Golden Rice is safe to eat, says FDA

Golden Rice, the staple food genetically designed to contain beta carotene, a precursor to vitamin A, has been judged safe to eat by the US Food and Drug Administration (FDA). A letter from the FDA on May 24 stated that the agency had no further questions about the safety of the rice, originally developed to provide a rich source of vitamin A for children whose diets are deficient in this nutrient.

The rice has now been declared safe in four countries, including Australia, New Zealand and Canada. None of these decisions, including the FDA's, is a formal approval, but rather the local regulators reviewed data submitted by the Philippines-based International Rice Research Institute (IRRI) and declared they had no further questions about the rice's safety. Many, however, will see this latest move from the US agency as a stamp of approval, says Jennifer Kuzma, who studies attitudes to genetic engineering at North Carolina State University in Raleigh. And the regulators' positive opinion will be incorporated into the Organisation for Economic Co-operation and Development's consensus documents on biosafety, which other countries consult to help guide their own decisions on food safety.

Although the US has no plans to grow or import the rice, the FDA's decision is still important, says Kuzma. "Other countries often look to the FDA as the first mover," she says. And it will protect against legal issues and help defuse any controversy should imports of regular rice ever become accidentally contaminated with Golden Rice.

Golden Rice was created in response to a major nutritional crisis affecting some of the poorest countries in the world. But because it is genetically modified (GM), the beta-carotene-enriched crop has struggled to overcome public fears over genetically modified organisms (*Nat. Biotechnol.* **30**, 1017–1019, 2012). Opposition has been fierce throughout, even though the Golden Rice Project has a humanitarian board that included the crop's creators, and set out to make the nutritionally enriched rice available to low-income farmers and researchers throughout the developing world. The hope is that now, with the FDA's endorsement and other approvals, regulators in countries like Bangladesh and the Philippines, which are in the process of considering applications, will be emboldened to allow large-scale cultivation of the rice.

Work on Golden Rice began in the late 1990s by plant scientist Ingo Potrykus at the Swiss Federal Institute of Technology in Zurich, and biochemist Peter Beyer, at the University of Freiburg in Germany, as a way to combat vitamin A deficiency in the developing world. The technology, first reported in 2000 (*Science* **287**, 303–305, 2000) and later in 2005 (*Nat. Biotechnol.* **23**, 482–487, 2005), consists of inserting genes that control the biosynthetic pathway for beta carotene, a precursor to vitamin A, into rice. Initially, Potrykus and Beyer added two genes to the plant—a phytoene synthase from daffodils and a phytoene desaturase from a common soil bacteria—to turn on the beta-carotene-synthesis pathway in the grains. The beta-carotene-rich grains turned a deep golden color, giving the rice its name.

Vitamin A deficiency affects 250 million children, causing blindness in an estimated 250,000–500,000 children each year. This nutrient deficiency also compromises the immune system, leading to death from common childhood diseases like measles or diarrhea. By improving access to vitamin A, the enriched crop could prevent around 1–2 million childhood deaths each year, says Adrian Dubock,

David Greedy/Getty Images

It's been a bumpy road for Golden Rice, but now four countries have given it a green light.

First migraine-prevention antibody approved

On May 17, the US Food and Drug Administration approved a first-in-class monoclonal antibody drug to prevent migraine headache. Amgen's Aimovig (erenumab) is the first biologic drug to target the calcitonin-gene-related peptide (CGRP) receptor. CGRP signaling contributes to migraine pain, by inducing blood vessel dilation and pain sensitization on the trigeminal ganglion, outside the central nervous system. The antibodies act to prevent migraine pain by blocking CGRP. Unlike existing small-molecule CGRP antagonists used to treat acute migraine episodes, direct targeting of the peptide or its receptor with a monoclonal antibody is more specific, with few or no apparent adverse effects, and can be used as prevention (*Nat. Biotechnol.* **36**, 207–208, 2018). In phase 2 and 3 studies in chronic and episodic migraine, Aimovig significantly reduced monthly migraine days and use of acute migraine medications compared with placebo. In an ongoing open-label extension study in episodic migraine (4–14 headache days per month), these effects were sustained for up to 15 months. Also, a dedicated phase 3b study (LIBERTY) in individuals with episodic migraine who had failed two to four prior treatments showed that those taking Aimovig had nearly threefold higher probability of cutting their migraine days by half or more compared with placebo. Anticipating a crowded field for CGRP biologics, Amgen set Aimovig's price at $6,900 per year—considerably lower than analysts' expectations. Other monoclonal antibodies targeting the CGRP pathway in late-stage development include Petach Tikva, Israel–based Teva Pharmaceuticals' eptinezumab, Alder Biopharmaceuticals' fremanezumab and Eli Lilly's galcanezumab. Unlike Aimovig, these antibodies target the peptide itself. Amgen is partnering with Novartis to co-commercialize Aimovig in the US. In the deal, the Basel-based pharma also gained exclusive commercialization rights to the drug in Europe, Canada and elsewhere. Following on the heels of the US approval, on June 1, the European Medicines Agency's Committee for Medicinal Products for Human Use recommended granting a marketing authorization for Aimovig.

"[The thrill] is tainted with the knowledge that people are sick and dying. I think that tempers the excitement, because there's a reality that accompanies that that's very, very sad." Nancy Sullivan of the NIH Vaccine Research Center expresses mixed feelings about the start of a long-awaited vaccine trial with the recent Ebola outbreak in the Democratic Republic of the Congo. (*STAT*, 22 May 2018)

New money flows to CARB-X for antimicrobials

The UK government and the Bill & Melinda Gates Foundation in May joined a partnership dedicated to the development of new antibiotics, vaccines, diagnostics and other products against drug-resistant bacterial infections. The UK's Global AMR (antimicrobial resistance) Innovation Fund is committing up to £20 ($26.6) million and the Bill & Melinda Gates Foundation up to $25 million over the next three years to CARB-X, a non-profit, public-private partnership set up with the mission of averting the threat of drug-resistant diseases. With the new support, CARB-X has now amassed more than $500 million to invest through 2021 to accelerate innovation by supporting early-stage projects and phase 1 clinical trials. Geneva-based CARB-X was formed in 2016 with support from UK charity Wellcome Trust, the US Department of Health and Human Services Biomedical Advanced Research and Development Authority (BARDA) and the National Institute of Allergy and Infectious Diseases (NIAID). It currently has 33 projects ongoing in seven countries, including five drug candidates advanced to phase 1 trials and two diagnostics now in the system-integration and testing phase. Of the 27 current drug projects, 11 focus on new targets and 9 on new antibiotic classes. Four are biologics: one is a vaccine against *Staphylococcus aureus* and the other three, against *Pseudomonas aeruginosa*, include recombinant lysin protein, a multispecific antibody and an antibody–drug conjugate. Two are small molecules targeting the microbiome: *Clostridium difficile* and carbapenem-resistant Enterobacteriaceae/vancomycin-resistant Enterococci. Of the six device and/or diagnostic projects, three focus on development of hospital-based systems for identifying bloodstream infections. May 2018 also marked the official launch of the Global AMR Research & Development Collaboration Hub, announced at the 71st World Health Assembly in Geneva. The initiative was conceived in 2017 with initial support from the Bill & Melinda Gates Foundation and the Wellcome Trust. The secretariat of the Global AMR R&D Hub will initially be based in Berlin, at the German Center for Infection Research. Its 18 members also include Russia, China, the US, France and the European Commission.

"What genetic difference is it that we are going to root for anyway—the immune system differences between Switzerland and Egypt?" Ethicist Arthur Caplan of NYU School of Medicine takes exception at Fox Sports and 23andMe's ad campaign "Root for Your Roots", where they team up to generate interest in the World Cup. (*leapsmagazine*, 4 May 2018)

who worked on the early stages of the rice's development and is now executive secretary of the Golden Rice Humanitarian Board, set up to provide strategic guidance to the Golden Rice Project. "That's more mortality than is associated with tuberculosis, malaria or HIV," he says.

But the development of Golden Rice, the first crop engineered with traits to benefit consumers rather than enhance production, has taken far longer than anyone anticipated says Dubock. "I originally thought in 2001 that it would be available by 2003," he says. "Instead it has taken almost 20 years."

In 2001, the Swiss agricultural biotech Syngenta, where Dubock worked, took on Golden Rice development, in a complicated licensing arrangement, involving 23 agreements with 16 licensees, aimed at ensuring the rice would be distributed free to subsistence farmers in the developing world. The company's scientists made several improvements to the rice, such as substituting the daffodil phytoene synthase with an equivalent gene from maize that improved beta-carotene production. The new strain produced up to 37 μg per gram, such that a single serving could deliver more than half the recommended daily intake of beta carotene. In 2004, Syngenta withdrew from the project and since then, development has been carried out at independent research institutes, such as the non-profit research and educational institute IRRI, supported by charities including the Rockefeller Foundation and the Bill and Melinda Gates Foundation.

The rice has overcome a number of technical hurdles and controversies along the way. A 2012 study in China, which found that Golden Rice was as effective as beta-carotene oil at providing vitamin A to children, was retracted in 2015 due to a failure to obtain informed consent from the children's parents and faked ethics approval documents.

And in 2017, a study in India that crossed Golden Rice with a local variety found that the resulting plants were stunted and pale, and yield was reduced by as much as 60–70%. Many opponents of genetically modified crops leapt on that result as proof that the project was doomed. But, in general, when researchers insert genes into a plant genome, they must ensure it is done in a way that allows their expression without interfering with other genes. Ashok Singh, a plant geneticist at the Indian Agricultural Research Institute in New Delhi who led the study, identified the problem.

The stunted rice came from a genetic transformation known as the R event, in which the insertion disrupted an important native membrane transport gene called *OsAux1*. A different transformation event, called the E event, did not disrupt any native genes and has similar agronomic characteristics to native rice. "The problem had nothing to do with Golden Rice itself, it was event-associated," he says. It was data from rice based on the E event that were submitted to the FDA and other regulators.

Most scientists expect technical difficulties, says Russell Reinke who leads the healthier rice program at IRRI. "That's just the process of science happening as it should," he says. Singh is concerned, however, about the low carotenoid content of the E-event rice (just 11 μg per gram of grain), and its stability in the grain during processing and storage.

The FDA also noted that the levels of beta carotene were too low to make any claims about nutrient content. At such concentrations, the rice is not a viable solution for vitamin deficiency, says Paul Johnston, head of the environmental charity Greenpeace's science unit at the University of Exeter, and puts paid to any nutritional claims. "Given that that's what it is intended to solve, you've got to question what the point of it is," he says.

Greenpeace and other opponents of GM crops say that other interventions, such as increasing consumption of conventionally bred sweet potatoes rich in beta carotene, and ensuring people eat a diverse diet, are more effective at combating vitamin A deficiency than Golden Rice.

But IRRI's Reinke says the FDA's nutritional value calculation was based on the relatively small amount of rice people eat in the US. Based on consumption levels in Asia, where rice makes up to 70% of the daily calorie intake, Golden Rice could provide as much as half the average daily requirement of vitamin A, he says. Johnston is not sure Golden Rice will ever make it to the field. "It's always in the future, the time span never seems to compress," he says.

But the rice's proponents say they are getting closer to full deployment. The most important next step is receiving regulatory approval from Bangladesh and the Philippines to cultivate and allow people to eat the rice. IRRI submitted applications to both countries last year. Once approved, the Golden Rice trait will still need to be bred into local varieties, and feeding trials will then be necessary to ensure it has the desired nutritional result. Singh estimates it will take at least five to six years after approval to finally get the rice onto people's plates.

Even if regulators give a green light, changing political or social attitudes could add further twists and turns into Golden Rice's long road to acceptance. "If it was just the regulations, I would say it will be very soon. But the politics are very hard to control," says Dubock. "But it is clear that we are getting closer."

Brian Owens *St. Stephen, New Brunswick, Canada*