
PHARM AND INDUSTRIAL CROPS



THE NEXT WAVE OF AGRICULTURAL BIOTECHNOLOGY



TABLE OF CONTENTS

INTRODUCTION | WHAT ARE THESE CROPS? | WHAT WILL THEY PRODUCE? | WHY USE CROPS?
WHAT ARE THE POTENTIAL BENEFITS? | WHICH CROPS ARE BEING USED? | WHAT COMPANIES AND UNIVERSITIES
ARE INVOLVED? | WHERE ARE THE CROPS BEING GROWN? | HOW BIG WILL THE INDUSTRY BE?
ARE ANY SUCH PRODUCTS CURRENTLY ON THE MARKET? | WILL THESE CROPS DELIVER ON THEIR PROMISE?
WHAT ARE THE RISKS? | POLICY RECOMMENDATIONS | SUMMARY | REFERENCES



Union of Concerned Scientists

THE NEXT WAVE OF AGRICULTURAL BIOTECHNOLOGY – THE PHARM AND INDUSTRIAL CROPS – IS MOVING TOWARD THE MARKETPLACE. THESE NEW CROPS – ESSENTIALLY BIOLOGICAL FACTORIES FOR A VARIETY OF CHEMICAL PRODUCTS – PRESENT IMPORTANT NEW POLICY CHALLENGES THAT DEMAND A VIGOROUS PUBLIC DEBATE. WE HOPE THIS BACKGROUND BRIEFING WILL HELP RAISE THE PROFILE OF THIS ISSUE WITH DECISION-MAKERS AND ENGAGE CITIZENS AND CONSUMERS IN GUIDING THE FUTURE OF THESE IMPORTANT NEW APPLICATIONS OF BIOTECHNOLOGY. ►

INTRODUCTION ►

So far, agricultural biotechnology has concentrated on adding traits — primarily herbicide tolerance and insect resistance (Bt) — that make crops cheaper or easier for farmers to grow and, in some cases, reduce the use of environmentally harmful pesticides. These crops have precipitated a complex and important debate, especially in the global marketplace. Because engineered crops may present risks, particularly to the environment, some critics (including UCS) believe that the federal government must strengthen the regulatory system governing agricultural biotechnology products so that their risks and benefits can be evaluated carefully before they come to market. Others have questioned the taking of any risks to enhance the production of crops already in over-supply.

While that debate still rages, a new generation of agricultural biotechnology crops looms. We're calling the new products — crops engineered as biological factories — pharm and industrial crops.

Some of these applications (particularly the pharm crops) promise benefits, such as low-cost drugs, important to consumers as well as farmers. On the other hand, again unlike the plants engineered for new agronomic traits, pharm crops pose obvious risks. Unless stringently regulated, gene escape will

put biologically active compounds in many unwanted places in the environment and food supply. No one wants drugs in their corn flakes.

WHAT ARE PHARM AND INDUSTRIAL CROPS? ►

Pharm and industrial crops are plants genetically engineered to produce medical and industrial products, including human and veterinary drugs and biologics and industrial and research chemicals. Crops intentionally treated with genetically engineered viruses that, in turn, produce an industrial or medical substance in the infected plants are also considered industrial or pharm crops. In general, the term “pharm crops” refers to plants producing drugs or biologics and “industrial crops” to those producing industrial or research chemicals.

Pharm and industrial crops are produced by the same methods used to genetically engineer food crops. Briefly, scientists use recombinant DNA techniques to locate and isolate genes of pharmaceutical or industrial interest. These “transgenes” are then inserted into a crop plant using one of several methods now standard in the industry. The resulting pharm or industrial plant then produces the protein product encoded by the transgene as if it were one of its own naturally occurring genes.

Farmers can grow pharm and industrial crops in the same way they do unaltered crops.

For most pharm and industrial uses, scientists plan to extract the novel proteins (or the compounds produced as a result of the function of the novel proteins) from the industrial or pharm crop and purify them before use. In such cases, the new proteins in the crops may or may not be harmful. In some cases, the novel products will be delivered in active form to people or animals in the edible fruit or other parts of the plant.

WHAT KIND OF SUBSTANCES DO PHARM AND INDUSTRIAL CROPS PRODUCE? ►

Scientists and companies are developing and testing a large number of crops producing pharmaceuticals, biologics, and industrial and research chemicals. (Biologics are diagnostic or therapeutic products derived from living sources and are typically complex mixtures not easily identified or characterized.) A few of the products are discussed below. Names of many more crop-produced chemicals which are under development are not available to the public because under federal laws companies may withhold this information as confidential business data. Except where noted, the products described have not been commercialized.

Pharmaceuticals or drugs. Pharmaceuticals (or drugs), which are, generally speaking, chemicals intended to diagnose, treat, or prevent diseases, are being produced in a number of pharm plants. Among them are alpha-galactosidase and gluco-

cerebrosidase, enzymes to treat Fabry's and Gaucher's diseases, respectively.

Other proteins called "defensins" are being manufactured in plants with hopes that their antimicrobial characteristics will make them useful replacements for antibiotics. Drugs are also being produced as anti-coagulants, blood substitutes, and hormones, and for wound repair and the treatment of anemia, liver cirrhosis, cystic fibrosis, HIV, and hepatitis B and C.

Biologics. Biologics are complex biological products such as antibodies, vaccines, and blood products used in human and veterinary medicine. In the biologics category, pharm plants are producing antibodies against the bacterium that causes tooth decay and for treatment of non-Hodgkin's lymphoma. Vaccines against hepatitis B, rabies, HIV, malaria, autoimmune diabetes, and cholera are being produced in tobacco, corn, or potato plants. These vaccines

will be purified from the plants before being given to humans, most likely by injection or as a pill.

Crop-derived vaccines meant to be presented as food (edible vaccines) have been produced against diseases including, among others, measles, polio, diphtheria, yellow fever, and various types of viral diarrhea. These vaccines are being made in tomato fruit and other plant

parts that can be eaten raw. (Cooking typically destroys the efficacy of vaccines.)

Plant-produced edible vaccines are also being manufactured for veterinary purposes. Scientists recently conducted clinical trials in which pigs were fed a vaccine produced in corn against transmissible gastroenteritis virus (TGEV), one of the most im-



portant diseases in swine. And a vaccine meant to promote resistance to mink enteritis virus, canine parvovirus, and feline panleukopenia virus has been made in blackeyed beans.

Industrial chemicals. Industrial chemicals are compounds used in the manufacture of products like paper, plastics, personal care items, and laundry detergents. Many industrial chemicals are enzymatic proteins that promote the chemical reactions necessary for a particular manufacturing process. Trypsin, an enzyme traditionally isolated from bovine sources and used in large volumes in the detergent and leather industries, for example, and laccase, another enzyme used in making detergents but also in the manufacturing of fiberboard, are being produced in transgenic corn.

Other useful industrial chemicals are the products of chemical reactions driven by enzymes, rather than enzymes themselves. Introducing particular enzymes into industrial crops can result in production of these types of industrial chemicals. For example, the first commercialized industrial crop incorporated a gene from the California bay tree to change the fatty acid biosynthesis pathways in canola. The added gene dramatically altered canola oil composition such that nearly 40% of the oil was comprised of lauric acid, a key raw material in the manufacture of soap, detergents, and cosmetic products. Conventional canola does not contain lauric acid.

Research chemicals. Chemical compounds used in research and diagnostic laboratories are referred to as research chemicals. The protein avidin, utilized for purifying other proteins, was the first research chemical commercialized from an industrial crop in 1997. Beta-glucuronidase, another enzyme used extensively for plant molecular biology research, was also commercialized in 1997.

Multi-purpose chemicals. The same plant-produced chemical may be used for different purposes. For example, the enzyme trypsin, discussed above as an industrial chemical, also has medical and research uses. Thus, corn plants engineered to synthesize trypsin are producing pharmaceuticals as well as industrial and research chemicals.

WHY ARE COMPANIES PRODUCING DRUGS AND INDUSTRIAL CHEMICALS IN CROPS? ➤

For years, manufacturers have used bacterial fermentation systems or mammalian cell cultures to produce industrial chemicals and drugs. More recently, transgenic mammals have been used as “bioreactors” to make valuable proteins in milk. For several reasons, however, a relatively new sector of the biotechnology industry views plants as preferable for protein production.

Companies have several reasons for turning to plants biofactories: cheaper production, more flexible manufacturing, and avoidance of controversies associated with animal systems.

Cheaper production. The biggest reason for turning to engineered crops is cheaper production. Companies believe production costs will be significantly lower than for bacterial fermentation, cell cultures, or animal bioreactors systems. The biggest factor in reducing costs is the high yields of recombinant proteins attainable in transgenic plants. Production costs for corn systems are estimated to be between \$10 and \$100 per gram for proteins that currently cost as much as \$1,000 per gram. Dollar figures based on large-scale tobacco production vary widely from less than \$10 per gram to \$1000 per gram.

If realized, the optimistic projections of these companies would represent substantial savings over current costs. Vaccines, for example, can cost thousands of dollars per gram.

Faster, more flexible manufacturing. Using a subsidized commodity like corn and the environment as a production (although notably not a purification/processing) facility could cut not only production costs but also capital investment in, and the time it takes to increase, manufacturing infrastructure. It could also allow for extremely rapid scale-up (or scale-down) of a production pipeline in response to market or other factors. New drugs could, theoretically, become available sooner.

Less controversy than animal production systems. Because most scientists believe that plants cannot transmit animal pathogens (that can cause diseases like mad cow), the companies creating pharm and industrial plants promote their products as safer than animal-sourced proteins. (Plants as bioreactors present their own risks of product contamination, however, from mycotoxins, pesticides, herbicides or endogenous plant secondary metabolites like nicotine and glycoalkaloids.)

Using plants as bioreactors also avoids any animal welfare and certain ethical concerns associated with cloning animals and using them as bioreactors.

Organism-specific advantages. Companies that produce pharmaceutical and industrial proteins in corn kernels claim their system alleviates problems of product storage, shipment and purification that often arise with bacterial and animal models.

WHAT ARE THE POTENTIAL SOCIETAL BENEFITS OF PHARM AND INDUSTRIAL CROPS? ➤

Companies have high hopes that their products will offer substantial societal benefits including lower drug prices for consumers, drugs unavailable any other way, new value-added products for farmers, and inexpensive vaccines for the developing world.

Lower drug prices. Expected savings on infrastructure and production costs lead companies producing pharm and industrial crops to predict drug prices 10 to 100 times lower than current prices. The cost of treating a patient with Fabry's disease, currently as much as \$400,000 a year, for example, is predicted to drop to approximately \$40,000 annually. Similarly, it is claimed that the leaves from only 26 tobacco plants could make enough glucocerebrosidase, currently one of the most expensive drugs in the world, to treat a patient with Gaucher's disease for a whole year.

Drugs unavailable any other way. Cheap production also means that drugs that could not be produced cheaply enough at high volume through conventional methods might become economically viable using genetically engineered crops. Monoclonal antibodies ("plantibodies") fall into this category. One company's idea for such a product is a monoclonal antibody against bacteria responsible for tooth decay, which could be used as a dental prophylactic. A topical therapeutic for herpes, as well as antibodies for the treatment of many other diseases, is also under development.

New value-added agricultural products. Although much about the arrangements between farmers and chemical and drug manufacturers remains unclear, these crops are being touted as a boon to

farmers. Some companies, as they solicit contract growers, are promoting these crops as an economically viable alternative to commodity production of corn or tobacco with claims that their “partners realize improved returns relative to other production systems.”

Inexpensive, easily delivered vaccines. Food plants engineered to contain pieces of disease agents can function as orally administered vaccines, avoiding the need for injection and syringes. Currently, tomatoes and other vegetables are under development for that purpose. Although the vaccines would still have to be standardized for dose and delivered to patients one at a time, the developers hope that the lower production costs and the convenience

of avoiding refrigeration would make the products attractive to the developing world.

WHICH CROPS ARE BEING USED? ►

Corn is by far the most popular pharm and industrial crop. Since the early 90's, the US Department of Agriculture has allowed more than 200 field trials of pharm and industrial crops. In nearly three quarters of these tests, corn has been the crop of choice. Other crops tested include tomato, rice, barley, alfalfa, sugarcane, soybean, potato, lettuce, lupine, tobacco, and rapeseed (canola). Significantly, most of these plants are food crops, many are feed crops, and all of them can be ingested in some way.

WHAT COMPANIES AND UNIVERSITIES ARE ENGINEERING PHARM AND INDUSTRIAL CROPS? ►

Below is a list of some of the companies and universities currently involved in the development of pharm and industrial crops, with website addresses if available.

COMPANIES

Applied Phytologics (www.apinc.com)

*Boyce Thompson Institute
for Plant Research
(<http://www.bti.cornell.edu>)*

CropTech (www.croptech.com)

DuPont (www.dupont.com)

EPlcyte (www.epicyte.com)

*Integrated Protein Technologies,
a subsidiary of Monsanto
(www.iptbio.com)*

*Large Scale Biology Corporation
(www.lsbcc.com)*

Medicago (www.medicago.com)

*Meristem Therapeutics
(www.meristem-therapeutics.com)*

Planet Biotechnology

ProdiGene (www.prodigene.com)

SemBioSys (www.sembiosys.ca)

*Stauffer Seeds
(www.staufferseeds.com)*

*Ventria Bioscience
(www.ventriabio.com)*

UNIVERSITIES

Iowa State University

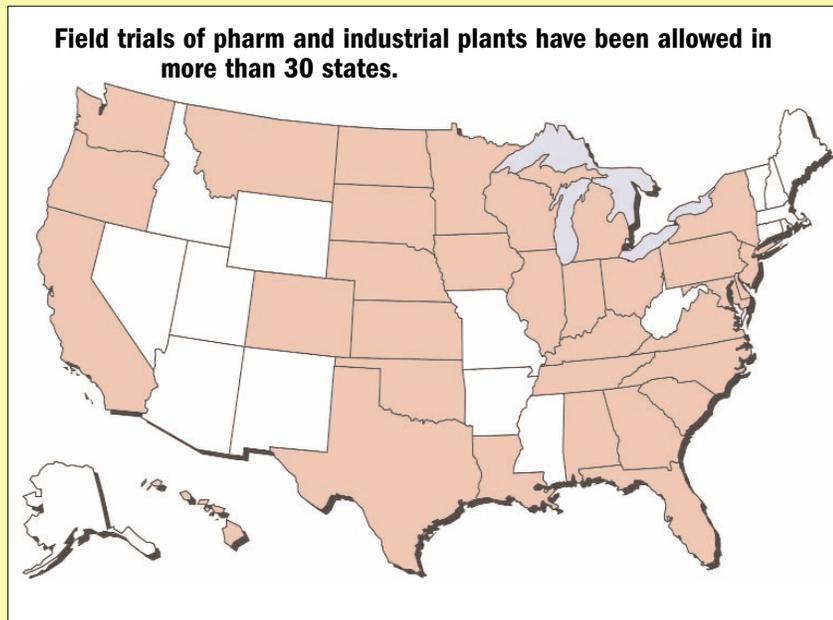
University of Hawaii

University of Wisconsin

Washington State University

WHERE ARE PHARM AND INDUSTRIAL CROPS BEING GROWN?

Field trials of pharm and industrial plants have been allowed in Alabama, California, Colorado, Delaware, Florida, Georgia, Hawaii, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maryland, Michigan, Minnesota, Montana, Nebraska, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, South Carolina, South Dakota, Tennessee, Texas, Virginia, Washington, Wisconsin, and Puerto Rico.



HOW BIG WILL THE PHARM AND INDUSTRIAL CROP INDUSTRY BE? ➤

Industry projects that the market for plant-produced pharmaceutical and industrial proteins could reach \$200 billion by the year 2010. Tens of companies are in the midst of developing literally dozens of pharm and industrial crops in order to capture a share of that potential market. One commercial partnership boasts of “more than 15 high value industrial and pharmaceutical products in development.”

Currently, most pharm and industrial crop products are still in the field-testing stage where trials usually start with very small plots, from under one acre to 10 acres. As the crops get closer to commercialization, the size of test plots can increase dramatically. For example, during a government-

sponsored workshop held in Ames, Iowa, in April 2000, one California-based company claimed to have received a “policy statement” from the USDA indicating that it was “good to go” on a “thousand acres of production material.”

Once companies receive the go-ahead for commercialization, the acres needed to meet market demand will vary considerably from product to product. Some may require large plantings. One company estimates that filling the current US need for a single specific blood protein, for example, would require a tobacco pharm crop consisting of “thousands or hundreds of thousands of acres.” By contrast, some products, such as therapeutic vaccines and certain research chemicals will likely require only tens of acres of pharm or industrial plants to meet the specific demands of those particular markets.

ARE ANY PHARM OR INDUSTRIAL CROP PRODUCTS CURRENTLY ON THE MARKET IN THE UNITED STATES? ➤

There are no pharm (pharmaceutical or biologic) products on the market, although several are nearing the end of the development pipeline. At least two research chemicals and one industrial chemical have been marketed and others are expected soon.

Avidin, isolated from transgenic corn and used as a research chemical, was one of the first recombinant proteins from a pharm or industrial crop commercialized. It has been available from the Sigma-Aldrich Chemical Company since 1997.

Corn-produced beta-glucuronidase, an enzyme used in research laboratories, was also commercialized in 1997.

Laurate canola, engineered to produce high-laurate oil useful in soaps, cosmetics, and other products, was approved for use in 1995 but has not been a commercial success.

The company producing trypsin in corn plants expected to have limited quantities of this protein, used for industrial, drug, and research purposes, commercially available “in late 2002 with scale up to meet market demand in 2003.”

Several vaccines produced in various pharm plants are currently undergoing pre-market testing. Some are in preclinical trials, many are in early clinical tests, and at least one — the non-Hodgkin's lymphoma therapeutic cancer vaccine — was slated for late clinical trials by mid-2002. Regulatory approval for some of these plant-derived medical products is expected by 2004.

In Canada, the anticoagulant, hirudin, was briefly grown commercially in transgenic oilseed rape plants. (The company ceased production because of the potential for contaminating oilseed rape used for food and feed.)

WILL PHARM AND INDUSTRIAL CROPS DELIVER ON THEIR PROMISE? ➤

As with potential benefits and risks, chances of succeeding in the market place and delivering on promises will vary from product to product.

For example, while developers of edible vaccines have made progress, they have encountered many obstacles. Whole fruits cannot be used as the delivery system, for example, because detached plant organs continue to be metabolically active and vaccine levels may therefore change, either increasing or decreasing, with time after harvest. (Potatoes sprouting in storage are a good example of this metabolic activity.) Processing (at least partially) and batch-monitoring of vaccine-containing fruits would therefore be necessary, making storage and processing-associated costs additional issues that must be addressed before edible vaccines, at least for the developing world, are economically viable.

There are also hurdles to overcome in reducing production costs. The most optimistic estimates often do not include research and development, sales-associated, and other costs. Many, including the president of Baxter Healthcare Corporation's recombinant DNA business, have suggested that purification of some proteins from pharm and industrial plants will pose considerable cost-related challenges. Some analysts have even suggested that extraction and sales of conventional food products like meal, oil, and starch might be necessary to make some pharm and industrial crops economically viable.

Purification will be a big issue, especially for the drugs and vaccines. Standards of purity for vaccines and drugs are very high. Effectively purifying foreign proteins away from plant-produced contaminants and/or agricultural products like pesticides could prove formidable.

Even if costs of production are reduced, those savings may not be passed on to consumers as lower prices. Virtually none of the biotechnology food products on the market today in the United States deliver price benefits to consumers.

WHAT ARE THE RISKS ASSOCIATED WITH PHARM AND INDUSTRIAL CROPS? ►

Many of the novel substances produced in pharm and industrial crops exhibit high levels of biological activity and are intended to be used for particular purposes, under very controlled circumstances. None of these substances is intended to be incorporated in food or to be broadcast into the environment.

The magnitude of the risks such crops pose depends on many factors including which chemicals are involved, what organisms or environments are exposed, and the level and duration of the exposure. Humans, animals and the environment at large may be at risk.

The major concern at this point is that that non-food substances will contaminate the food supply. Substances intended for use as human drugs are especially problematic because they are intended to be biologically active in people.

Below is an overview of some potential harms to human and animal health and ecosystems, followed by a section on how genes might escape from the fields in which they will be grown.

Potential harms to human and animal health.

The novel chemicals produced by pharm and industrial plants are generally proteins or short polypeptides. (Some novel proteins, in turn, produce chemicals that usually are not proteins.) Both proteins and non-proteins can harm people and animals. Some proteins can act, among other things, as toxins, hormones, or allergens.

Chemicals vary in form and activity through their production cycle and are not always harmful. To illustrate, hirudin, a powerful blood thinner for treatment of heart attacks and strokes, was grown in canola as an inactive compound: only after extraction and purification from canola seeds did it become biologically active.

In addition, the intended mode of use can affect the likelihood of harm. Just because a substance would be bioactive if injected, for example, does not mean that it would be harmful if ingested.

Some of the most problematic substances include toxins, hormones, and allergens.

Toxins. Avidin is an example of a potential toxin. Avidin binds extremely tightly, essentially irreversibly, to biotin, a B vitamin necessary for basic metabolism. The tightness of the avidin-biotin bond makes avidin useful as a tool in research laboratories. Binding biotin effectively inactivates it, which can lead to biotin deficiency in living beings, including humans.

Biotin deficiency in humans affects first the skin, then the central and peripheral nervous systems and intestinal tract. If allowed to progress without treatment, biotin deficiency can be serious.

Because biotin is an essential nutrient in almost all organisms — deer, squirrels, mice, and birds — animals browsing in avidin-corn fields may also be affected, as might plants, earthworms, and soil microorganisms. (In view of its toxic potential, some researchers are exploring its possible use as a broad-spectrum bio-pesticide.)

Hormones. Hormones are of particular concern because they can produce substantial physiological effects in minute doses. Higher-than-normal levels of human growth hormone, for example, can cause gigantism in children and acromegaly (overgrowth of bone and connective tissue associated with reduced life expectancy) in adults.

Hormones are often developed as drugs and some are being developed in pharm plants. For example, human growth hormone, used to treat hypopituitary dwarfism in children, has been produced in transgenic tobacco. Some chemicals may mimic hormones and thereby disrupt endocrine function.

Allergens. Substances that can induce an allergic response are called allergens. Proteins that elicit immune responses upon ingestion in food are called food allergens and adding new proteins to food crops via genetic engineering may suddenly render familiar food dangerous to sensitive populations. Most proteins do not act as food allergens in humans, but the relatively few that do can be very dangerous. Proteins can also elicit immune responses if injected.

Plant-derived pharmaceutical and industrial proteins have the potential to cause unintended immune or sensitization responses in people who might unknowingly consume them as well as in patients treated with them. Plants modify the proteins they produce differently than do mammals and other organisms, and these modifications may affect characteristics related to allergenicity.

Routes of exposure to people and livestock – the food and feed system. Since most pharm and industrial plants are also the crops that provide food for people and feed for livestock, a major concern is the contamination of the food and feed supplies. Pharm and industrial plants have two major routes into the food and feed system: seed mixing and pollen flow.

Seed mixing. Physical mixing of seeds can occur during seed production, on the farm as a result of using the same machinery to plant or harvest both food crops and pharm and industrial crops, during seed storage or transport, or at the grain elevator or mill.

Pollen flow. Pollen flow is a more indirect way of introducing new genes into food. Wind-borne pollen from corn, currently the most popular pharm and industrial crop, can travel more than 50 yards, making possible fertilization of nearby corn, intended for food, by pharm or industrial plants. As a result, unsuspecting farmers who did not plant pharm corn could nevertheless wind up with food and feed crops contaminated with drugs, harvest them, and offer them for sale to mills. If seed corn is contaminated with drug genes, farmers could unknowingly plant food and feed corn containing biologically active proteins.

Pollen flow is an even wider route of exposure when plants like canola are used as pharm or industrial crops. Reportedly, canola pollen can spread as far as 15 miles from a parent plant and can not only fertilize other canola plants, but other crop plants (including turnip, Chinese cabbage, rutabaga and fodder rape) as well.

In situations where farmers save harvested seed to plant the next growing season, the contaminating genes and gene products may persist year after year.

Routes of exposure to the environment.

Novel pharm and industrial substances have many routes to the environment. Since genetic engineers often cannot completely confine expression of new genes to particular tissues, pharm and industrial proteins will probably be produced throughout the plants. As discussed above, most of the pharm and industrial genes will be carried, and sometimes expressed, in pollen.

Grazing wildlife. Even if all the pollen, as well as the seeds and other plant material, associated with every pharm and industrial crop remained within the confines of the fields in which they were planted, wildlife could still be exposed. As anyone who has attempted to keep deer out of a vegetable garden

or birds from fruit trees can attest, animal consumption of field crops is essentially unavoidable.

Pollinators, herbivorous insects, and soil inhabitants.

Pollinators and herbivorous insects will undoubtedly frequent pharm and industrial crop fields as well. Microbes and other animals present in the soils of pharm and industrial crop fields will also be exposed to the compounds produced in these plants via a process scientists refer to as “rhizosecretion” (the exudation of substances from plant roots or when the agricultural byproducts of these crops are plowed back into the earth to “dispose” of them through composting.

Weedy relatives. Although corn and soybeans do not have wild and weedy relatives in the United States, canola and other important plants do. Canola pollen flow could create a wild mustard weed capable of producing a pharm or industrial compound, and such a weed would likely need little human intervention, as compared to a crop plant, to perpetuate itself. Pharm and industrial canola crops thereby threaten not only human food and animal feed supplies but also the greater environment with exposure to biologically active compounds.

Bioaccumulation. Some biopharmaceuticals may have physiochemical properties that could make them persist in the environment or cause them to accumulate in living organisms, dramatically increasing their potential to contaminate ecosystems and their capacity to eventually make their way into the human and farm animal food chains.

POLICY RECOMMENDATIONS ►

Pharm crops should be tightly regulated to protect against their risks to human health, the food supply, and the environment. Addressing these risks is also essential to the advancement of the technology—even one discovery of a food product contaminated

with engineered drugs could hobble the technology, if not stop it in its tracks.

Under the federal framework for oversight of biotechnology products, the US Department of Agriculture (USDA) and the Food and Drug Administration (FDA) have primary responsibility for regulating pharm crops. The USDA oversees the environmental phases of pharm crop production while the FDA steps in to regulate drug production and purity, clinical testing, and commercialization.

Those agencies have begun efforts to strengthen oversight of pharm crops, but it is a difficult task. Among other challenges, the regulatory system for pharm crops, like other parts of the federal biotechnology framework, was cobbled together from statutes originally enacted for other purposes. As a result, the current system is not appropriately tailored to pharm crops and therefore does not adequately protect against their risks.

As the centerpiece of new regulation, UCS has urged the USDA and FDA to take the following steps to ensure that the food supply is completely protected against contamination from pharm crops:

1. USDA and FDA should jointly set zero contamination of the food supply as the goal of the agencies’ pharmcrop policy.

Exposing consumers to drugs through food crops is an unacceptable risk to human health. In addition, the discovery of drugs in food items would cause momentous and costly disruptions in the food system. To guard against these serious consequences, USDA and FDA should work together to set zero contamination of the food supply as the goal of the agencies’ pharm crop policy.

2. USDA and FDA should establish a public scientific advisory committee on pharm crops to consider and advise the agencies on the full range of measures available to meet the goal of zero contamination of

the food supply. To determine which measures—or combination of measures—can achieve a zero-contamination goal, USDA and FDA should convene a panel of experts. The agencies should charge the committee with defining and evaluating all available measures and approaches, including at a minimum the ones listed below, for their contribution to preventing contamination of the food supply.

Potential measures include:

Zoning. Growing pharm crops in designated areas, perhaps states or counties, where they would not encounter food crops could prevent outcrossing and severely reduce opportunities for physical mixing.

Spatial separation. If pharm plants are grown at a sufficient distance from food crops, viable pollen will not reach food crops.

Temporal separation. Outcrossing can also be prevented by planting pharm and food crops so that they flower at different times. If plants do not flower in the same time period, pollen produced by the pharm plants will not encounter receptive eggs to fertilize in the food crops.

Disallowing food crops. Both physical mixing and outcrossing would be substantially reduced if only nonfood (and nonfeed) crops were used for pharmaceutical production.

Dedicated machinery and infrastructure. Dedicating farm machinery (planters, combines, trucks) and grain-handling infrastructure (elevators, trucks, railroad cars) solely to pharm crops would decrease the likelihood of physical mixing.

Indoor production. Growing pharm crops indoors would eliminate outcrossing and, if the facilities were used solely for pharm crops, would also avoid physical mixing.

Sterile pollen. Requiring that pharm crops produce sterile or no pollen would help reduce outcrossing.

Engineering chloroplasts. Splicing drug genes into chloroplasts would reduce outcrossing substantially because pollen typically contains few, if any, chloroplasts.

Suicide genes. Genetic engineers may be able to devise suicide-gene cassettes that would reduce the viability of pharm crop seeds. Although sterile, such seeds would still carry the drug products of interest and would be a food contamination problem if moved into the food system. Suicide genes would also not inhibit the expression of drug genes if transferred to neighboring crops via pollen.

The USDA/FDA pharm-crop advisory committee should deliberate in public. Its members should be selected for their expertise in relevant scientific disciplines and crop production. The panel should be balanced to include representatives from academia, the food and pharm-crop industries, consumer and environmental organizations, and organic and conventional commodity crop grower groups. The committee's report should be written by its members and made public in a timely fashion.

3. USDA and FDA should use the advisory committee's report to devise regulatory requirements to be imposed on growers, handlers, and transporters of pharm crops.

Once the government has the results of the committee's work, it should evaluate the cost and feasibility of adopting the options or combinations of options that meet the goal of zero contamination of the food supply. Once it has selected the appropriate measures, the government should impose them as mandatory conditions on the field testing and commercial growth of pharm crops.

4. USDA and FDA should impose a moratorium on field tests and commercial production of engineered pharm crops until they have convened the scientific advisory committee and established a regime that the scientific community believes will assure the goal of zero contamination of the food supply.

The pharm-crop industry is already struggling in the wake of previous contamination episodes: the StarLink Bt-corn contamination of food products in 2000 and ProdiGene Company's mixing of pharm

corn with soybeans at a grain elevator in 2002. Too much is at stake to allow more such incidents, which remain possible as long as pharm crops are grown without adequate confinement. To avoid a "StarLink with drug genes," USDA and FDA should impose a moratorium on field tests and commercial production of engineered pharm-crops. That delay should last until they have convened the scientific advisory committee and established a regime that the scientific community believes will assure the goal of zero contamination of the food supply.

SUMMARY ▶

Pharm and industrial crops represent a new wave of biotechnology crops different from the herbicide-tolerant and Bt crops that have dominated the scene until now. The promised benefits (new and cheaper drugs) could be important to many consumers. At the same time, these crops pose obvious and important risks of contamination of the food supply and the environment with non-food substances. It is vital to regulate this emerging industry so that its benefits can be obtained, without undue risks to human and animal health and the environment.



REFERENCES ►

- Anonymous. 2002. "Going with the flow." *Nature Biotechnology* 20:527.
- Anonymous. 2001. "Pharming plants underground." *Nature Biotechnology* 19:802.
- Anonymous. 2000. "A new crop of transgenic plant technologies." *Genetic Engineering News* 20(4):8.
- Daniell, H. 2002. "Molecular strategies for gene containment in transgenic crops." *Nature Biotechnology* 20:581-86.
- Doran, P.M. 2000. "Foreign protein production in plant tissue cultures." *Current Opinion in Biotechnology* (13):199-204.
- Giddings, G. et al. 2000. "Transgenic plants as factories for biopharmaceuticals." *Nature Biotechnology* 18:1151-55.
- Herrera, S. 2001. "Against the grain." *Red Herring* 104:55-57.
- Hood, E.E. et al. 1999. "Molecular farming of industrial proteins from transgenic maize." In: *Chemicals Via Higher Plant Bioengineering*, F. Shahidi et al., eds. New York: Kluwer Academic/Plenum Publishers, pp. 127-147.
- Kramer, K.J. et al. 2000. "Transgenic avidin maize is resistant to storage insect pests." *Nature Biotechnology* 18:670-74.
- Ma, J. K-C. 2000. "Genes, greens, and vaccines." *Nature Biotechnology* 18:1141.
- Maliga, P. 2001. "Plastid engineering bears fruit." *Nature Biotechnology* 19:826-27.
- Malone, M.E. 2002. "Scientists focus on the tobacco plant as possible cancer-fighter: Genetically altered crops may someday produce drugs to combat many diseases." *Boston Globe*, February 5, p. C1.
- National Research Council. 2002. *Environmental Effects of Transgenic Plants: The Scope and Adequacy of Regulation*, Washington, D.C.: National Academy Press.
- Pollack, A. 2000. "New ventures aim to put farms in vanguard of drug production." *New York Times*, May 14.
- Ruf, S. et al. 2001. "Stable genetic expression of tomato plastids and expression of a foreign protein in fruit." *Nature Biotechnology* 19:870-75.
- Sloan, H.R. 2002. "Biotin deficiency." *eMedicine Journal*, Vol. 3, No. 3, March 22 (www.emedicine.com/ped/topic238.htm).
- Smyth, S. et al. 2002. "Liabilities and economics of transgenic crops." *Nature Biotechnology* 20:537-41.
- Tokar, B. 2001. "Biohazards: The next generation? Genetically engineering crop plants that manufacture industrial and pharmaceutical proteins." Prepared for the Edmonds Institute, 20319-92nd Avenue West, Edmonds, Wash.

