

# **MANUFACTURING DRUGS AND CHEMICALS IN CROPS:**

Biopharming Poses New Threats to Consumers, Farmers,  
Food Companies and the Environment

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# Manufacturing Drugs and Chemicals in Crops

## Biopharming Poses New Risks to Consumers, Farmers, Food Companies and the Environment

### Executive Summary

The biotechnology industry has promised to benefit farmers and consumers with revolutionary new products, yet it has created a host of problems. From contamination of the food supply with StarLink corn, to loss of exports due to commingling and cross-pollination with non-engineered crops, to lawsuits by biotech companies against farmers -- the industry has had negative impacts. Today, a new threat faces us all as a few maverick biotechnology companies are secretly planting a generation of crops that contain biopharmaceuticals, industrial enzymes, antibodies, and even contraceptives.

This report details the threats that these crops pose, the extent to which they have been planted across the U.S., the failure of regulatory agencies to serve the public, and a set of recommendations to protect farmers, consumers, food companies and the environment.

#### **What is “biopharming”?**

“Biopharming” is an experimental application of biotechnology in which organisms are genetically engineered to produce pharmaceutical proteins and chemicals they do not produce naturally. While most of these substances are kept secret as confidential business information (6.3), a few known examples include a contraceptive, potent growth hormones, a blood clotter, blood thinners, industrial enzymes, and vaccines. Corn is by far the most popular biopharm plant, followed by soybeans, tobacco and rice. Some 400 biopharm products are reportedly in the pipeline, and over 300 open-air field trials have already been conducted in unidentified locations across the country.

State	No. of Field Trials
Nebraska	37
Hawaii	36
Puerto Rico	35
Wisconsin	27
Iowa	20
Florida	14
Illinois	14
Texas	13
California	11
Maryland	11
Kentucky	10
Indiana	9

Crop	No. of Permits & Acknowledgements
Corn	134
Soybeans	22
Viral-vectored tobacco	10
Rice	9
Tobacco	9

*Table 1 (left): Top twelve open-air biopharm field trial states: 1991 to 6/18/02.*

*Table 2 (above): Top five crops for open-air biopharm experimentation: 1991 to 6/18/02*

#### **Could drugs and chemicals contaminate the food supply?**

Contamination of non-engineered or organic corn by engineered insecticides is already widespread. Iowa farmer Laura Krouse has seen her sales of open-pollinated corn drop 50-75% due to genetic pollution with engineered traits. An expert committee of the National Academy of Sciences foresees the same with biopharm crops:

*“...it is possible that crops transformed to produce pharmaceutical or other industrial compounds might mate with plantations grown for human consumption, with the unanticipated result of novel chemicals in the human food supply.”<sup>1</sup>*

There is already one report of biopharm contamination. According to Chris Webster of the drug company Pfizer:

***“We’ve seen it on the vaccine side where modified live seeds have wandered off and have appeared in other products.”<sup>2</sup> (6.3.3)***

Biopharm traits could spread through pollen carried by wind or insects, spilled seed, unharvested seed sprouting the next year (“volunteers”), and biopharm seed residues carried by farm equipment to conventional fields (5.4, 7.3.2). The editors of Nature Biotechnology warn bluntly:

***“Current gene-containment strategies cannot work reliably in the field ... Can we reasonably expect farmers to [clean] their agricultural equipment meticulously enough to remove all GM seed?”<sup>3</sup>***

Corn is especially risky for pharmaceutical applications because it readily cross-pollinates and its pollen can travel for over a mile. This is demonstrated by engineered StarLink corn, which contaminated food products and corn seed stock with a potentially allergenic protein even *with* the use of gene containment measures. Nevertheless, 2/3 of open-air biopharm field trials have been in corn, and experts warn that current isolation standards will not prevent contamination of normal corn (5.4.1, 6.4.5). Engineered viruses used to infect plants with drug genes could spread to related crops (4.7).

Gene containment mechanisms such as male sterility and tissue-preferred promoters are known to be “leaky.” The proposed use of Terminator seed-sterility technology to mitigate biopharm gene flow is unacceptable due to technical flaws, potential health & environmental hazards, and because it would serve to legitimize Terminator's chief intended use, which is to end the practice of seed-saving (5.6). Companies like ProdiGene have also proposed “dual-use” of biopharm plants – extracting the drug/chemical and then selling the rest for use as food or animal feed. Incomplete extraction would mean drug or chemical residues in food products and feed (4.3).

### **If food becomes contaminated, could these substances harm human health?**

- \* Plants process proteins differently than animals or humans. Thus, experts are concerned that a plant-produced “human” protein could be perceived as foreign by the body and elicit an allergic reaction, including life-threatening anaphylactic shock (4.1).
- \* Growth factors such as erythropoietin are active at billionths of a gram when injected, and “may be harmful by inhalation, ingestion or skin absorption.”<sup>4</sup> Those handling the substance are advised to wear a respirator and chemical-resistant gloves (4.9, 7.7).
- \* Trichosanthin, a potent abortion-inducing drug, has been introduced into tobacco by means of an engineered virus which is also known to infect tomatoes, peppers, and other tobacco relatives (4.7.3; Appendix 4).
- \* The research chemical/insecticide avidin causes a vitamin deficiency, and the blood clotter aprotinin can cause pancreatic disease in animals and perhaps humans. Both have been engineered into corn grown out-of-doors (4.5; Appendices 2 & 3).
- \* Corn-grown industrial enzymes such as trypsin and antitrypsin are known allergens. Trypsin corn is to be grown on hundreds of acres throughout the Corn Belt in 2002 (4.10).

### **Could plant-grown drugs and chemicals harm the environment?**

Conventionally-produced drugs are already a growing pollution nightmare, and plant-grown drugs and chemicals could make things worse (5.1). According to Dr. Glynis Giddings et al:

***“Biopharmaceuticals usually elicit responses at low concentrations, and may be toxic at higher ones. Many have physiochemical properties that might cause them to persist in the environment or bioaccumulate in living organisms, possibly damaging non-target organisms...”<sup>5</sup>***

- \* Aprotinin and other digestion-inhibiting enzymes shorten the lives of honeybees, while avidin is known to kill or chronically impair 26 species of insects (5.3.1).

- \* The risks to wildlife that eat biopharm corn and other crops increase as scientists learn to generate ever-higher concentrations of drugs and chemicals in these crops (5.1.2, 5.3.2).
- \* These substances have not been tested for effects on soil life, even though other engineered proteins are known to leak from roots and persist in the soil for months (5.2).

## **How are plants that grow drugs and chemicals regulated?**

The U.S. Dept. of Agriculture (USDA) has primary authority for experimental biopharm crop cultivation. USDA keeps all drug and chemical crop sites secret from the public and neighboring farmers, hides the identity of the drug or chemical in most cases, and condones biopharm companies' preferred practice of "anonymously" planting these crops without identification, security measures or notification of neighbors (6.3). Joe Jilka of ProdiGene, speaking of his company's corn engineered to produce a pig vaccine (TGEV), appears more concerned about theft than public safety (6.3.3):

*"...the best way to secure it is to grow it just like any other corn. In other words, the anonymity of it just completely hides it. You know, our TGEV corn grown [sic] was up here by Story City right by the interstate, and no one could have ever seen it."*<sup>6</sup>

USDA's gene confinement measures are intended to "minimize" rather than prevent contamination (6.4.5). The few environmental assessments conducted by the USDA are of poor quality (6.5.2), and show a disturbing willingness to bend the rules. For instance, a trial of alfalfa engineered with industrial enzymes was allowed to proceed despite the presence of non-engineered alfalfa "within 200 yards of the test site," less than the accepted isolation distance. The USDA approved the field trial plan even though it allowed open flowers, increasing the contamination risk, over the objections of the Wisconsin Dept. of Agriculture (6.4.5). USDA is not qualified to evaluate the health risks of biopharm crops (6.4.3), allows commercial use of biopharm plant products (6.4.4), and is too understaffed to exercise adequate on-the-ground oversight, for the most part allowing companies to regulate themselves (6.5). An expert committee of the National Academy of Sciences strongly criticized the USDA for these and other regulatory lapses and deficiencies.

The FDA will play some yet-to-be-defined regulatory role in the later stages of biopharm crop development. When contacted by telephone, FDA representatives were unwilling to speak about the agency's possible involvement in the review of biopharm trials conducted thus far, citing confidentiality claims by business, but public statements are not reassuring:

*"And I think to be honest, the FDA is used to applying regulations to manufacturing plants, but not to plants used for manufacturing. So a lot of this is new to us as well, and that's why I won't be able to answer any questions at the end!"*<sup>7</sup>

## **Would biopharming mean cheaper drugs and chemicals?**

Biopharm companies hope that growing drugs and chemicals in plants will be cheaper than conventional production methods through replacement of high-cost production facilities with the flexibility of low-cost contract farmers, meaning higher profits (7.1). However, others believe that biopharming will prove to be expensive and/or non-viable due to difficulties in purifying drugs and chemicals from plants (4.2), the costs of mitigating gene flow (7.3.1, 7.3.2), and litigation and liability costs from contamination (7.4). Barry Holtz of Large Scale Biology, a leading biopharm company, discounts glib predictions of "\$5 dollar a gram proteins," estimating that even high-volume plant-grown drugs would cost "hundreds to thousands of dollars a gram" to produce<sup>8</sup> (3.2).

The *sales* price would be higher still, as biopharm companies will have to recoup a huge load of sunken costs for research and development of this novel production system. Contrary to industry's oft-repeated promise of cheap drugs and chemicals, one of the only commercialized plant-grown products, the research chemical avidin, actually costs the same as the conventional version extracted from eggs, \$46-47 per 5 mg, or over \$9,000/gram (3.2). Initial hopes that plants engineered with vaccines could be delivered cheaply in raw form (e.g. bananas) have foundered due to inability to achieve consistent, or sufficiently high, vaccine levels in plants. Some scientists now believe that the vaccines (if successfully developed)

would have to be extracted from plants and processed into pill or powder form, increasing the cost of delivery (4.6).

## **What do drug-growing plants mean for farmers?**

Biopharm companies normally contract with selected farmers to grow their drug or chemical crops. But *all* farmers are exposed to substantial liability from biopharming, whether they choose to plant these crops or not: 1) Neighboring farmers whose fields become contaminated with drug or chemical traits could sue biopharmers; 2) Biopharm companies could discover their patented drug traits in conventional farmers' contaminated fields, and then sue, alleging violation of the company's "intellectual property" rights; 3) Government agencies could bring enforcement actions for breach of regulations (7.4).

Other disadvantages of biopharming for growers include health risks from inhalation of and contact with potent drugs and chemicals (7.7), intrusive on-site inspections by company managers and government regulators, expensive and time-consuming changes in farming practices (e.g. to mitigate contamination) (7.3), and possible loss of export markets due to contamination (7.5). Against these risks and drawbacks, farmers are being promised a slight premium for biopharm crops, though probably not sufficient to cover the added costs and risks. In 2001, however, ProdiGene-Stauffer Seeds CEO Anthony Laos reneged on the company's promise of a modest 40% premium to corn biopharmers, admitting: "we cannot guarantee acres or premiums."<sup>9</sup> Biopharm acreage is projected by most in the industry to be rather low, so few will plant these crops in any case (7.2).

## **Are there other ways to produce these drugs and chemicals?**

Proven methods include extraction from animal or human tissues and production in animal, bacterial and yeast cell cultures. Newer techniques include plant cell cultures and secretion of biopharm proteins from plant roots into hydroponic media. In contrast to open-air biopharming, these methods are contained, greatly reducing contamination risks; they allow complete control of growth conditions, meaning more consistent drug quality; and purification is easier than from whole-plant tissue. One drug already grown in plant cell culture is the anticancer drug Taxol. Applied Phytologics has experimentally produced the same cystic fibrosis drug (alpha-1-antitrypsin) in both open-air rice plantings and rice cell culture, obtaining very high yields and purity with the latter method. (Appendix 5)

## **With all these risks, should open-air biopharming be permitted at all?**

In a submission to the Canadian Biotechnology Advisory Committee, geneticist and biochemist Dennis R. McCalla and colleagues point to the potential health impacts from inadvertent consumption of plant-grown vaccines, stating that there is a "very high probability" that "plants engineered to produce pharmaceuticals, enzymes [and] industrial chemicals" will contaminate the human food supply. "Only species that are not consumed by humans or by livestock should be permitted for the production of these substances"<sup>10</sup> (3.3; see "Recommendations"). The Genetically Engineered Food Alert Coalition agrees, and recommends that only contained, non-food alternatives to open-air biopharming be allowed.

## **Endnotes**

<sup>1</sup> "Environmental Effects of Transgenic Plants: The Scope and Adequacy of Regulation," Committee on Environmental Impacts Associated with Commercialisation of Transgenic Plants of the National Academy of Sciences, National Academy Press 2002, p. 68.

<sup>2</sup> See "Plant-Derived Biologics Meeting" transcript, April 5 & 6, 2000. [www.fda.gov/cber/minutes/plnt2040600.pdf](http://www.fda.gov/cber/minutes/plnt2040600.pdf), p. 77.

<sup>3</sup> Nature Biotechnology (2002). "Going with the flow," Editorial, Vol. 20, No. 6, June 2002, p. 527.

<sup>4</sup> "Erythropoietin: Material Safety Data Sheet," Sigma Chemical Company. Available at [www.sigmaaldrich.com](http://www.sigmaaldrich.com).

<sup>5</sup> G. Giddings et al (2000). "Transgenic plants as factories for biopharmaceuticals," Nature Biotechnology, 18, pp. 1154.

<sup>6</sup> "Plant-Derived Biologics Meeting" transcript, [www.fda.gov/cber/minutes/plnt2040600.pdf](http://www.fda.gov/cber/minutes/plnt2040600.pdf), pp. 77-79.

<sup>7</sup> Michael Brennan of the FDA, as quoted in ref. 5, p. 52.

<sup>8</sup> Plant-Derived Biologics Meeting transcript, [www.fda.gov/cber/minutes/plnt1040500.pdf](http://www.fda.gov/cber/minutes/plnt1040500.pdf), p. 75.

<sup>9</sup> Stauffer Letter (2001). Letter from Anthony Laos to Customers, Summer 2001, see [www.staufferseeds.com](http://www.staufferseeds.com).

<sup>10</sup> McCalla et al (2001). "Regulation of Genetically Modified Food: A Submission to the Canadian Biotechnology Advisory Committee," April 17, 2001. See: [www.rsc.ca/foodbiotechnology/indexEN.html](http://www.rsc.ca/foodbiotechnology/indexEN.html).

# **Manufacturing Drugs and Chemicals in Crops: Biopharming Poses New Risks to Consumers, Farmers, Food Companies and the Environment**

## **Recommendations**

- 1) Stop granting permits for open-air cultivation of all crops genetically engineered with biopharmaceuticals (such as vaccines), industrial chemicals, or other substances with potential human health impacts.** Crops engineered with industrial biochemicals are not approved for human consumption. Crops engineered with drugs are, at best, approved for consumption only by people with a doctor's prescription.
- 2) Allow, at most, the genetic engineering of chemicals or biopharmaceuticals into those non-food crops that do not pose the risk of food contamination.** The USDA has issued "split approval" permits allowing cultivation of ten food crops engineered to produce biopharmaceuticals or chemicals that are not approved for general human consumption in more than 300 field trials conducted across the country from Hawaii, to Iowa, to Florida. The USDA should end this practice to ensure that these substances never enter the human food supply.
- 3) Require non-food crops engineered with chemicals or biopharmaceuticals to be cultivated indoors and establish a tracking system governing the handling and disposal of byproducts to prevent environmental contamination.** As there has been virtually no study of the environmental toxicity and persistence of biopharmaceuticals and chemicals engineered into plants, it is irresponsible to permit their open-air cultivation.
- 4) Explore contained alternatives to open-air biopharming for production of biopharmaceuticals.** In addition to currently used techniques such as bacterial, yeast and mammalian cell cultures, plant cell cultures and rhizosecretion (secretion of biopharmaceuticals from plant roots) show much promise. Unlike biopharming, these methods are conducted in controlled production facilities, and so do not present the risk of contamination.