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## BUSINESS AND REGULATORY NEWS

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## Protein biopesticide may be next wave in pest control

Julie Grisham

A new type of protein-based biopesticide that gives a wide range of plants broad resistance to pests was approved by the US Environmental Protection Agency (EPA; Washington, DC) in April. The product, called Messenger, activates gene expression to induce a plant's natural defenses to pathogens and then quickly degrades, leaving no detectable residue. Eden Bioscience (Bothell, WA), the private biotech company that makes Messenger, says the product also improves quality, yield, and overall crop performance, and is an environmentally friendly substitute for more traditional, often toxic pesticides. However, many environmental and industry groups say they don't know enough about the product to comment.

Messenger is "the first product that offers growers a novel, effective, and environmentally sound tool for plant disease management; plant growth enhancement; and insect, mite, and nematode suppression," according to company literature. "The benefits to consumers are terrific," says Jerry Butler, Eden president and CEO.

Messenger is based on the harpin protein, which is derived from *Erwinia amylovora*, the common bacterium responsible for the fire blight disease of apples, pears, and related ornamental plants. After finding that harpin induced the hypersensitive response in plants—when plant cells essentially commit suicide in order to contain the spread of disease—researchers at Cornell University (Ithaca, NY) identified the gene responsible and characterized the protein in 1992 (*Science* 257, 85–88); Zhongmin Wei, who was first author, is now vice president of research at Eden. The team later found that harpin induced the systemic acquired resistance (SAR) pathway, acting as a kind of "immune-system booster," providing protection against a range of pathogens from bacteria to fungi to viruses.

According to Steven Beer, a plant pathology professor at Cornell and the leader of the research team, activation of the SAR pathway has not been completely characterized, but it is known that harpin activates physiological and molecular signaling and induces the activity of pathogenicity-related genes and proteins. In addition, Eden research has found that treatment with harpin activates the jasmonic acid–ethylene pathways and other plant growth systems that result in resistance to insects and enhanced plant growth. Messenger is manufactured by engineering the harpin gene into a weakened strain of *Escherichia coli*, but the *E. coli* is not released into the environment.

Novartis Crop Protection (Greensboro, NC) also has a product that acts on the SAR pathway. Actigard, which is synthetic, is undergoing US approval and is already sold in Europe, where it has been marketed since 1996 as an immune system activator called Bion. But a Novartis spokesperson says the package claims for Actigard will differ greatly from Messenger's in that it will be recommended only as a tool for disease management and not as a growth booster.

One industry expert, who wished to remain anonymous, suggests the claims for Messenger, especially the secondary effects of increasing plant growth and ripening rates, may be overblown. But Diana Horne, regulatory action leader for the Biopesticides and Pollution Prevention Division at EPA, believes Messenger has "tremendous potential" to reduce plant disease and that it boosts growth rates because "biomass is significantly increased" when the product is used. She says farmers who participated in field tests are anxious to use the product.

Indeed, Eden's Butler points out that because Messenger is virtually nontoxic, it is safe to farmers who apply it and its packaging requires no special treatment before disposal. "This is the right way to use biotechnology," he says. It "avoids the perceptions of the downsides of traditional biotech" because it does not involve altering a plant's DNA.

Charles Benbrook, an environmental consultant based in Sandpoint, ID, says he believes the product is part of a "veritable revolution in plant protection" and that it would be an "important and promising biopesticide" (if available on a cost-effective basis) because it greatly reduces the need for traditional pesticides such as methyl bromide, which are known to have deleterious effects on human health and the environment. Furthermore, some experts think Messenger could be the next *Bacillus thuringiensis* (Bt) toxin: a widely used natural pesticide that is generally accepted as being safe for the environment.

However, Mark Lipson, policy program director for the Organic Farming Research Foundation (Santa Cruz, CA), says the fact that Messenger is manufactured using transgenic methods means that it would be prohibited from use under current rules for organic farmers. Meanwhile, a spokesperson for environmental group Greenpeace (Washington, DC) says his group is still reviewing the technology and has no comment on it yet, and other environmental and industry groups also say they are not familiar enough with the product to comment.

Benbrook does note the importance of managing the product's use in order to avoid problems of acquired resistance. But Butler says Eden is not worried about resistance developing because the natural mechanism of resistance that Messenger activates does not cause a lot of selection pressure. EPA's Horne adds that Messenger doesn't interact directly with disease-causing pests.

Eden was founded in 1994 and has raised more than \$38 million to fund development of Messenger technology, its only focus. The Cornell Research Fund, which has an equity stake in Eden, holds the first patents on harpin, which it has licensed to Eden on a worldwide exclusive basis. In addition, Eden has about 160 non-US and US patents either already approved or in the works. Butler has no fears that the company has put all of its eggs in one basket because he believes "the fundamental science is terrific." He would not speculate on Messenger's potential market, but says Eden plans to seek regulatory approval worldwide, especially in developing countries, and expects to begin marketing and selling Messenger in the southeastern US in the next month or so.



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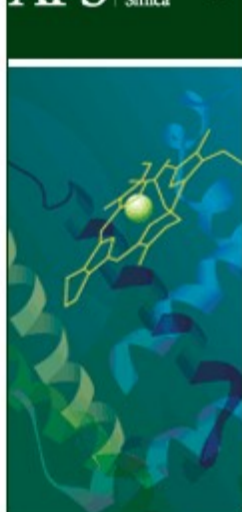
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