigns they will never win in the foreseeable future. They will never stop the growth of GM technology; they will never stop nuclear energy or fossil fuel energy; they will never stop the sustainable management of forests for timber production; and they will never stop salmon aquaculture. This creates an opportunity for an endless campaign of propaganda, supporting an endless fundraising campaign to support even more propaganda. As a political strategy it is quite brilliant, except they didn't actually devise it themselves, it just happened that way. It happened that way because the campaigns they won are now over, and as they gradually abandoned science and logic in favor of zero-tolerance policies, they inevitably ended up with unwinnable campaigns. Unfortunately we will have to put up with these campaigns for a long, long time."[39]

With respect to biofortified Golden Rice as the technology is in the seed, no manufacturing, packaging, distribution or change of cultural practice is required for populations to improve their nutritional status, and to be able to take advantage of opportunities available to them. The agronomy and cooking qualities and taste will be identical to the variety into which the nutritional trait is introduced. And each grain is labeled naturally, by its golden color , allowing choice. Fortification and supplementation do not offer these advantages for addressing micronutrient deficiencies and are therefore not sustainable for poor populations.

It is becoming clear that the organic food industry is also occupying House #3. To try and justify the higher prices required by lower productivity the organic industry want consumers to believe that 'organic food' is more nutritious (it isn't[40]), tastes better (it doesn't), is better for the environment (it isn't[41 eg p.180]) and safer (it isn't[16]) than food produced by conventional agriculture. In terms of hazards, "organically grown crops," put people in hospital regularly and kill them sometimes.[42] If people want to grow, buy and consume organic crops why shouldn't they?

But why doesn't the same tolerance apply in the other direction to GMO-crops? Possibly, as to continually refresh fear about GMO-crops assists the organic producers and their associations to meet their commercial targets.[42,43] Perhaps another reason the organic food lobby oppose GMO-crops is because nothing could be more organic than GMO-plants using their own genomes to, for instance, improve their nutrition, improve their ability to efficiently use water or nitrogen from the air and control only the insects which eat the crop. And perhaps, because in the case of donated traits, such as the source of vitamin A in Golden Rice, there is no opportunity for an industry to make profits from people's preferences.

How has the suspicion of GMO-crops delayed the development of Golden Rice?

As has been explained, in most countries, for a genetically engineered crop to be registered as safe to be made available to growers and consumed, details of the genetic structure of the specific transformation event have to be understood and described, and preferably certain general parameters applicable to site of insertion of the DNA allow the smoothest passage through the regulatory process.

Regulation is based, in most jurisdictions, on a single transformation event, that is a single genetic insertion into, in the Golden Rice case, the genome of rice. All subsequent steps are through conventional breeding. It is also preferable, to minimise any future problems of presence of the trait in crop imports to other countries, (known as 'low level presence' or 'adventitious presence') for only one lead transformation event to be introgressed into all varieties of the target crop, in each country where the specific variety is agronomically adapted to the target region, and preferred by the consumers or processors in that region. In the case of Golden Rice the lead transformation event was created once in about 2004, in UK. No genetic modification has occurred of Golden Rice anywhere else, including Asia, since then.

Given the web of international trade in crops, and nationally asynchronous registration of GMO-crops for use, adventitious presence means non-compliance with a nations regulatory rules and, although not a safety issue, can imply significant direct and indirect penalties for those held responsible for the physical materials containing the transformation event. Ensuring compliance is also very expensive.[44] Most rice is consumed very close to where it is grown, and with Golden Rice the trait is highly visible in each polished grain and the target growers are smallholders not rice exporters, nevertheless the potential liability issue is frightening for all institutions public, and private. There is no vitamin A deficiency in Europe, and little rice is grown in Europe, so why register Golden Rice there? Only to anticipate and reduce the impact of any unintended (or provocatively intentional) importation. Surely the cost of such registration is an unnecessary burden for Golden Rice, where no one has been able to propose anything other than benign benefits from its consumption. The concern about financial liability, the cost of inspecting and sending back whole cargoes of crops, impedes scientific collaboration between institutions until the lead event is thoroughly characterized, which increases the risks of losses of expensive research material in one location of crops through natural disaster or protest destruction. It also limits research contributions from scientists in other institutions, in the case of Golden Rice, from the expert

licensee network of public sector rice research institutions and their rice breeders. This also slows down researches pace.

As each insertion of genetic material is random and each transformation event is unique, a selection of the specific transformation event to take forward has to be made from all those available, after understanding how the phenotype behaves agronomically–ultimately in open fields–and in other respects, for example how much micronutrient is accumulated and retained after harvest. Although technologies are developing all the time to make this data collection faster and cheaper to allow selection of the 'lead event', the generation of a sufficient pool of transformation events to select from – usually a minimum of 300 and maybe several thousand – takes skill and a combination of science and experience, as well as time and money. Experience with Golden Rice in the early years of the millennium demonstrated that the public sector did not, at that stage, have the capability to generate a pool of transformation events to choose from.

Selectable markers are required in the genetic engineering process to allow identification of cells which have incorporated the new genetic material from which to grow, and then select useful new gmo-plants. The European Union advises scientists and institutions generating genetically-engineered crops to avoid the use of antibiotic selectable markers. They acknowledge that there is no scientific reason for this but they recognize public opinion may be less concerned about gmo crops if they do not contain such markers. However, historically there have been few alternative selectable marker systems, and arguably such preferences gives too much power to those that have the alternatives.

A major problem with both cost and severe delay implications is the insistence in most parts of the world which are signatories to the Cartagena Protocol that growing GMO-crops has to proceed through a sequence of controlled environments. First in glass houses with filtered air and water and access restricted to specific individuals, then in screen houses and finally contained field trials. In each case all plant parts have to be autoclaved or burned onsite after harvest. Only after the results show no environmental untoward effects can regulatory clearance be given for commercial scale planting in open fields. In one country where Golden Rice was first grown from seed it was in an extremely expensive "Phytotron" facility with completely artificial environment in the growth chambers.

The problem with all of this is that it is unnecessarily complex, and plants do not develop their natural phenotype until they are grown in open fields with all the natural biotic and abiotic stresses involved. Plant breeders are unable to use their skills properly before the crop is grown in the open field. In these circumstances researchers are forced to use genetic markers which may not be proper proxy for the trait of interest. Experience with Golden Rice is that genetic markers alone are insufficient to optimally track the nutritional trait in breeding programmes.

Plant selection from any of the plant breeding processes, should be based on the phenotype exhibited in the open field, e.g., as practiced for thousands of years. Plant breeding is a very skilled and essential process, and the local regulations arising from Cartagena Protocol needlessly delays its application by years. As an example of the differences possible, the first open fields of Golden Rice were grown in the USA (which, like Canada, is not a signatory to the Cartagena Protocol[45]) in 2004 and 2005. In Asia, due the local regulations derived from the Cartagena Protocol, a confined field trial of Golden Rice was possible for the first time only in 2008, and multi-location field trails only 5 years later in 2013. This delays plant breeders being able to observe the plants phenotype in the field.[46]

It may be possible to anticipate, before any undesirable phenotype shows up in field trials, from genomic data that such undesirable effects may be expected. But this depends on precise knowledge of the genes and their function, which may not have been elucidated, and the vigilance of busy scientists to obtain and calmly interrogate all relevant data. This process is vulnerable to human error much more than field trials where, through plant breeder observation, individual plants with undesirable characteristics are literally weeded-out before breeding programmes continue with the plants exhibiting only the desirable traits.

Even when field trials proceed, the Cartagena Protocol derived local regulations either publicise the location, and/or make them very obvious by special, and expensive, security measures. As a result of either or both, anti-gmo crop activists may destroy the field trials, as occurred in Philippines in August 2013 with Golden Rice.[47] The hypocrisy of preventing data being gathered by those who often claim that there is insufficient data gathered concerning GMO-crops was clear to the scientific community, who expressed outrage.[48]

Another adverse effect of the Cartagena Protocol is the suspicion engendered and increased bureaucracy involved with international shipment of gmo-seed between research collaborators _ "transboundary movement of living modified organisms." Firstly the institution in the country interested in importing the seed has to formally make a request to the institution in the exporting country. This has to be considered by a committee, who have to agree, and then seek an export license. The importing country has to create an import license too, before shipment can occur. This is in addition to any plant hygiene regulation procedures in place between many countries for international shipment of any plant materials to prevent spread of plant diseases, and in addition to any intellectual property licenses and material transfer agreements required to be put in place by the parties. In India, more than a year's delay occurred (and 30 politically inspired questions in the Indian Parliament) before the initial free Golden Rice license was signed, and a further year passed after their request before Indian scientists received Golden Rice seed. As an added complication of the very few, and at this early stage of research extremely costly to produce, Golden Rice seeds – less than 10 of each transformation event–initially available to be sent, India's phytosanitary service wanted to test to destruction, and also archive, a significant proportion of them.

In the time of Normal Borlaug, the father of the 1960's green revolution and winner of the Nobel Peace Prize, when Asia requested seed from Mexico he mailed it in an envelope. Only good came of such transport. And crop plants have been being moved around the world to new places for hundreds of years without ill effect.[15]

In 2001 the inventors of Golden Rice had completed a novel transaction. Professors Potrykus and Beyer licensed their technology to Syngenta for commercial uses. In exchange Syngenta agreed to support the inventors' humanitarian project, in several ways, including technology improvements subsequently made by Syngenta scientists. The inventors, who are still closely involved with the strategic management of their project, aim to make the Golden Rice technology a public good, free of any cost or license fees, available only in public-sector rice germplasm, and developed only by public-sector institutions. There will be no charge for the nutritional trait within the seed to smallholder farmers who sell locally (most rice is consumed close to where it is grown). No individual or organization involved with the development of Golden Rice will benefit financially from its adoption.[5] At the same time, and with Syngenta's assistance, initially perceived as problematic intellectual property issues,[49] for Golden Rice were easily resolved with the good will of collaborators.[6,50]

The suspicions set up by the Cartagena Protocol provide the basis for strange influences even on legal systems. Can one believe in an impartial legal system when a higher court finds as follows in connection with the destruction of University field trials of a GMO-crop Bt aubergine (= bt talong in the Philippines) by anti-gmo political activists including Greenpeace and MASIPAG:

"Thus, it is evident and clear that bt talong is a technology involving the deliberate alteration of an otherwise natural state of affairs. It is designed and intended to alter natural feed-feeder relationships of the eggplant. It is a deliberate genetic reconstruction of the eggplant to alter its natural order which is meant to eliminate one feeder (the borer) in order to give undue advantage to another feeder (the humans). The genetic transformation is one designed to make bt talong toxic to its pests (the targeted organisms). In effect, bt talong kills its targeted organisms. Consequently, the testing or introduction of bt talong into the Philippines, by its nature and intent, is a grave and present danger to (and an assault on) the Filipinos' constitutional right to a balanced ecology because, in any book and by any yardstick, it is an ecologically imbalancing event or phenomenon. It is a wilful and deliberate tampering of a naturally ordained feed-feeder relationship in our environment. It destroys the balance of our biodiversity. Because it violates the conjunct right of our people to a balanced ecology, the whole constitutional right of our people (as legally and logically construed) is violated."[51]

Are Scientific Institutions also Vulnerable to Suspicion of Anti-GMO-Crop Bias?

On August 8th 2012 the American Journal of Clinical Nutrition published online a paper by Tang et al.[52] concerning research involving Chinese children and the bioconversion of beta carotene from a single serving of spinach, beta-carotene in oil or Golden Rice. The field research had been completed in 2008, 4 years previously. The data showed that a bowl of ~100 to 150 g cooked Golden Rice (50 g dry weight) can provide ~60% of the Chinese Recommended Nutrient Intake of vitamin A for 6–8-y-old children and that bioconversion was better than from spinach, and equivalent to beta-carotene in oil. Twenty-two days later, on August 30th 2012 Greenpeace issued a press release condemning use of a GMO-crop, Golden Rice, with Chinese children as 'guinea pigs of American researchers.' Actually, Dr Tang, and several of the other clinicians involved in the research were born and or are resident in China. Dr Tang, with 25 years' experience of similar research, and co-workers had previously conducted similar research with Golden Rice in USA with adults,[53] and with children in China with other, non GMO-crop sources of beta-carotene.[54] Only Tang's 2012 research with gmo Golden Rice was criticized by Greenpeace.

More than a decade earlier in 2001, Greenpeace had also issued a Press Release in which it was claimed that Golden Rice could not be effective as an intervention against vitamin deficiency as an adult would have to eat at least 12 times the normal intake of 300 grams (e.g. 3.6 kilograms) of rice to obtain the daily recommended amount of provitamin A. Clearly in 2012, in the light of Dr Tang results, Greenpeace were highly motivated to discredit her published results, but were unable to substantiate their 2012 allegations.

Nevertheless, prompted by public hysteria induced by those allegations, the Chinese authorities investigated also, and found different irregularities. They were particularly dismayed by initial denial of involvement in the research by some of the Chinese clinicians who were very intimidated by Greenpeace's allegations, the public hysteria and had also been physical intimidated in the middle of the night at home by police seeking confessions that they had cooked Golden Rice in their kitchens. (In fact it was imported already cooked and frozen into China, in full compliance with national and international law). As a result several of the clinicians were sanctioned by the Chinese authorities, who also accused Dr Tang of irregularities and pressured her institution, Tufts University, to take investigatory action.

The Tufts investigation took a long time. Eventually they issued a statement:

"TUFTS UNIVERSITY STATEMENT
September 17, 2013
Tufts University has always been and remains deeply committed to the highest ethical and scientific standards in research. When questions were raised about whether a study published in the /American Journal of Clinical Nutrition/ adhered to requirements for human subjects research, the Tufts Institutional Review Board (IRB) and Tufts University launched both internal and external reviews of the study activities. The University also conducted a scientific review to determine whether the journal manuscript accurately reported the study research methods, measurements and findings. In undertaking these reviews, the IRB members and the external reviewers examined the study documentation and interviewed a number of research team members.

These multiple reviews found 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.

While the study data were validated and no health or safety concerns were identified, the research itself was found not to have been conducted in full compliance with IRB policy or federal regulations.

Reviews found insufficient evidence of appropriate reviews and approvals in China. They also identified concerns with the informed consent process, including inadequate explanation of the genetically-modified nature of Golden Rice. The principal investigator also did not obtain IRB approval for some changes to study procedures before implementing the changes.

Tufts has taken substantive corrective and preventive actions to address these findings. The principal investigator is unable to conduct human subjects research for two years, during which time she will be retrained on human subjects research regulations and policies. For the two years following, she will be eligible to conduct human subjects research as a co-investigator under the direct supervision of a principal investigator. The IRB has also revised its policies and procedures to ensure that in the future, research conducted outside the United States and/or in cultural contexts with which the IRB is not adequately familiar is reviewed more carefully. We have notified all relevant agencies in the United States and China of our findings, and the principal investigator has also notified the publishing journal.

We regret that deviations from certain approved protocols and standards occurred. Tufts has strengthened our policies and procedures to prevent recurrence of such problems, and we remain committed to conducting research of the highest quality, with rigorous oversight."

None of Greenpeace's nor the Chinese authorities' different criticisms of the research were upheld by Tufts IRB, who did not visit China although all the allegations concerned conduct of the field portion of the research conducted in China.

The detailed reasoning for, design and methods of conduct of the research was agreed in advance with the Tufts IRB in a Protocol in 2003, and again in 2008. This included the detailed wording to be use in the Informed Consent Form to be used with subjects. That the subjects were children and one of the materials was produced by genetic engineering was clearly taken into account by the Principal Investigator and the Tufts IRB, and the agreed Protocol also complied with all then current legislation and guidance concerning such research. In China, unlike in USA, Protocols once agreed did not require renewal if the research is delayed. So the 2003 Protocol was used in China in 2008 when this research was conducted due to delays associated with producing the specific Golden Rice required by the sophisticated design. (Fungus and mites in 2 seasons consumed the small growth chamber's Golden Rice crop in southern USA.)

The Tufts Institutional Review Board (IRB):

- Claimed that the inability of Dr Tang to produce the completed Informed Consent Form from China was indicatory of incomplete ethical clearances, despite the Tufts IRB approved Protocol stating that such records would be stored in China, and Tufts preventing Dr Tang from communicating with Chinese colleagues during the investigation to obtain the records.
- Ignored clear photographic evidence of group meetings with research subjects, parents and teachers concerning informed consent for the research reported. And when faced with this photographic evidence, then demanded a transcript of what was said in these long and open meetings (held in Chinese language of course).
- Following Dr Tang's "temporary suspension of research privileges at Tufts University until final corrective actions are decided and ratified by the convened IRB," then forbade her from discussing her research at a European science conference concerning "Hidden Hunger," in the view of one US legal expert infringing her academic freedom and also US First Amendment freedom of speech.
- Ignored an NIH letter of 2009 robustly rebutting criticisms of the same research, based on 2003 clearance by the Department of State, made by the 'Keep Wales GM Free' activist group in 2009.[1]
- Found her guilty of not following rules which were only introduced after the field research was completed.
- Ignored differences in procedure between the US and China during the period of the research. And ignored the fact that both Tufts IRB and the Chinese authorities changed their regulations governing such research after the investigation, thereby implying that former rules had not been transgressed.
- Advised her to withdraw her application for promotion during the investigation, with no explanation. And subsequently withheld about 50% of her pay for 2 months, claiming 'budget difficulties.'
- Made no reference in any of the official communications drafted by Tufts, in connection with communicating the results of their investigation, of the fact that the initial criticisms of the research were raised by a political campaigning group, Greenpeace.
- Found unacceptable a letter to the editor of the American Journal of Clinical Nutrition (AJCN) personally drafted and sent by Dr Tang explaining the results of Tufts investigation of her conduct, as she personally was obligated to do by Tufts rules, and giving her comments on it. Tufts found the letter unacceptable and redrafted it. One Tufts official forged the signatures of the American authors of the paper on the Tufts redrafted form of the letter which purported to be from all the authors to AJCN. However, Dr Tang was the only author to have seen the Tufts version before it was sent, and Dr Tang only agreed that it be sent under extreme duress.

  (As a result of this Tufts drafted letter AJCN on several occasions over an 8 month period from December 2013 requested that the authors of the paper voluntarily retract the paper, threatening, again several times, that otherwise the journal would unilaterally retract the paper, for 'ethical breaches' in conducting the research.)
- Criticized and emphasized (including in the Tufts University statement of 17 September 2013 reproduced above) as a significant ethical violation that Dr Tang had used precisely the words agreed in the Tufts IRB approved Protocols

("Golden Rice is a new rice which makes beta-carotene, thus giving the rice a yellow (Golden) color") to describe Golden Rice in the Informed Consent Letters (notarized as translated accurately into Chinese language) with subjects and their parents: "Golden Rice is a new rice which makes beta-carotene, thus giving the rice a yellow (Golden) color."

The Tufts IRB approving the Protocol were well aware of the fact that Golden Rice was genetically engineered: "Recently, scientists have genetically engineered "golden rice" that contains 1.6 μg ß-C in a gram of dry rice" is a quote from the agreed Protocol.

It is difficult, in the light of all these criticisms, especially the last, to avoid the supposition that some individuals of the Tufts University IRB, and/or their external advisory committee, in 2013 believed that by their nature genetically engineered crops such as Golden Rice are intrinsically dangerous. Such beliefs, despite all scientific evidence to the contrary, would cause what would otherwise be viewed as minor issues as having serious ethically questionable dimensions.

With such secretive organisations as Greenpeace – membership lists are not published, and nor have been the names of the Tufts committees involved–and similar anti-gmo political activist organisations, such apparent bias could be due to members of the review boards sharing that organisations beliefs and objectives.

Even the suspicion of anti-science bias in an academic institution is of deep concern especially as, as explained by the President of Tufts University: "IRBs are created by federal law as independent bodies that review, approve and oversee human subjects research. . . . . The federal laws that create IRBs and govern their procedures do not provide for appeal of final IRB findings. . ."

As a result of all the criticisms of Dr Tang and the professional sanctions against her by Tufts she has closed her world class laboratory and retired after a quarter of a century during which she has become a global expert on carotenoids and worked assiduously to assist those who suffer from vitamin A deficiency. She is a highly ethical person, and takes her responsibilities extremely seriously. (In 2009, she excluded from a set illustrating the research, photos which included the Chinese children, to protect their identity pursuant to her Protocol obligations to maintain the confidentiality of the individuals.)

As a result of the prolonged intransigence of the institutions to amend their positions Dr Tang has recently initiated legal proceedings against both AJCN and Tufts University. This has been made possible through financial support of a concerned philanthropist. We must now await the outcome of legal process in connection with this saga.[55-57] It is a dark day when only those who can afford legal representation have a chance of opposing apparent prejudice against gmo crops, and which is so extreme it defames serious clinical researchers. Without the philanthropists financial support it is clear that there would be no chance of justice.

The Cartagena Protocol Itself Poses a Greater Risk to the Environment and Human Health than GMO-Crops

The premise on which the Cartagena Protocol is constructed is false. There are no risks to the environment and human health from biotechnology, including GMO-crops, any greater than there have been from any crop breeding technology for the last 60, or 70 or 10,000 years. The Cartagena Protocol itself poses a greater risk to the environment and human health than GMO-crops.

It is clear that the Cartagena Protocol, as far as GMO-crops are concerned, is not fit for its CBD purpose. Through the CBD, the Cartagena Protocol does not provide "a comprehensive and holistic approach to the conservation of biological diversity, the sustainable use of natural resources and the fair and equitable sharing of benefits deriving from the use of genetic resources."[13 Introduction]

In fact it does the opposite. It restricts scientific collaboration and openness, it encourages monopolistic behavior and it reinforces the arguments of a series of politically inspired fear mongers whose campaigning activities are at the expense, at the least, of anxiety among innocent members of society. It encourages extensification of agriculture, further decreasing the wild lands available for biodiversity. It reduces the ability of agriculture to adapt to climate change, and it increases the dependency of the poor on established food production systems, rather than allowing their own scientists to adapt their own crops to local conditions for the basic right and dignity of self-sufficiency in food.

The Cartagena Protocol does not create "an enabling environment for the environmentally sound application of biotechnology, making it possible to derive maximum benefit from the potential that biotechnology has to offer, while minimising the possible risks to the environment and human health."[13 Introduction]

The stifling of scientific progress it causes is also an insidious risk to the environment and human health. The United Nations must address the Cartagena Protocols inappropriateness for GMO-crop plants in the light of decades of relevant scientific evidence. Its over-cautiousness is not warranted and several UN goals have been negatively affected by it.

As but one example, Golden Rice could have been assisting with reducing child mortality (Millennium Development Goal #4) and maternal mortality (Millennium Development Goal #5) for years already if it had not been for the Cartagena Protocol. Another related example: in 1992 at the UN's first Conference on Nutrition it was noted that supplementation (for example with the then controversial vitamin A capsules as an intervention for vitamin A deficiency) was only a temporary measure in addressing nutritional deficiencies, and that food based nutrition was to be preferred.[58] Again Golden Rice could be complementing other vitamin A deficiency interventions, and probably saving lives and sight already if research and development had not been slowed down by the ramifications of and suspicions due to the UN's Cartagena Protocol.

"If the river is too high, raise the bridge"

The Cartagena Protocol was produced by the UN 30 years after the concerns based on lack of experience of recombinant DNA technology applied to crop plants discussed in the 1970's, and without any reflection of the experience and knowledge gained in the intervening 3 decades. Even though the Cartagena Protocol only came into effect in 2003, the suspicion the Protocol has bred has been promulgated for the whole of the decade and a half since its publication in 2000. It is unwise to expect any rapid relaxation, let alone cessation of its unfortunate grip soon. Those most likely to have impact on cessation are those with vested self-interests in maintaining the status quo.

What can be achieved, in the meantime, to attempt to mitigate the risks which the Cartagena Protocol represents?

Firstly, nations should not appoint ministers responsible only for "The Environment." Countries could usefully follow the example of the UK where the relevant Government department is called "The Department for Environment, Food and Rural Affairs." This encourages a holistic perspective balancing relevant factors: "The environment" does not exist in a vacuum.

Secondly, as the Cartagena Protocol relates to the "transboundary movement of any living modified organism resulting from modern biotechnology that may have adverse effect on the conservation and sustainable use of biological diversity" countries which are neighbors, or share an agro-ecological zone may wish, between themselves, as is their sovereign right recognized by the Convention on Biological Diversity, to define the relevant boundary for the purposes of the Cartagena Protocol as the edges of that zone, rather than national boundaries. This would allow for much easier research collaboration between them. They could also perhaps decide in the light of the copious evidence available since the Cartagena Protocol was drafted, that there actually is no evidence "of any adverse effect on the conservation and sustainable use of biological diversity" from GMO-crops and so the Convention does not apply to them.

Thirdly, countries may, between themselves, want to redefine modern biotechnology so that every crop developed since the 1940's is included, or perhaps exclude all crops utilizing biotechnology which is no longer considered "modern" because its processes have been extensively used for crops cultivated already on millions of acres. Either interpretation would have the impact of reducing the stifling bureaucracy applied to GMO-crops.

It appears that some European politicians are considering redefining 'modern biotech crop,' around transgenic GMO-crops, so as not to have to address the political mess they have got themselves into. It should be noted however that the Cartagena Protocol applies to all crops of "modern biotechnology" (not just transgenics) and, according to an advisory committee to the UK Government's Department for Environment, Food and Rural Affairs, the European regulatory system is fit for purpose for neither classification.[59] So any redefinition of 'modern biotech crop' will not be helpful in this context.

Of course it would assist the speed of cancellation of the Cartagena Protocol if country Parties started to formally withdraw from it. In place it would be sensible for them to apply, for example, the regulatory system used by Canada for modern crops, which does not concentrate on the technology used to produce a crop, but what the crop is, and what its properties are.

Canada, the USA and UK have all withdrawn some or all of the "charitable" tax free status of Greenpeace as they are a political campaigning group. And India has recently banned foreign funding of local campaign groups, including Greenpeace, as they are a "significant threat to national economic security."[31] To further reduce the emotional agitation of populations and trade caused by those political lobbying groups which leverage the suspicion caused as a result of the misplaced concerns of the CBD and Cartagena Protocol, governments should do 2 things. Stop direct funding support of the activists lobbying activities, please European countries take note:[60,61] "The European Commission website reveals that a staggering 150 million euros (£119 million)[US$201m] was paid to the top 9 green NGOs from 2007–13.[62] And secondly, cease the charitable, tax exempt treatment of the activists – which is actually indirect support with taxpayers money, which many taxpayers would not agree to if they reflected on it.[63]

Conclusion

Sixty-one years since Watson and Crick described DNA in the journal Nature is but a glimpse of time in the 10,000 years during which man has been applying human intellect to improving crop production by selecting genetically different variants. Yet more has happened in biology in that time than in all the decades preceding it.

Principle 1 of the Rio Declaration on Environment and Development states "Human beings are at the centre of concerns for sustainable development. They are entitled to a healthy and productive life in harmony with nature."[11]

It is sad that current global society has to incur the pain, environmental damage and death due to delays to advancement in agricultural science. All caused by the regulations, developed by national governments which are signatories to the UN's Convention on Biodiversity and its Cartagena Protocol. The ideas and concerns upon which the Cartagena Protocol is based were initially debated 50 years ago, and by now have been proved to have no merit. Nevertheless, apart from the direct costs, they feed suspicion of a useful and benign crop breeding development.

With respect to Golden Rice the costs of opposition to GMO-crops in India alone have been calculated at $200m per year for the past decade.[64] Globally in 2010 vitamin A deficiency killed more children than either HIV/Aids, or TB or malaria[5] – somewhere around 2 million preventable deaths in that one year alone. That is 6000 preventable deaths, mostly of young children, every single day. Although Golden Rice is a startling example of the costs of delays in GMO-crop development, many other differently useful crop traits which can benefit the environment and human health are also dangerously delayed.

The logical #1 agenda item for the next Meeting of the Parties to the Cartagena Protocol in Korea during late September and October 2014,[65] and all subsequent meetings until such action,

is to agree that the Cartagena Protocol is cancelled for crops produced using modern biotechnology. And subsequently to dismantle the web of related "industry" – biosafety research, government committees, unnecessary international meetings, data dossiers etc etc. All these systems should migrate back to the systems used for the approval of all other crop varieties, to release the real skills of agricultural and nutritional research and seed breeding, to release the full potential of a modern understanding of plant genetics for the benefit of humans and the environment.

The United Nations has a huge and pressing responsibility to address the impediments it has put in the way of GMO-crops, though the Cartagena Protocol of "reconcil[ing] the respective needs of trade and environmental protection with respect to a rapidly growing industry, the biotechnology industry,"[13] and through all its agencies, including WHO, UNICEF and FAO, take a more robust, scientifically– and religiously[66,67]–supported policy stance on GMO-crops, despite the remaining suspicions of many, often not scientifically trained, individual staff members of those organisations.

Note

1. On 30 Apr 2009, at 14.37, NIDDK Inquires (NIH/NIDDK) wrote:

Dear Dr. John:

Thank you for writing to Dr. Raynard S. Kington, acting director of the National Institutes of Health (NIH), concerning your formal protest of the use of golden rice in an NIH-supported project, Retinol Equivalence of Plant Carotenoids in Children, led by Dr. Guangwen Tang, at Tufts University in Boston. Your e-mail was forwarded to my office for reply.

As mentioned in our previous communication, while vitamin A deficiency is a rather rare condition in the United States., it is a significant problem in China and in much of the developing world. Because vitamin A deficiency can lead to serious problems such as blindness and death, clinical research such as Dr. Tang's is important to further define the functions of vitamin A and its metabolites and to identify the levels required to improve health and alleviate disease.

The collaborative project Dr. Tang led was designed by Chinese and U.S. investigators to alleviate vitamin A deficiency in children. Many safeguards were built-in to ensure that the study was carefully planned and monitored to protect the children who participated. The application was first reviewed and approved by Institutional Review Boards (IRB) at both Tufts University and the Chinese Academy of Preventive Medicine. Ensuring that adequate safeguards were in place for children who would be involved in the project, the reviews from both IRBs included human subject safety. Furthermore, while the approval of U.S. Food and Drug Administration and the U.S. Department of Agriculture was not required to conduct the study, project investigators welcomed and received advice and counsel on safety, nutritional, and regulatory issues from both agencies.

Dr. Tang's detailed application for NIH funding was also evaluated in a two-step peer review process required by law to ensure high scientific standards among funded projects. The application was first peer-reviewed by the Nutrition Study Section in the NIH Center for Scientific Review and approved with high enthusiasm. NIDDK's Advisory Council, whose members are non-government scientific experts and public representatives, then conducted a second review of the project and approved it for funding.

The proposed project was then sent by NIH's Fogarty International Center to the Department of State for secondary review to identify any potentially negative foreign policy implications, including human safety concerns. The Department of State cleared the proposed research on January 16, 2003.

Throughout the entire project, NIDDK scientists reviewed required progress reports from Dr. Tang. Under an NIH-approved Data Safety Monitoring Plan, an independent, institutional safety officer monitored interim study data for any potential problems and reviewed participants' translated, informed consent statements.

Lastly, while some research indicates that genetically modified foods show promise for correcting or preventing nutritional deficiencies, further research is needed on the availability of vitamin A in different plant foods, including genetically modified foods such as golden rice. It should also be noted that Dr. Tang's project focused not only on golden rice, but also on other food sources of vitamin A, including spinach and pure Beta-carotene (B-C) in oil.

Evidence-based peer-reviewed information about genetically modified foods is available at: http://www.nature.com/nbt/journal/v23/n4/abs/nbt1082.html.

Consumer-based information about genetically modified foods is available at: www.ars.usda.gov/is/AR/archive/sep02/rice0902.pdf

We hope this information is helpful.

Leslie Curtis

US Department of Health and Human Services

National Institutes of Health

National Institute of Diabetes and Digestive and Kidney Diseases

Office of Communications and Public Liaison

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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