



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

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What is “biopharming”?

“Biopharming” is an experimental application of biotechnology in which plants 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, a few known examples include a topical 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. U.S. Dept. of Agriculture records show that since 1991, at least 346 open-air field trials of crops engineered to produce pharmaceutical, industrial and novel compounds have been authorized in unidentified locations in 37 states.¹

State	No. of Field Trial Authorizations
Nebraska	38
Hawaii	37
Puerto Rico	37
Wisconsin	27
Iowa	22
Illinois	16
Florida	14
Texas	14
Maryland	13
California	12
Kentucky	10
Indiana	10

Crop	No. of Field Trial Authorizations
Corn	138
Soybeans	23
Viral-vectored tobacco	10
Rice	9
Tobacco	9

Table 1 (left): Top twelve open-air biopharm field trial states: 1991 to 2/16/04.

Table 2 (above): Top five crops for open-air biopharm experimentation: 1991 to 2/16/04.

Could drugs and chemicals contaminate the food supply?

Pharmaceutical traits can spread through dispersal of seed or pollen. Seeds can be transported long distances by birds or animals. Harvesting equipment can carry biopharm seed residues to conventional fields, or seeds can be spilled from trucks. Perhaps most difficult to control are "volunteers," unharvested seed that sprouts the next year. Corn pollen can travel for over a mile on the wind, and insects can fertilize conventional crops with biopharm pollen. Thus, it is no surprise that an expert committee of the National Academy of Sciences has concluded that containment of pharmaceutical and other biotech traits is virtually impossible.²

Two contamination incidents involving industry leader ProdiGene, Inc. in 2002 prove the point. In Nebraska, volunteer biopharm corn sprouted among soybeans planted in the same field the following year. 500,000 bushels of soybeans intended for infant formula and veggie burgers were contaminated, and had to be destroyed, one step away from the food supply. In Iowa, biopharm corn cross-pollinated a neighboring field, necessitating destruction of 150 acres of potentially contaminated corn.³

Even the editors of *Nature Biotechnology*, the industry's leading journal, are concerned. In a scathing editorial entitled "Drugs in crops - the unpalatable truth," they state:

"...we should be concerned about the presence of a potentially toxic substance in food plants. After all, is this really so different from a conventional pharmaceutical or biopharmaceutical manufacturer packaging its pills in candy wrappers or flour bags or storing its compounds or production batches untended outside the perimeter fence?"⁴

The risk of contamination increases exponentially as companies gear up from field trials of a few acres to commercial plantings of dozens to hundreds of acres.

Gene containment mechanisms such as male sterility and chloroplast transformation are known to be “leaky.” One biopharm crop touted as being male-sterile (avidin corn) actually has partially or fully fertile pollen in 18% of tested plants. 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. 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.

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.
- * Growth factors such as erythropoietin are active at billionths of a gram when injected, and “may be harmful by inhalation, ingestion or skin absorption.” Those handling the substance are advised to wear a respirator and chemical-resistant gloves.
- * 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.
- * 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.
- * Corn-grown industrial enzymes such as trypsin and antitrypsin are known allergens. Trypsin corn was grown on hundreds of acres throughout the Corn Belt in 2002.

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. 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...”⁵

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

How are plants that grow drugs and chemicals regulated?

The U.S. Dept. of Agriculture (USDA) has primary authority for experimental biopharm crop cultivation. Despite recently strengthened regulation, USDA still 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. Joe Jilka of ProdiGene, speaking of his company’s corn engineered to produce a pig vaccine (TGEV), seems more concerned about theft than public safety:

“...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 [Iowa] right by the interstate, and no one could have ever seen it.”⁶

USDA's gene confinement measures are intended to "minimize" rather than prevent contamination. The few environmental assessments conducted by the USDA are of poor quality, and show a disturbing willingness to bend the rules. USDA allows commercial use of biopharm plant products, and is too understaffed to exercise adequate on-the-ground oversight, for the most part allowing companies to regulate themselves. Under pressure from consumer groups and food companies, USDA finally agreed in January 2004 to conduct an environmental impact assessment of biopharming, though it has no mandate to examine potential impacts on wildlife.

FDA does not regulate biopharm field trials or assess the potential health impacts of contaminated food crops, limiting its role to assessment of the extracted pharmaceutical itself at the clinical trial stage (after years of field trials). Even in the area of biopharm drug safety, FDA has issued only recommendations, not regulations. For instance, FDA has *not* prohibited use of pesticides on drug crops, has no clear protocols for allergenicity testing of these drugs, and leaves open a loophole for potential dual-use of biopharm crop residues for food or animal feed.⁷

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, which would mean higher profits. However, others believe that biopharming will prove to be expensive and/or non-viable due to difficulties in purifying drugs and chemicals from plants, the costs of mitigating gene flow, and litigation and liability costs from contamination. Barry Holtz of Large Scale Biology, a leading biopharm company, undermines industry's exaggerated public predictions of "\$5 dollar a gram proteins," with his own estimate that even high-volume plant-grown drugs would cost "hundreds to thousands of dollars a gram" to produce.⁸

The *sales* price would be higher still, as biopharm companies will have to recoup a huge load of sunken costs for 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, costs twice as much as the conventional version extracted from eggs.⁹ 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 ever successfully developed) would have to be extracted from plants and processed into pill or powder form, increasing the cost of delivery.

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) Food companies with contaminated products could sue farmers or biopharm companies; 2) Government agencies could bring enforcement actions for breach of regulations; 3) Biopharm companies could discover their patented drugs in conventional farmers' contaminated fields, and then sue, alleging violation of the company's patent.

Other disadvantages of biopharming for growers include health risks from inhalation of and contact with potent drugs and chemicals, intrusive on-site inspections by company managers and government regulators, expensive and time-consuming changes in farming practices (e.g. to mitigate contamination), and possible loss of export markets due to contamination. 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, former ProdiGene-Stauffer Seeds CEO Anthony Laos reversed the company's promise of a modest 40% premium to corn biopharmers, admitting: "we cannot guarantee acres or premiums."¹⁰ Biopharm acreage is projected by most in the industry to be rather low, so few will plant these crops in any case.

How does biopharming compare to other production methods?

Despite 13 years of field testing, not a single plant-made pharmaceutical has received FDA approval. In contrast, over 100 biopharmaceuticals like insulin are produced in drug factories employing animal, bacterial and yeast cell cultures, a \$41 billion industry. Others are extracted from animal or human tissues. These methods produce real drugs that are helping people now. 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 good results with the latter method.

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

The number of biopharm field trials in the U.S. has dropped dramatically from a peak of 42 in 2000 to just 6 in 2003. This is attributable to strong opposition from consumer groups, the food industry¹¹ and a growing number of scientists. As a result, biopharming is now being irresponsibly promoted in developing countries - one more example of exporting a "dirty" industry overseas to take advantage of weak regulation.¹² 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."¹³ Friends of the Earth agrees, and recommends that only contained, non-food alternatives to open-air biopharming be allowed.

Endnotes

¹ See USDA's GE crop field trial website at www.nbiap.vt.edu/cfdocs/fieldtest1.cfm. Search on "phenotypes" antibody, industrial enzyme(s), novel protein and pharmaceutical protein for the crops considered in this report.

² "Biological Confinement of Genetically Engineered Organisms," National Academy of Sciences, National Academy Press 2004. See www.nap.edu/catalog/10880.html.

³ Toner, M. "Alarms sound over 'biopharming': Tainted crops cast doubt on gene altering," *The Atlanta Journal and Constitution*, 11/17/02; Ferber, D. "Something funny down on the pharm," *Popular Science*, April 2003.

⁴ *Nature Biotechnology*, February 2004, Vol. 22, Number 2, p. 133.
See: <http://www.nature.com/cgi-taf/DynaPage.taf?file=/nbt/journal/v22/n2/full/nbt0204-133.html>.

⁵ G. Giddings et al (2000). "Transgenic plants as factories for biopharmaceuticals," *Nature Biotechnology*, Vol. 18, p. 1154.

⁶ "Plant-Derived Biologics Meeting" transcript, www.fda.gov/cber/minutes/plnt2040600.pdf, p. 77.

⁷ See "Guidance for Industry: Drugs, Biologics and Medical Devices Derived from Bioengineered Plants for Use in Humans and Animals" at www.fda.gov/cber/gdlns/bioplant.pdf. See also comments by Friends of the Earth at www.foe.org/biopharm/commentsguidance.pdf.

⁸ "Plant-Derived Biologics Meeting" transcript, www.fda.gov/cber/minutes/plnt1040500.pdf, p. 75.

⁹ From 2/18/04 search of Sigma-Aldrich website: www.sigmaaldrich.com. Compare product A8706 (corn avidin) and A9275 (egg white).

¹⁰ Stauffer Letter (2001). Letter from Anthony Laos to Customers, Summer 2001.

¹¹ "No Use of Food or Feed Crops for Plant-Made Pharmaceutical Production Without A '100% Guarantee' Against Any Contamination, Says NFPA," National Food Processors Association, Feb. 6, 2003. See: www.nfpa-food.org/news_release/020603newsrelease.htm.

¹² See www.molecularfarming.org and www.molecularfarming.com/stats.html.

¹³ 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.

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For the fully-documented report on which this fact sheet is based, see www.foe.org/biopharm.



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