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A golden opportunity, squandered

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Even when used to make products of negligible risk and that contribute significantly to public health, recombinant DNA technology (a.k.a. 'genetic modification', or GM) applied to agriculture has a tough row to hoe. 'Golden Rice', which has been enriched by the addition of genes that allow rice to synthesize β-carotene (the precursor of vitamin A) in its edible endosperm, has endured resistance from activists and a decade of imposing and gratuitous obstacles to regulatory approval. This is an ominous precedent for other 'biofortified' foods made with recombinant DNA technology.

The announcement in November 2008 by a group of multi-national European scientists that they had produced an extraordinary new, recombinant DNA-modified tomato variety garnered a great deal of media attention worldwide. This variety, which contains two snapdragon transcription factors, boasts deep purple skin and flesh and contains levels of antioxidants threefold greater than its unmodified parent. Most important, when fed to highly cancer-susceptible mice, the tomatoes significantly extended the life span of the animals [1].

These tomatoes are a so-called functional food, one fortified or enhanced with something that confers health benefits. This is not a new idea: for more than 80 years, iodine has been added to table salt to prevent hypothyroidism and goiter (see http://www.iccidd.org/pages/protecting-children/fortifying-salt/history-of-salt-iodization.php). Newer functional foods, including eggs with enhanced levels of omega-3 fatty acids to reduce the incidence of heart disease and probiotic yogurt with extra bacteria to aid digestion, are becoming more common.

The announcement of the enhanced-antioxidant tomato received wide attention from the press and scientific community, but an equally momentous achievement of plant genetic modification that is almost a decade old has been largely ignored. That innovation is 'Golden Rice', a collection of new rice varieties biofortified, or enriched, by the introduction of genes that enable the edible endosperm of rice to produce β-carotene, the precursor of vitamin A (see http://www.goldenrice.org). (It is converted in the human body, as needed, to the active form.)

Why are these new varieties so important? After all, most physicians in North America and Europe never see a single case of vitamin A deficiency in their professional lifetimes. The situation is very different in many developing countries, however. Vitamin A deficiency is epidemic among poor people whose diet is comprised largely of rice (which contains neither β-carotene nor vitamin A) or other carbohydrate-rich, vitamin-poor sources of calories.

In developing countries, 200–300 million children of preschool age are at risk of vitamin A deficiency, which can be devastating and even fatal. It increases susceptibility to common childhood infections such as measles and diarrheal diseases and is the single most important cause of childhood blindness in developing countries. Every year, ~500 000 children become blind as a result of vitamin A deficiency and 70% die within a year of losing their sight (see http://www.cdc.gov/nccdphp/dnpa/immpact/micronutrient_facts.htm).

Why not simply supplement children's diets with vitamin A in capsules or add it to some staple foodstuff, the way that we add iodine to table salt? It's a good idea in theory, except that neither the resources – hundreds of millions of dollars annually – nor the infrastructure for distribution are available.

Recombinant DNA technology offers a cheaper and more feasible solution: Golden Rice, which, after the insertion of two genes coding for phytoene synthase (*psy*) and phytoene desaturase (*crt* I), is able to accumulate β-carotene in the endosperm, the edible portion of the genetically altered rice grains (see http://www.goldenrice.org/Content2-How/how1_sci.html). The concept is simple: although rice plants do not normally synthesize β-carotene in the endosperm because of the absence of two necessary enzymes of the biosynthetic pathway, they do make it in the green portions of the plant. By using recombinant DNA techniques to insert the two genes that express these enzymes, the pathway becomes functional and the rice grains accumulate therapeutic amounts of β-carotene. Golden Rice and the enhanced-antioxidant tomatoes are examples of what has been called the 'second generation' of plants developed with recombinant DNA technology – those that provide consumer-directed benefits, as opposed to plants that offer only improvements in agronomic properties.

Golden Rice offers the potential to make contributions to human health and welfare as historic as those made by the discovery and distribution of the Salk polio vaccine. With wide use, it could save hundreds of thousands of lives a year and enhance the quality of life for millions more. But one aspect of this shining story is tarnished. Intransigent opposition by anti-science, anti-technology activists – Greenpeace, Friends of the Earth and a few other radical groups – has provided already risk-averse regulators political 'cover' to adopt an overly precautionary approach that has stalled approvals.

There is absolutely nothing about Golden Rice that should require endless case-by-case reviews and bureaucratic dithering. As the journal *Nature* editorialized in 1992, a broad scientific consensus holds that 'the same physical and biological laws govern the response of organ-

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isms modified by modern molecular and cellular methods and those produced by classical methods. . . . [Therefore] no conceptual distinction exists between genetic modification of plants and microorganisms by classical methods or by molecular techniques that modify DNA and transfer genes.' [2]

Putting it another way, government regulation of field research with plants should focus on the traits inherent in the host plant and in the introduced genes that might be related to risk-invasiveness, weediness, toxicity and so forth – rather than on whether one or another technique of genetic manipulation was used.

In spite of its vast potential to benefit humanity – and negligible likelihood of harm to human health or the environment – a decade after its creation Golden Rice remains hung up in regulatory red tape with no end in sight (see http://www.goldenrice.org/Content2-How/how4_regul.html). Lactoferrin and lysozyme produced in recombinant DNA-modified rice by 'biopharming' (which is often cited as the 'third generation' of recombinant DNA-modified plants) and used to treat children with diarrhea has endured similar regulatory delays (see http://www.washingtontimes.com/news/2004/jul/05/20040705-095035-5659r/).

If Golden Rice had been created with conventional techniques of genetic improvement (which is not possible for technical reasons), it would have required 2–3 years to breed relevant local varieties and to produce seed for distribution. Because all plants produce high amounts of carotenoids, their presence in rice will not introduce any new substances into the environment or provide any additional selective advantage in the field. β-carotene is already present in the food supply and is, in (U.S.) regulatory terms, 'Generally Recognized As Safe', or GRAS (see http://www.cfsan.fda.gov/~dms/gras-ov.html); as such, it would not require a pre-market governmental review. Cancer-preventing tomatoes, take notice.

In contrast to plants modified with recombinant DNA technology, those constructed with less precise techniques, such as hybridization or mutagenesis, generally are subject to no government scrutiny or requirements (or opposition from activists) at all. That absence of scrutiny applies even to the numerous new plant varieties that have resulted from 'wide crosses', hybridizations that move genes from one species or genus to another across what used to be thought of as natural breeding boundaries. (One arguable exception is Canada, where regulations are, in theory, triggered by whether a trait in a given species is 'novel', but the reality is that recombinant DNA-modified organisms there are subjected to a far higher standard than those crafted with conventional technologies.) It should be noted that the commonly cultivated and consumed varieties of rice – all of which have been developed with conventional techniques – are the product of wide crosses [3] and, therefore, are 'transgenic' by any reasonable scientific definition. However, these constructions are less precisely crafted, less well characterized and less predictable than recombinant DNA constructions. Thus, we have a situation in which for more than two decades the degree of regulatory scrutiny (and therefore, the time and expense required for the development of new varieties) has been *inversely* proportional to the perceived degree of risk. This is absurd.

Regulators and activists are not the only villains of the piece. The media – and even scientific journals (see Ref. [4]) – have been undiscriminating and overly tolerant of the misrepresentations and distortions of anti-biotechnology activists, and politicians have opposed recombinant DNA technology for reasons of trade protectionism.

Judith Rodin, the President of the Rockefeller Foundation, announced in October 2008 that her organization will provide funding to the International Rice Research Institute to shepherd Golden Rice through national regulatory approval processes in Bangladesh, India, Indonesia and the Philippines (see http://www.rockfound.org/about_us/speeches/101708food_prize.shtml). Although this is presumptive good news, what is really needed is a multifaceted, aggressive effort to reform regulation so that new genetic constructions will be able to succeed even if they do not enjoy the patronage of a powerful benefactor. Employing a laboratory metaphor, the regulatory travails of Golden Rice are analogous to a positive control in the laboratory that doesn't work: in other words, if we cannot move *this* product expeditiously through the regulatory labyrinths and into the rice-cookers of the developing world, then the application of recombinant DNA technology to biofortified foods is truly 'cooked'.

In an April 2008 editorial in the journal *Science*, Nina Fedoroff, an eminent plant geneticist at Pennsylvania State University who is currently serving as senior scientific advisor to the U.S. Secretary of State, wrote: 'A new Green Revolution demands a global commitment to creating a modern agricultural infrastructure everywhere, adequate investment in training and modern laboratory facilities, and progress toward simplified regulatory approaches that are responsive to accumulating evidence of safety. Do we have the will and the wisdom to make it happen?' [5]

The Golden Rice story makes it clear that the answer is, not yet.

References

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