

A GROWING CONCERN

**Protecting the Food Supply in an Era of
Pharmaceutical and Industrial Crops**



Union of Concerned Scientists

Citizens and Scientists for Environmental Solutions

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Protecting the Food Supply in an Era of Pharmaceutical and Industrial Crops

Technical Report

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Introduction, Conclusions, and Recommendations of the Union of Concerned Scientists

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UCS is a nonprofit partnership of scientists and citizens combining rigorous scientific analysis, innovative policy development, and effective citizen advocacy to achieve practical environmental solutions.

The goal of the UCS Food and Environment Program is a food system that encourages innovative and environmentally sustainable ways to produce high-quality, safe, and affordable food, while ensuring that citizens have a voice in how their food is grown.

More information about UCS is available on its website at www.ucsusa.org.

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The Union of Concerned Scientists is solely responsible for the UCS introduction, conclusions, and recommendations included (on colored paper) with the technical report.

EXECUTIVE SUMMARY

In the spring of 2003, the Union of Concerned Scientists (UCS) convened an expert workshop on protecting the U.S. food and feed supply from contamination by crops genetically engineered to produce pharmaceuticals and industrial chemicals. The experts who participated in that workshop wrote the technical report A Growing Concern: Protecting the Food Supply in an Era of Pharmaceutical and Industrial Crops independently of UCS, which developed policy recommendations based on its own analysis of this report.

Below is the executive summary of the experts' report, followed by the executive summary of UCS's conclusions and policy recommendations.

TECHNICAL REPORT

AUTHORS: *David Andow, Henry Daniell, Paul Gepts, Kendall Lamkey, Emerson Nafziger, and Dennis Strayer*

Food crops, primarily corn, are currently being genetically engineered to produce pharmaceuticals and industrial chemicals. These crops are referred to as “pharma” crops when they produce drugs, hormones, and other therapeutic agents, and industrial crops when they produce compounds such as plastics for use in industry. Throughout our report, the term pharma crop is used to encompass both types.

While the commercial and health benefits of these crops could be substantial, there are risks to the food supply and the environment associated with their commercial production. Many pharma and industrial products could harm humans, livestock, or wildlife if ingested in active forms. Of the many possible risks associated with these products, this report focuses only on those related to contamination of the human food and animal feed supplies.

There are two major routes by which pharmaceutical and industrial transgenes can inadvertently contaminate commodity crops and, therefore, the food and feed supply. One of these is the

physical mixing of seed—pharma seed can be inadvertently spilled or mixed during seed production, harvest, storage, transport, and handling. Contamination can occur by direct mixing of the crops in the growing year or potential future contamination from volunteer plants the following year. The other route is pollen, which contains the male reproductive cells necessary for the fertilization of plants and the production of seed. Pollen containing genes for the pharma product can pollinate commodity crops, leading to contamination during the growing year.

The Central Dilemma

The U.S. commodity corn and soybean production systems are structured to mix grain from many sources before it is ultimately used. Without substantial modification, such a system cannot protect the human food and animal feed supply systems from contamination by pharma crops.

This problem raises the fundamental dilemma associated with pharma crops. The compounds produced by genetically engineered pharma plants are expected to lead to useful products that would have beneficial effects on human or animal health. At the same time, these compounds can

contaminate the food supply and the environment, possibly resulting in detrimental health effects on humans or animals and putting food companies at risk for lost markets, legal liability, and brand damage.

We addressed this problem by answering the following question: Is it possible to design a system for producing pharma products in genetically engineered corn or soybean—two plants often used or proposed for pharma production in the United States—without contaminating human food or animal feed?

Virtually Zero Contamination

In determining how to maintain a food/feed supply without contamination by pharma and industrial crops, our report first addresses the meaning of the term “without contamination,” then adopts the standard of *virtually* zero contamination (rejecting a zero contamination standard as impossible to attain). A virtually zero standard recognizes the impossibility of preventing contamination entirely.

By promoting a virtually zero contamination standard, we advocate for pharma crop production to be conducted in such a way that the likelihood of contamination would be so low as to be nearly zero. The adequacy of existing pharma crop confinement systems is assessed against this standard throughout the report.

Report Outline

A Growing Concern identifies the points at which commodity corn and soybean production—and therefore the U.S. food and feed system—could be contaminated by pharma crops.

Chapter 1 provides background material and defines the scope of the report. Chapter 2 describes the potential routes of contamination of non-pharma corn and soybean, concentrating on those related to pollen movement and seed mixing.

Chapter 3 discusses various methods by which contamination could be blocked; these confinement measures are broadly classified as zoning, spatial separation, temporal separation, dedication of machinery and infrastructure, physical and biological confinement, and disallowing food and feed crops as pharma crops.

The report then addresses the three phases of corn and soybean production in depth, identifies points at which food/feed crops are vulnerable to contamination by pharma crops, and evaluates the confinement measures suggested in Chapter 3. Chapter 4 describes the seed production processes for both crops; Chapter 5 addresses on-farm production; and Chapter 6 examines post-harvest shipping, handling, and storage.

Chapter 7 briefly addresses the potential for using non-food/feed plants for pharma production, recognizing that a full examination of this topic is beyond the scope of this report. Chapter 8 synthesizes the report’s major conclusions and makes recommendations.

Conclusions and Recommendations

The Current Corn and Soybean Production Process. Our report concludes that the current production process and production areas for corn and soybean cannot be used without substantial modification to ensure virtually zero contamination of the human food and animal feed supplies.

Recommendations:

- Eliminate as many steps as possible in each of the seed development, seed production, crop production, and handling, storage, and delivery operations.
- Develop corn and soybean production and management systems that will ensure virtually zero contamination of the food and feed supplies through collaboration between

industry, academia, and regulatory bodies. If broad-based consensus cannot be reached, it would be inadvisable to initiate further use of corn and soybean as pharma crops.

Future Prospects for Pharma Corn and Soybean. Theoretically, the goal of virtually zero contamination could be achieved using corn and soybean as pharma crops, but this would require such substantial changes in production practices, management systems, and oversight that a major effort will be required. Our conclusion is that the pharma crops system must be completely separate from the food/feed system. Specifically, although pharma corn and soybean could be grown either in geographically isolated regions of the country or embedded in areas of commodity crop production, both would require new production systems be put in place.

It would be possible to produce pharma crops in areas isolated from commodity crop production if geographic isolation zones and the necessary management and oversight can be established and maintained in a way that ensures virtually zero contamination of the food and feed supplies. Similarly, it would be possible to grow corn and soybean pharma crops embedded in the same areas as corn and soybean commodity production if appropriate management, spatial separation, and biological confinement can be developed, implemented, and enforced in a way that ensures virtually zero contamination of the food and feed supply.

An appropriate management and oversight system would involve considerable discipline and reproducibility in the production process, predetermined performance standards, documentation and auditing, and third-party monitoring and approval. Such a system and any associated biological confinement must also include redundancy and fail-safe mechanisms.

Recommendations:

- Develop the infrastructure and information needed to implement and maintain pharma crop production in areas geographically isolated from commodity crops. Specifically, synthesize studies of pollen flow, isolation, and crop production areas to determine whether further research is needed to establish the scientific basis for geographic isolation zones.
- Develop strategies that would allow individual growers or groups of growers to develop case-by-case plans for well-defined spatially separated production areas embedded within commodity production areas. These strategies would need to meet the specific management, separation, confinement, and oversight objectives outlined above.

Use of Non-Food/Feed Crops. Our report suggests that non-food/feed crops should be seriously considered as pharma crops in order to ensure virtually zero contamination of food and feed. However, additional safeguards will be necessary, including: confinement management systems and third-party oversight similar to that proposed for corn and soybean; barriers to pollen and seed gene flow (e.g., no wild relatives, low propagule viability, sterility); minimum production areas for the pharma crop; and limited acreage for the non-pharma crop.

Recommendations:

- Encourage research on non-food/feed crops as potential pharma crops.
- Develop the information and technology necessary for pharma crop production in non-food/feed crops as soon as possible to ensure virtually zero contamination of the

food/feed supply and enable pharma crop production to succeed. This may require some research incentives, as our genetic engineering expertise with other crops is not on the same level as corn and soybean.

CONCLUSIONS AND POLICY RECOMMENDATIONS OF THE UNION OF CONCERNED SCIENTISTS

AUTHORS: *Margaret Mellon and Jane Rissler*

UCS carefully reviewed the technical report *A Growing Concern: Protecting the Food Supply in an Era of Pharmaceutical and Industrial Crops* and developed its own conclusions and policy recommendations. We strongly agree with the experts' major conclusion that corn and soybean cannot be used for pharma crop production without major changes designed to protect our food system from contamination.

UCS strongly agrees with the experts' major conclusion that corn and soybean cannot be used for pharma crop production without major changes designed to protect our food system from contamination.

Since contamination of the food supply is likely to be ongoing, we believe that pharma crops should not continue to be developed. Considering the serious potential health and economic consequences of a contamination event, *UCS recommends that the United States Department of Agriculture (USDA) halt the outdoor production of genetically engineered pharma and industrial crops immediately,*

until a system is put in place that can produce drugs and industrial substances without putting our food system and food industry at risk.

UCS also recommends that the USDA explore the indoor cultivation of engineered food and feed crops to produce drugs and industrial chemicals. This system would employ artificially illuminated facilities such as caves or secure greenhouses, operated in conjunction with a new management system along the lines discussed in Chapter 6 of the technical report.

We agree with the report's authors that it might be possible in the future to put together an effective new system that would allow corn or soybean to be used as pharma crops. But as the experts make clear, such a system would require extensive changes. Establishing that system, especially if it permits pharma crop production embedded in commodity crop regions, would require new management systems, new regulations, new restrictions on farmers who do not grow pharma crops, and new equipment and technologies—all built from the ground up. Although theoretically possible, the magnitude of this undertaking leads us to doubt that the USDA could establish, monitor, and ensure the successful operation of the new system.

The best way to reap the benefits of pharma crops and simultaneously protect the food system is to stop now and begin investing in other methods of biopharmaceutical production such as alternative crops and fermentation and cell culture systems. Therefore, *UCS recommends that the USDA spearhead a major campaign to encourage and fund alternatives to the use of food and feed crops in pharma and industrial crop production, particularly the search for suitable non-food/feed crops.* We agree with the experts that this effort should begin as soon as possible and should include incentives that enable scientists to explore new crops and agronomic systems.

A Final Note on the Relationship between the Experts' and UCS's Recommendations

The conclusions and policy recommendations of the Union of Concerned Scientists are based on the expert analyses in the technical report, but are solely the views of UCS. One of our policy

recommendations—that the outdoor production of genetically engineered pharma food and feed crops be halted immediately—is not addressed in the technical report and is not necessarily shared by its authors.

INTRODUCTION, CONCLUSIONS, AND RECOMMENDATIONS OF THE UNION OF CONCERNED SCIENTISTS

AUTHORS: *Margaret Mellon and Jane Rissler*

Food crops, primarily corn, are currently being genetically engineered¹ to produce drugs, vaccines, and industrial chemicals. These crops are referred to as “pharma” crops when they produce therapeutic agents, and industrial crops when they produce compounds used in manufacturing or other industries. Although this discussion primarily covers pharmaceutical applications, we believe most of the analysis also applies to industrial applications and often use the term pharma to encompass industrial uses.

The developers of pharma crops hope they will reduce drug production costs compared with cell culture or fermentation systems and, in some cases, make possible the production of drugs that cannot be produced at all by other systems. However, substances produced by pharma and industrial crops—including hormones, vaccines, diagnostic compounds, and plastics that were never intended to be eaten—can be toxic or harmful if accidentally ingested.

Pharma and industrial crops are visually indistinguishable from food and feed crops,² so without efforts to segregate the two, potentially harmful substances can easily move into the food system—directly as a result of physical seed mixing or indirectly through biological routes such as pollen transfer. Pollen transfer can also move pharma and industrial genes to the seed system,

where these genes can perpetuate themselves unnoticed.

BUILDING TOWARD A CRISIS

Pharma crops have been under development in both the laboratory and field for more than a decade. They are of interest from a food safety perspective because almost all drugs are intentionally bioactive and many have effects at low concentrations (Freese 2002b; UCS 2003, 2004).

Substances produced by pharma and industrial crops—including hormones, vaccines, diagnostic compounds, and plastics that were never intended to be eaten—can be toxic or harmful if accidentally ingested.

Although the Union of Concerned Scientists (UCS) is unaware of any publicly available figures on the extent of the pharma crop industry, it is certainly only a fraction of the size of the commodity crop system. U.S. Department of Agriculture (USDA) information provides a glimpse into this young industry: according to its data on field tests of genetically engineered crops (ISB 2004),

1 Genetically engineered crops are also referred to as transgenic or genetically modified (GM) crops or genetically modified organisms (GMOs).

2 Food is consumed by people; feed is consumed by livestock and other animals.

the department has approved at least 125 and perhaps 200 or more applications to test pharma and industrial compounds in engineered crops since 1991.³ More than 15 companies, along with five universities, have been involved in pharma and industrial crop field testing. Corn is the crop of choice; others include soybean, rice, sugarcane, tomato, safflower, and tobacco.

The reported acreage of pharma and industrial crop trials in the USDA database is small. Because many applicants withhold acreage from the public as confidential business information, we do not know the size of unreported or total field trial acreage. We do know, however, that the USDA anticipates a significant increase in the number of requests for field tests and the scale of production over the next few years (USDA APHIS 2003a). If the industry were to expand, eventually there could be hundreds or even thousands of products.

So far, none of the substances produced in pharma crops have been approved by the Food and Drug Administration (FDA) for use as pharmaceuticals, although several are in clinical trials (BIO 2002). Chemicals produced by several engineered crops have been commercialized for research or industrial uses (*Feedstuffs* 2002; ProdiGene 1997).

The Problem Surfaces

The common practice of growing pharma and industrial crops in areas where food and feed versions of the same crops are grown facilitates contamination of the food supply via both biological and physical routes.⁴ More than two years ago, recognition of the industry's growth and its potential risks led UCS, Friends of the Earth, and

The common practice of growing pharma and industrial crops in areas where food and feed versions of the same crops are grown facilitates contamination of the food supply.

other environmental and consumer groups to urge the federal government to strengthen regulations protecting the food system (Brasher 2002; Freese 2002b; Hileman 2002).

Environmentalists' concerns were validated by the fall 2002 discovery that pharma corn plants had emerged as volunteers in a Nebraska soybean field, were harvested, and subsequently contaminated a grain elevator full of commodity soybeans (Gillis 2002a). ProdiGene, the company producing this pharma corn, was also responsible for pharma corn discovered in an Iowa soybean field later that fall (Gillis 2002b).

These incidents underscored how easily food system contamination could occur and galvanized food processors, UCS, and other groups to press even harder for USDA and FDA action. Some have asked the federal government to tighten its requirements on food crops used as pharma and industrial crops and even urged the exclusive use of non-food crops (for example, GMA 2002, 2003). Others have called for a ban on the use of food crops as pharma crops and for restricting pharma crop production to indoor facilities (Freese 2002b).

³ The uncertainty about the number is a result of USDA policy that allows applicants to withhold information from the public as confidential business information. For lists of pharma and industrial crop field trial applications, see Freese (2002a) and USDA APHIS (2004a).

⁴ We use the term "contamination" here to refer to seeds or genes that are unwanted in a particular place for one reason or another. Corn, for example, is unwanted in soybean shipments, where it is properly called a contaminant. The term has no negative connotation other than the sense that a particular entity is for some reason unwanted or inappropriate where it is found.

The Government's Response

The two federal agencies charged with overseeing pharma and industrial crops responded to the growing concern by strengthening their oversight. The FDA proposed new, but voluntary, guidelines for the industry (FDA 2002), and the USDA strengthened the permit conditions that apply to field tests of genetically engineered pharma and industrial crops.⁵

In a May 2002 letter to pharma crop developers, the department detailed permit conditions applying to pharma barley, corn, rice, sugarcane, and tobacco, and required crop-specific confinement measures such as isolation distances and flower bagging (USDA APHIS 2002). The letter also advised pharma crop growers in general terms to consider post-harvest restrictions such as monitoring for volunteers and cleaning seeding and transplanting machinery to prevent seed mixing.

In March 2003, the department requested comments on steps it had taken to strengthen its 2002 requirements (USDA APHIS 2003a).⁶ Among the new provisions were requirements for longer isolation distances in corn (no growing corn within one mile of a field test site involving open-pollinated corn), submission and approval of seed cleaning and drying procedures, and implementation of training programs for test site personnel. The USDA also announced it would increase the number of on-site inspections.

Finally, the department issued a letter to pharma crops permit applicants in January 2004 providing greater detail on the kind of information to include in permits, including product description, confinement methods, and packag-

ing requirements (USDA APHIS 2004b). The letter also contained proposed criteria for approved training programs and standard operating procedures such as the cleaning of equipment and storage facilities in pharma crop operations.

Although these steps show that the USDA has put together many of the elements of a comprehensive management system to oversee pharma and industrial crop production, they have failed to allay concerns. The system, despite being headed in the right direction, is still a work in progress. The piecemeal manner in which its provisions were issued makes it unclear whether they are voluntary or mandatory. In addition, the USDA has not addressed the possibility of a ban on food and feed crops as pharma crops.

The USDA system is also unsatisfactory because its goal is ambiguous. It fails to state whether the department aims to prevent food system contamination completely or just reduce pharmaceutical substances to "safe" or "acceptable" levels. The lack of a clearly defined goal makes it difficult to evaluate the system's effectiveness.

The Industry's Response

Recently, the industry has begun developing voluntary systems to protect the food and feed supply from pharma crops. A working group of the Biotechnology Industry Organization, the industry trade association, has developed a confinement strategy for pharma crops based on a critical control points approach. Although the details have not yet been published, the regime appears to envision a comprehensive "closed-loop" system separate from commodity crop production (Keon

5 The USDA's permit authority derives from its ability to restrict the movement of plant pests under the Plant Protection Act. 7 USC 7701-7772.

6 In August 2003, the department issued an interim rule that requires plants engineered to encode compounds for industrial use be introduced only under permit (USDA APHIS 2003b). This rule makes it possible for the department to apply conditions applicable to pharmaceutical-producing crops to industrial crops as well. The rule will remain in effect only until December 31, 2004.

2004; Phillips 2004). UCS is interested in learning more about the plan, but we are skeptical of any wholly voluntary approach.

The UCS Response

In 2003, UCS undertook its own project to examine the feasibility of protecting the U.S. food and feed system from contamination by new crops genetically engineered⁷ for pharma and industrial purposes. We wanted to know whether any of the options for confinement, including some not considered by the USDA, alone or in combination, would be sufficient. The question our project sought to answer is whether it is possible to use food crops to produce large numbers of drugs and plastics without contaminating the U.S. food and feed system.

A STANDARD OF COMPLETE PROTECTION

Pharmaceutical substances vary in their effects, the levels at which they cause problems, and whether they remain active after ingestion. While many substances clearly represent a problem even at very low levels (e.g., orally administered hormones), others may not. This suggests that some pharmaceuticals could be present in the food system without ill effects and raises the question of whether the standard for regulation ought to be complete prevention of contamination or reduction of contamination to “safe” or “acceptable” levels.

UCS believes the USDA should adopt the most stringent standard possible—complete protection of the food system—for three reasons:

- 1. The discovery of a pharmaceutical in food could have enormously disruptive effects regardless of the substance’s effects or the levels at which it is found.**

The discovery of contaminating substances can cause enormous disruption throughout the food chain as elevator operators and others attempt to clear the system of contaminated product. As demonstrated by the StarLink incident in 2000, the costs of such disruption can run into the hundreds of millions of dollars.⁸

UCS believes the USDA should adopt the most stringent standard possible—complete protection of the food system from pharma crop contamination.

Contamination of food by pharmaceutical substances poses especially large risks to retail food companies. Consumers who unwittingly ingest pharma products in foods are likely to direct their ire—and their lawsuits—against the companies that sold them the food. Apart from any legal liability, the publicity associated with such incidents could severely damage valuable brands. Purveyors of organic food products are at special risk because many consumers expect organic food to be free of all engineered genetic sequences and products, not just pharmaceuticals.

Importantly, contamination can have negative economic consequences even if the substances involved do not cause demonstrable harm to consumers or are present below legal tolerances. For many consumers, the publicity surrounding the discovery of any amount of drugs in a well-known brand of breakfast cereal or taco shells would be more than enough reason to turn toward competitors’ products. Such changes in consumer preferences can cost food companies millions of dollars.

⁷ Non-engineered crops are also being used for industrial purposes but generally warrant less concern than engineered crops. Genetic engineers can introduce a virtually unlimited set of new bioactive gene products into plants, making possible a large range of engineered crops with novel substances.

⁸ In 2000, the StarLink corn variety containing a novel gene product not approved for food uses was nevertheless planted by farmers and sold into the food system (Lambrecht 2001).

A government policy aimed at ensuring safe levels of pharma genes in corn flakes would inevitably permit some level of pharmaceutical substances in foods—and a successful pharma crop industry could mean thousands of such substances. We believe consumers and food companies alike simply will not accept a government program that sanctions drugs in the food system. Put another way, “Only Safe Levels of Drugs in U.S. Food” is untenable as a motto for the USDA pharma crop program. The only acceptable goal of U.S. pharma crops policy is to keep pharmaceutical and industrial substances out of food altogether.

It is worth noting that food companies are not the only entities at economic risk from pharma crop contamination. An incident involving the discovery of drug genes in food could also deliver a devastating blow to the future of food biotechnology, which is already under pressure (*Nature Biotechnology* 2004). Many consumers in other parts of the world are uneasy about genetically engineered food, and the discovery of pharma genes in grain destined for a country with a high level of consumer resistance could do serious harm to the agricultural biotechnology industry. As is the case for food companies, even if a biotech firm can demonstrate that its substances are only present in food at low or “safe” levels, that would not likely be enough to quell the uproar.

2. A regulatory system establishing tolerances for pharma crops would be a waste of resources.

A policy of reducing pharma contamination to acceptable levels would require a regulatory system to evaluate substances and establish tolerance levels designed to protect public health. Such a system, processing hundreds or even thousands of applications for pharma and industrial chemicals, would be expensive to set up and operate. It

would require scientifically trained professionals to conduct food safety evaluations and other personnel to enforce requirements once they are set. This expenditure of professional and other resources is not justified considering that none of the substances are intended for food use in the first place. It would be much more efficient to set up a system that prevents contamination completely.

3. Risk assessments are imperfect.

Even if the government did set up an expensive regulatory system, the public might still not be confident that the approved levels of pharma compounds did not threaten its health. The regulatory evaluations of compounds would be based on risk assessment, an imperfect science dependent on what is known about the chemical activity and toxicity of substances, the degree to which they are in active or inactive form, and whether there are thresholds below which they are not harmful. Accurate assessment, therefore, requires an understanding of the connections between chemicals and a variety of disease or health-related end points. This understanding is incomplete at best. (Scientists know more about cancer, for example, than developmental disorders.)

In short, risk assessment science is not sufficiently robust to guarantee that all harmful chemicals will be screened from the food supply. In many cases, society must accept risk assessment as the best that can be done to inform regulatory decisions about chemical substances. That argument does not apply in this case.

For these reasons, UCS advocates complete contamination prevention—a strict performance standard—as the goal of federal regulatory policy for pharma and industrial crops. (This standard, which has been refined by the authors of the following technical report and articulated as “virtually zero contamination,” is discussed in greater detail in Chapters 1 and 8.)

CAN THE FOOD SUPPLY BE COMPLETELY PROTECTED?

As discussed above, pharma crops have been under cultivation for more than a decade. During that time, the crops have been placed under progressively stronger regulatory regimes. But these regimes have not been designed to meet the goal articulated above: the complete protection of the food supply. The task before us is to determine how, from this point forward, we can achieve that goal.

To help understand the challenges of meeting such a goal, UCS asked a straightforward question: is strict confinement possible? To focus our efforts, we limited the crops to corn and soybean.

The Experts' Workshop

UCS brought six experts together in 2003 to work through the problem and provide analysis and advice. The workshop participants included experts with long experience in U.S. corn and soybean production as well as scientists with expertise in biological, physical, and management approaches to confinement.

As background for the workshop, UCS first asked the group to compile a list of all potential confinement measures applicable to pharma corn and soybean and assess their strengths and weaknesses. The experts not only considered measures currently employed by the USDA, but also indoor production, disallowal of food crops, and new methods based on sophisticated molecular biological techniques. We then asked the workshop participants to determine the points in corn and soybean production at which contamination of the food and feed supply is likely to occur. The objective was to assess the effectiveness of each confinement measure in blocking identified routes of contamination.

To structure the analysis, corn and soybean production was divided into three phases: seed production, on-farm production, and post-harvest grain handling, storage, and shipping. Contamination would need to be blocked in all three phases to completely protect the food system.

UCS did not ask the experts to debate the wisdom or appropriateness of a zero contamination standard, nor did we ask for policy recommendations. We simply asked, "What confinement measure or set of measures, if any, would ensure complete protection of the U.S. food and feed supply from contamination by pharma crops?"

We chose to focus on corn and soybean for the following reasons: 1) corn is the most commonly engineered crop for both pharmaceutical and industrial chemical production, and soybean, though not used as frequently as corn, has been used for antibody and industrial enzyme production; 2) because corn and soybean are major U.S. commodity crops, common ingredients in processed food, and important agricultural exports, their contamination by pharma products could cause substantial disruption to the food supply and export markets and pose risks to human health; and 3) because corn and soybean represent opposite ends of the outcrossing spectrum,⁹ they provide an opportunity to consider the relative importance of biological and physical contamination routes in the food system.

After the day-and-a-half workshop, the experts undertook a highly collaborative process that resulted in the technical report *A Growing Concern: Protecting the Food Supply in an Era of Pharmaceutical and Industrial Crops*. UCS edited the text for clarity and consistency, but the analysis, conclusions, and recommendations presented in Chapters 1 through 8 are solely those of the experts.

⁹ Corn is a highly outcrossing crop while soybean is predominantly self-pollinating.

UCS REVIEW OF THE TECHNICAL REPORT The Experts' Analysis

Chapter 1 provides background material and explains why the technical report was prepared.

Chapter 2 provides details on the two major routes of contamination: physical mixing of seed and biological transfer of pollen.

Chapter 3 lays out the confinement options available to block contamination by these routes. The list of options considered by the experts is surprisingly long, ranging from zoning to cutting-edge molecular interventions, and the options vary considerably in effectiveness, readiness, and expense.

In general, it was disappointing to learn that new molecular interventions, although promising, are only partially effective at best, and for the most part are not yet ready for deployment. Chloroplast engineering only recently became available to control pollen flow in soybean. Other approaches such as genetically engineered male sterility, cleistogamy, and apomixis are currently unavailable in either corn or soybean.

Similarly, complex genetically engineered seed sterility mechanisms are still in the experimental stage and may never be effective enough by themselves to completely block the movement of pharma crop genes in corn and soybean. On the other hand, innovative management systems appear to be evolving toward a potentially significant role in confinement.

Chapters 4, 5, and 6 form the heart of the analysis by describing the three major phases of corn and soybean production chains: seed production, on-farm production, and post-harvest handling, storage, and transport. Each of these chapters identifies points of vulnerability to contamination through pollen dispersal and seed mixing, and evaluates the applicability of relevant confinement options.

Chapter 7 briefly discusses non-food and non-feed crops that may be pharma crop candidates.

The analyses in Chapters 1 through 7 are rich in detail and insight, and we recommend the entire report to readers—especially those who might be tempted to skip right to the excellent summary.

In Chapter 8, the experts elegantly synthesize their analyses and present their conclusions and recommendations. Although they were not asked to comment on the stringent “no contamination of the food system” or “complete protection of the food system” standard advocated by UCS, the report authors took the initiative to discuss and refine the concept in Chapter 8. Without prompting by UCS, the experts endorsed the appropriateness of a “virtually zero contamination” regulatory standard in the context of pharma crops.

A glossary of technical terms appearing in the text has been prepared by UCS and can be found at the end of the report.

The Experts' Conclusions

The major conclusion of the technical report is:

“As they are currently produced, stored, and transported, corn and soybean cannot be used as pharma crops in the United States while ensuring virtually zero contamination of the food and feed supplies.” (Conclusion #4)

Nevertheless, the experts go on to say that a virtually zero contamination standard could theoretically be achieved if “substantial changes in production practices, management systems, and oversight” of pharma corn and soybeans were implemented.

More specifically, the technical report concludes that pharma corn and soybean could be grown either in isolated regions of the country away from the major areas of corn and soybean

The experts concluded that corn and soybean—as currently produced, stored, and transported—cannot be used as pharma crops while ensuring virtually zero contamination of the food supply.

production, or even within the Corn Belt—provided completely new systems are put in place. Briefly, according to the experts, it would be necessary to establish geographic isolation zones with new management and oversight regimes in order to grow pharma crops in isolation from other commodity crops.

To grow pharma crops embedded in areas of traditional commodity crop production, the experts say an even more elaborate system would be required:

“An appropriate management and oversight system would require considerable discipline and reproducibility in the production process, predetermined performance standards, documentation and auditing, and third-party monitoring and approval. Furthermore, this system and any associated biological confinement must include redundancy and fail-safe mechanisms to safeguard the food and feed supply.” (Conclusion #6)

The Experts’ Recommendations on Continued Use of Corn and Soybean

To prepare for the implementation of new pharma crop production systems, the authors had three key recommendations. First, “Studies of pollen flow, isolation, and crop production areas should be synthesized to determine whether further research is needed to establish the scientific basis for geographic isolation zones” (Recommendation #5).

Second, “Strategies should be developed that would allow individual growers or groups of growers to develop case-by-case plans for well-defined spatially separated production areas within commodity production areas” (Recommendation #6).

Finally, the experts stressed that if the use of corn or soybean as pharma crops is to succeed, “The infrastructure and information needed to develop, implement, and maintain pharma crop production in areas geographically isolated from commodity crops and/or embedded in commodity production areas must be developed as soon as possible” (Recommendation #7).

The Experts’ Recommendations on Non-Food/Feed Crops

The experts also considered crops other than food and feed crops for pharma crop production, and the resulting need to find and/or develop alternative crops. They concluded that, “To ensure virtually zero contamination from future pharma crops, the use of non-food/feed crops should be considered seriously” (Conclusion #9).

The experts recommended that, “The information and technology necessary for pharma crop production in non-food/feed crops should be developed as soon as possible to...enable pharma crop production to succeed” (Recommendation #9).

Understanding the key role of funding in groundbreaking projects, the experts also noted that developing alternative crops “may require some research incentives, as our genetic engineering expertise with other crops is not on the same level as corn and soybean” (Recommendation #9).

The Experts’ Recommendations on Research Needs

The experts acknowledge the fact that “none of the proposed strategies—non-food/feed crops, geographic zoning, or local physical and biologi-

cal confinement—is ready for immediate use in pharma crop production” (Chapter 8, p. 119). In response, they have compiled a list of research gaps that need to be addressed immediately in order to develop the scientific basis for ensuring virtually zero contamination of the food and feed system. These gaps include new crops for pharma and industrial use, geographic zoning, and local confinement (which encompasses new molecular methods such as nuclear male sterility and chloroplast engineering).

Also threaded through the report’s chapters are the experts’ recommendations for establishing new management systems designed “from the ground up” to address confinement issues.

UCS CONCLUSIONS AND RECOMMENDATIONS

UCS has reviewed the technical report carefully and we strongly agree with the experts’ major conclusion that corn and soybean cannot be used for pharma crop production while completely protecting our food system from contamination—at least without major changes in the pharma corn and soybean production system. Since changes on this scale have yet to be implemented, we believe that contamination of the food system may have already occurred and may become more likely during all three phases of pharma crop production.

In our view, the United States should not continue to develop pharma crops while contamination is likely ongoing. Even though the scale of pharma crop production is small in comparison with commodity crop production, it is significant enough to threaten the food supply. Furthermore, the industry has commercialized several research and industrial chemicals, has several pharmaceutical products in clinical trials, and has already submitted 100 to 200 applications to the USDA for testing additional products in more than 30 states.

Considering the serious potential health and economic consequences of a contamination event, *UCS recommends that the USDA halt the outdoor production of genetically engineered pharma and industrial crops immediately, until a system is put in place that can produce drugs and industrial substances without putting our food system and food industry at risk.*

UCS recommends that the USDA halt the outdoor production of genetically engineered pharma and industrial crops immediately, until a system is in place to produce drugs and industrial substances without putting the food system at risk.

UCS also recommends that the USDA explore the indoor cultivation of engineered food and feed crops to produce drugs and industrial chemicals. This system would employ artificially illuminated facilities such as caves (Bouchie 2001) or secure greenhouses, operated in conjunction with a new management system along the lines discussed in Chapter 6.

We agree with the technical report that it might be *possible* to put together an effective new system that would allow corn or soybean to be safely used as pharma crops. But as the report makes clear, such a system would require extensive changes. The experts identified a large number of points of vulnerability in the commodity production system, and blocking contamination at each of those points, through all three phases of production, represents an enormous challenge—not only to regulatory agencies and biotechnology

companies but also to farmers who would have to modify many parts of their operations.

Establishing a new system, especially one that would allow pharma crop production embedded in commodity crop regions, would require new management systems, new regulations, new restrictions on farmers who do not grow pharma crops, and new equipment and technologies. Although theoretically possible, the magnitude of this undertaking leads UCS to doubt that the USDA could establish, monitor, and ensure the successful operation of the new system.

We believe the United States stands at a crossroads on pharma crops. It can develop a completely new system that will allow the safe use of corn, soybean, and other food and feed crops as pharma crops, or embark on a campaign to develop alternative crops. Either way will take time and the investment of scientific, legal, and management resources.

The analyses in the following technical report have forced us to conclude that the better option is disallowing the use of food crops and working to find and develop alternative pharma crops. It is a difficult choice. Everyone can agree that lower drug production costs are a desirable goal, and we recognize the fact that corn and soybean have substantial advantages as pharma crops. That being said, the food system that extends from field to fork both here and abroad is vital to our health and central to our economy.¹⁰ We must not put this system at any further risk of contamination.¹¹

The best way to reap the benefits of pharma crops and simultaneously protect the food system is to stop now and begin investing in other methods of biopharmaceutical production such as

alternative crops and fermentation and cell culture systems.¹² This may be a challenge, but it is one well within the capability of the U.S. agricultural, pharmaceutical, and industrial establishment. Society has every reason to expect that a concerted effort to develop non-food pharma crops and improve fermentation and cell culture systems will succeed.

Therefore, *UCS recommends that the USDA spearhead a major campaign to encourage and fund alternatives to the use of food and feed crops in pharma and industrial crop production, particularly the search for suitable non-food/feed crops.* We agree

The best way to reap the benefits of pharma crops and simultaneously protect the food system is to stop now and begin investing in other methods of biopharmaceutical production such as alternative crops and fermentation and cell culture systems.

with the experts that this effort should begin as soon as possible and should include incentives that enable scientists and agronomists to explore new crops and agronomic systems.

It should be noted that the use of non-food/feed crops would substantially reduce the potential for pharma crop contamination of the food supply but not eliminate it entirely, since pharma crop debris and seeds could still commingle with

10 In 2001, the food and fiber system, including trade, farm, and services, accounted for 12.3 percent of the U.S. gross domestic product (Edmondson 2004).

11 A 2004 editorial in *Nature Biotechnology* took a similar position, endorsing “foolproof segregation between food crops and drug crops” and rejecting the use of food crops in drug production. In its words, “Let’s grow pharma plants, but let those plants be *Arabidopsis*, or flax, or duckweed.”

12 A leading example of drugs successfully produced in plant cell culture is the anti-cancer drug taxol. See Freese (2002b), Appendix 5, and references therein for examples of other drugs that have been produced in cell culture.

food and feed crops. In addition, alternative pharma and industrial crops could pose risks to the environment. We therefore urge that the process for identifying non-food/feed crop alternatives include the goal of selecting candidate plants that would pose minimal risks to both the food/feed system and the environment.

Among the alternative crops considered in Chapter 7, tobacco is the furthest along in development. At least one company, Planet Biotechnology, has produced a pharma product in engineered tobacco that has progressed to clinical trials (BIO 2002).

While tobacco is not eaten, it is ingested by people who smoke and chew tobacco products, and as noted above, pharma tobacco, like other alternative crops, would pose a small risk to the food supply and unknown risks to the environment. Therefore, any system used to produce pharma tobacco should be operated in conjunction with a management system especially designed for this crop. In addition, the federal government should thoroughly examine the potential for engineered-tobacco products to contaminate the food/feed supply, consumer tobacco products, and the environment before approving them for commercialization.

Looking to the Future: a Bio-based Economy

The analysis described above is based on current market conditions, in which genetically engineered pharmaceutical and industrial crops are essentially niche crops within a commodity grain system dominated by food and feed crops. Some have suggested that these conditions may

change in the coming decades—that U.S. agricultural production may shift away from food and feed crops toward a wider deployment of industrial crops, including those grown as energy crops, chemical feedstocks, and other industrial substances. The aim of this so-called bio-based economy would be to substantially replace fossil fuels with crop-based products.

Bringing such a vision to fruition would constitute a major transformation of American agriculture. The experts' analysis suggests that efforts to promote a bio-based economy need to take into account threats to the food system, and to the extent that new energy or feedstock crops are genetically engineered to produce novel substances, these crops would pose threats similar to those discussed above. For this reason, serious efforts to create a bio-based economy would require a strategic rethinking of the relationship between industrial and food systems, and any decisions that would move U.S. agriculture in that direction should involve all the stakeholders, including consumers, food companies, and scientists.

A Final Note on the Relationship between the Experts' and UCS's Recommendations

The conclusions and policy recommendations of the Union of Concerned Scientists are based on the expert analyses in the technical report, but are solely the views of UCS. One of our policy recommendations—that the outdoor production of genetically engineered pharma food and feed crops be halted immediately—is not addressed in the technical report and is not necessarily shared by its authors.

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Chapter 1

INTRODUCTION

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During the early 1970s, Paul Berg, Herbert Boyer, and Stanley Cohen ushered in the era of biotechnology by pioneering techniques that allow the direct manipulation of genes (DNA sequences). Since then, scientists have been able to identify the genes for desirable traits in one organism and transfer those genes into other organisms. The molecular processes for transferring genes among organisms are often referred to as biotechnology or, more specifically, genetic engineering. Plants or animals containing genetic material from unrelated sources are called transgenic.

Specific applications of genetic engineering in plants, animals, and bacteria are abundant and increasing in number. The greatest commercial successes of biotechnology involve agronomically improved transgenic crops and engineered microorganisms used for drug production.

EVOLUTION OF THE GENETIC ENGINEERING INDUSTRY

Since the first discoveries in the early 1980s, crop genetic engineering has proceeded at a rapid pace. By the early 1990s, commercial prototypes were being field tested, and only a few years later, genetically engineered versions of major crop

plants were commercially available in the United States. “First-generation” genetically engineered plants were major crops intended to benefit farmers. Herbicide-tolerant (HT) soybean, for example, along with insect-resistant and HT corn and cotton, and to a lesser extent HT canola comprise about 99 percent of all U.S. acres currently planted with genetically engineered crops. HT crops shifted herbicide use to glyphosate or glufosinate, and insect-resistant Bt crops¹³ were developed to protect plants against stem-boring insect pests.

We are now in the midst of the “second generation” of genetically engineered crops, mostly elaborations of first-generation crops. For example, a second kind of Bt corn, targeting some root-feeding pests, has recently been marketed. Many Bt crops now also contain an HT trait, and two Bt traits are now available combined in cotton and corn. The second generation also includes small commercial acreages of virus-resistant squash and papaya.

The “third generation” (expected between 2005 and 2010) promises to increase the number of agronomically significant transgenes in soybean, corn, cotton, and other crops. Most importantly for this report, however, the third generation of engineered crops is also likely to contain many more “pharma” crops—those that produce chemicals intended for pharmaceutical and industrial uses.¹⁴

¹³ Bt crops, which are produced by incorporating toxin genes from *Bacillus thuringiensis* (Bt) into the crop genome, typically produce toxins that kill certain insect pests. The pests die after ingesting the toxins. There are several hundred different Bt toxins, each of which kills different kinds of insects.

¹⁴ The second generation also includes a few crops engineered to produce pharmaceutical and industrial compounds. Most are genetically engineered corn varieties that produce drugs and compounds for industrial or research uses. The acreage of these crops is minuscule compared with genetically engineered crops that have agronomically significant traits.

In general, pharmaceutical uses encompass the production of therapeutic agents for humans and animals, including drugs and vaccines. Industrial uses range widely from enzymes to plastics to lubricants. The Union of Concerned Scientists has written elsewhere on the uses and risks of this new generation of genetically engineered crops (UCS 2003, 2004).

Briefly, the benefits of these products, especially new therapies, could be considerable. (See box, “The Promise of Pharma Crops.”) On the other hand, the products may pose serious health, environmental, and commercial risks. None of these substances is intended for food use and many of them, especially pharmaceuticals, may be bioactive at very low concentrations.

The Promise of Pharma Crops

Agricultural-scale production of therapeutic proteins and vaccines (especially for diseases prevalent throughout the world) may be effective in providing large quantities of the desired products at a lower cost than is currently possible. For example, about 170 million people are infected with the hepatitis C virus (WHO 2000), and more than one-third of the world population is infected with hepatitis B (WHO 2002). A large majority of hepatitis C-infected patients have severe liver cirrhosis.

The annual requirement for treatment with insulin-like growth factor for each cirrhotic patient is 600 mg at a cost of \$30,000/mg. The current annual cost of interferon therapy for viral hepatitis is \$26,000 (Cowley 2002). In 2003, the UN Human Poverty Index showed that 1.2 billion of the developing world’s 4.8 billion people were living on less than one dollar per day, while a further 2.8 billion were living on less than two dollars per day. If a pharma crop could substantially reduce the cost of these therapies, many people could possibly benefit.

RISKS

While the commercial and health benefits of pharma and industrial crops could be substantial, there are risks to the food supply and the environment associated with their large-scale production. Many pharma and industrial products will be potentially toxic substances that could harm humans, food animals, or wildlife if ingested in active forms.

Of the many possible risks associated with these products, this report will focus only on the contamination of food and feed crops. While there are differences between crops genetically engineered for pharmaceutical and industrial uses, they pose similar risks to consumers and the food industry because they all produce substances not intended for food use that may inadvertently end up in food.

There are two major routes by which pharmaceutical and industrial transgenes can inadvertently contaminate commodity crops, and therefore the food and feed supply. One is the physical mixing of seed—pharma seed can be inadvertently spilled or mixed during seed production, harvest, storage, transport, and handling. The other is pollen, which contains the male reproductive cells necessary for the fertilization of plants and the production of seed.

This report focuses primarily on dispersal of pharma genes by pollen and seeds, a topic developed in more detail in Chapter 2. Methods to reduce such gene flow are discussed in Chapter 3 and have been reviewed recently (Daniell 2002; NRC 2004).

CORN AND SOYBEAN AS PHARMA CROPS

Corn and soybean—both major food crops grown on about 27 to 28 million hectares (about 70 million acres) each year—are currently being engineered to produce pharma and industrial compounds. The characteristics that make corn

and soybean dominant grain commodities also make them ideal for use as pharma crops.

Both are inexpensively and reliably produced, reducing pharma production risks. Seeds of both crops can be stored inexpensively for relatively long periods of time (corn more so than soybean), so the pharma product can be quickly retrieved from storage and purified on demand. Both seeds are relatively simple chemically, making the isolation of pharma products from grain economically and technically feasible. In addition, both crops are technically amenable to genetic engineering, so in principle nearly any pharma product can be produced in either of these crops. Neither has a close, sexually compatible wild or weedy relative in the United States to which pharma genes could escape by gene flow. From an exclusive production perspective, therefore, corn and soybean are ideal for pharma production.

THE CENTRAL DILEMMA

However, the U.S. commodity corn and soybean production systems are structured to mix grain from many sources before it is ultimately used. Because of this, without substantial modification, the present commodity system will not be able to keep the human food and animal feed supply systems distinct from each other. Moreover, once a transgene enters the commodity system it may be difficult to remove it, as illustrated by the continuing occurrence of StarLink corn in the human food supply (Taylor and Tick 2003).

This problem raises the fundamental dilemma associated with pharma crops. The compounds produced by genetically engineered pharma plants are expected to lead to useful products that would have beneficial effects on human or animal health. At the same time, these compounds can contaminate the food supply and the environment and may have detrimental health effects on humans or animals, putting food companies at risk for

market losses, legal liability, and brand damage.

As a society, we simply have not seriously addressed this dilemma: is it possible to produce these compounds in ways that protect consumers and the food industry? This report tackles this problem by answering the following question: Is it possible to design a system for producing pharma products in genetically engineered corn or soybean—two plants often used or proposed for pharma production in the United States—without contaminating human food or animal feed?

This problem is complicated because the present corn and soybean production system handles three kinds of grain products: commodity grains, identity-preserved (IP) grains, and seed. Commodity grains are usually used for food and feed products without differentiation among varieties or hybrids. IP grains are used for food and feed purposes that require specific characteristics associated with individual varieties, hybrids, grains, or production methods. Seed is used for the production of commodity or IP grains and is grown and handled where traceability and quality standards are part of the system. However, these quality standards are insufficient to ensure protection of the food and feed supply from pharma product contamination. Complicating matters further, there are ranges of separation and segregation within each of these systems.

To address the problem, it is essential to understand the corn and soybean production systems as value chains—differentiated supply chains formed by a string of companies or collaborating operations that work together to produce specific products or services. These value chains would likely include transgene suppliers, seed companies, farmers, buyers and handlers of grain, and ultimately end users. A value chain of collaborating business entities requires cooperation, usually governed by contractual arrangements between the various parties in the chain. Without the full

cooperation of all participants, it will be difficult to find a solution to the problem.

VIRTUALLY ZERO CONTAMINATION

In this report, we propose the standard of *virtually zero* contamination of the food and feed systems. The basic idea underlying this standard is that the likelihood of contamination is so low that contamination is nearly zero.

In choosing the standard, we rejected a zero contamination standard as impossible to attain. Events of minuscule effect or vanishingly small probability would violate this standard. For example, one seed of a pharma crop that enters the food supply only once in five years would be enough to violate a zero contamination standard. Such a standard would be impossible to monitor or enforce. A virtually zero standard is the level of contamination that admits the impossibility of zero contamination.

We also rejected other standards as too weak or impractical. For example, a standard of undetectable contamination changes with each advance in the sensitivity of detection. This is neither an appropriate way to ensure the safety of the food and feed systems nor an appropriate way to manage the perception of risk.

A standard based on acceptable or tolerable risk begs the question of acceptable or tolerable to whom. Such a standard would have to address complex issues including consumer choice, sensitive populations, and decision-making processes, and each product would have to be assessed to determine whether it meets “acceptable” levels. Setting levels, assessing products case-by-case, and enforcing levels once products are in the marketplace would require resource-intensive regulatory intervention. Such regulation of the food and

feed risks of products that are not intended for use in food or feed seems unwise.

As discussed further in Chapter 8, establishing a system that will meet a performance standard such as virtually zero contamination¹⁵ is a better option. By promoting a virtually zero contamination standard, we advocate that pharma crop production be conducted in a way that effectively prevents the contamination of the food and feed supply. We will assess the adequacy of confinement systems against this standard throughout the report.

REPORT OUTLINE

In this report, we examine corn and soybean production for the points at which commodity crops—and therefore the food and feed systems—could be contaminated by pharma crops.

We divide corn and soybean production into three phases: seed production, on-farm production, and post-harvest handling and transport. For each phase, we then identify potential contamination routes and evaluate strategies to block them. For food and feed systems to be protected against contamination, routes of contamination must be blocked in all three production phases.

We base our analysis on our knowledge of current corn and soybean production systems and the scientific literature associated with corn and soybean production. For pharma crops, it is quite likely that current production systems will be modified to comply with new regulatory requirements. Also, we expect that many pharma crops will be grown on a much smaller scale than other crops because of these requirements. The goal of this report is to identify crucial steps that will be needed to commercialize pharma crops in the United States in a safe and responsible manner.

¹⁵ Contamination is a term that is sometimes considered judgmental. Other terms, such as “unintended presence,” “adventitious presence,” and “undesirable impurity,” are awkward and not readily understood. For lack of a better alternative, we use the term contamination without its judgmental implications.

Chapter 2 describes the potential routes by which non-pharma corn and soybeans can become contaminated, particularly pollen movement and seed mixing. Chapter 3 discusses various methods by which contamination could be blocked. These confinement measures are broadly classified as zoning, spatial separation, temporal separation, dedication of machinery and infrastructure, physical and biological confinement, and disallowing food and feed crops as pharma crops.

We then examine the three phases of corn and soybean production in depth to identify points at which food and feed crops are vulnerable to

contamination by pharma crops and evaluate the confinement measures suggested in Chapter 3. Chapter 4 examines the seed production processes for both crops, Chapter 5 examines on-farm production, and Chapter 6 examines post-harvest shipping, handling, and storage. Chapter 7 briefly examines the potential for using non-food/feed plants for pharma production (recognizing that a full examination of this problem is beyond the scope of this report). Chapter 8 synthesizes the major conclusions of this report and makes recommendations.

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Chapter 2

ROUTES OF CONTAMINATION

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To evaluate the prospects for preventing contamination of the food supply by pharmaceutical transgenes, we must first identify the routes by which such contamination might occur. The two major routes of contamination (i.e., the presence of pharma transgenes where they are not wanted) are through pollen and seed. Pollen is essential for sexual reproduction and seed formation in corn and soybean. Eliminating the dispersal of pollen is one of the most straightforward ways to prevent biological contamination at a very early stage.

Seeds can be dispersed either naturally, by wind or animals, or by human handling through spillage during seed production, harvest, transportation, and storage. In addition, seeds can be mixed with other seed stocks during these same operations. Seeds spilled during harvesting, for example, can give rise to plants called volunteers in the next growing season. Grain residues left in a harvester can lead to the mixing of grain from different sources of the same crop.

POLLEN DISPERSAL

Pollen is dispersed mainly by wind and animals. For example, after an insect visits a flower in one population, pollen grains from that flower can stick to its body and be deposited in a flower of a different population.

Pollen dispersal is a natural and widespread phenomenon; at least 12 of the 13 most important food crops in the world cross with wild

relatives (Ellstrand 2003; Ellstrand, Prentice, and Hancock 1999). Pollination involving transgenes may move genes for new traits, including pharma traits, from one plant to another.

Unlike synthetic pesticides such as DDT or parathion, which are ultimately degraded in the environment, genes (including transgenes) are replicating molecules. They are able to maintain themselves in living organisms, where they become subject to evolutionary forces such as migration and selection. In some cases, they become extinct in the environment, but in others where, for example, they provide a fitness benefit, their frequency may increase and they may spread in wild plant populations.

Pollen can carry transgenes between crop varieties or between crops and wild or domesticated relatives (Ellstrand, Prentice, and Hancock 1999). This kind of crossing usually leads to viable and fertile offspring that often display more vigorous growth than either parent (Harlan and de Wet 1971). If pharma transgenes are transferred to and maintain themselves in populations of wild relatives, they could ultimately be reintroduced into non-pharma crops.

Various factors influence the magnitude and geographic extent of pollen movement, including the reproductive mode of the plant, the topography of the surroundings (including the distances among populations), biological and physical characteristics of pollen, environmental factors such as climate and weather, and factors affecting the success of hybridization. Among the latter are the sexual compatibility between parents, presence of compatible plants within pollination distance,

sufficient overlap in flowering time, and the actual occurrence of fertilization (Gepts and Papa 2003).

The biological features of corn (*Zea mays*) and soybean (*Glycine max*) differ from one another in ways that affect the likelihood of genes escaping from the crops (Fehr 1980; Russell and Hallauer 1980; Smith 1995). The major difference between the two is that corn is a wind-pollinated plant whose offspring result from unions of pollen and eggs that come from different corn plants (outcrossing), while soybean tends to produce offspring that are the result of unions between pollen and eggs from the same plant (selfing), with only occasional outcrossing involving insect pollinators.

Characteristics of Corn Reproduction

Corn is a species with separate female and male flowers on the same individual plant. The female flowers are found in the ear on the side of the main stem, whereas the male flowers, called anthers, are located in the tassel at the top of the plant.

Each flower in the ear consists of an ovule, style, and stigma. The ovules contain the eggs, which are fertilized by pollen grains. The styles, also called silks, are pollinated when they emerge from the ear's husks. The stigma is the receptive part of the style to which pollen adheres.

An ear has approximately 1,000 ovules. By contrast, anthers in an average tassel will produce approximately 4.3 million to 5.2 million pollen grains (Westgate, Lizaso, and Batchelor 2003). Thus, for each ovule, corn plants produce some 5,000 pollen grains (Kiesselbach 1999). The large number of pollen grains is characteristic of wind-pollinated plants (Cruden 2000).

Two features prevent the release of seeds from a corn ear at maturity as happens in wild corn in Mexico. First, the ear is surrounded by husks, and, second, the ear does not break up to free the seeds.

In corn, male and female flower parts mature at different times to avoid self-pollination. Silks

appear one to three days after the anthers on the same plant have started shedding their pollen, and become receptive to pollen when they emerge from the husks. It may take up to five or six days for all silks to emerge from the husks. Each silk may remain receptive for up to 10 days, but high temperature and low humidity decrease this period.

Pollen shedding usually starts three hours after daybreak and continues for one to three hours. Under cooler temperatures and higher humidity, pollen dispersal may be delayed until noon and continue well into the afternoon. Individual pollen grains remain viable for two hours at the most (Luna et al. 2001). The total period of pollen shedding from a tassel can vary from one to two days to more than a week. So, the actual pollen dispersal time and duration of a given variety are variable and unpredictable because they depend on weather conditions. Whether dispersed pollen will be able to effect pollination depends on the presence of receptive silks, which, as noted above, is dependent on weather conditions.

Corn pollen is dispersed by wind over rather short distances because individual grains are heavy and large compared with pollen grains of other species. The dispersal distance is positively correlated with the size of the source field and wind speed (Raynor, Eugene, and Janet 1972). Other factors that influence pollen movement are gravity, wind direction, turbulence, air density and viscosity, pollen radius, and sedimentation velocity (Di-Giovanni and Kevan 1991; Di-Giovanni, Kevan, and Nasr 1995). Work by Jones and Brooks (1950; cited in Treu and Emberlin 2000) indicates that corn pollen has been observed at 800 meters (0.5 mile) from the source as measured by an outcrossing frequency of 0.2 percent.

Experimental data (Table 2-1) show that pollen concentration 60 meters downwind of the source is equal to one percent of pollen concentration one meter from the source (Raynor, Eugene, and Janet

1972). Luna et al. (2001) observed barely detectable outcrossing at 200 meters (0.1 mile) and none at 300 meters (0.2 mile). Ortiz-Torres (1993; cited in Castillo-González and Goodman 1997) observed 10 to 60 percent cross-pollinated grains in border rows and two to three percent 15 meters from the borders.

In another study, pollen density was higher inside a cornfield at 171 grains per square centimeter (0.15 square inch) and decreased rapidly away from the field to 14 grains per square centimeter (0.15 square inch) at a distance of two meters (six feet). A single rainfall removed 54 to 86 percent of pollen grains on leaves (Pleasant et al. 2001). *These observations show that long-distance dispersal would be unlikely but not impossible, suggesting that physical isolation or zoning is necessary to prevent the escape of pharma transgenes.*

Characteristics of Soybean Reproduction

Soybean is a predominantly self-pollinating species with very low outcrossing rates. In domesticated soybean, outcrossing rates of only 1 and 0.5 percent have been reported for adjacent plants within rows and between plants of adjacent rows, respectively (Weber and Hanson 1961, cited in Fehr 1980). Ahrent and Caviness (1994) and Nakayama and Yamaguchi (2002) reported a mean of 0.7 percent outcrossing in domesticated soybean, with a range of 0 to 5.89 percent.

Soybean is a highly self-pollinated plant in large part because anthers and stigma are close to each other in the flower. (Unlike corn, single flowers of soybean contain both female and male organs.) The stigma is receptive to pollen one day before flower opening and remains receptive for two days after flower opening. In most flowers, the anthers open and shed their pollen directly on the stigma on the day the flower opens. Under certain circumstances, such as cooler weather,

Table 2-1 **Experiments on Pollination Distances in Corn**

Sources ^a	Size of source field	Measure	Distance measured
Cross-pollination			
1	—	10-60% 2-3%	1 meter (border) 15 meters
2	45 meters x 45 meters	8-23%	1 meter (border)
3	4,000 meters ² block	1 event each No event	150 and 200 meters 300 and 400 meters
4	44 meters x 8 meters	Less than 5%	32 meters
Pollen grains			
5	18 meters diameter	3.8 x 10 ⁶ grains or 1,100 grains/meter ²	32-60 meters

^a1. Ortiz-Torres (1993; cited in Castillo-González and Goodman 1997); 2. Murillo-Navarrete (cited in Castillo-González and Goodman 1997); 3. Luna et al. (2001); 4. Chilcutt and Tabashnik (2004); 5. Raynor, Eugene, and Janet (1972).

pollen shedding and fertilization take place within closed flowers (Erickson 1975). On average, each of the 10 anthers produces 300 to 800 pollen grains (Palmer, Albertsen, and Heer 1978). Within 10 hours of flower opening, pollen germinates and fertilizes the egg in the ovule (Fehr 1980).

Soybeans may also be cross-pollinated by insects. With nectar consisting of 30 to 50 percent dissolved solids, soybean flowers attract insects (Erickson 1975) such as honeybees, bumblebees, leafcutter bees, Halictid bees, and thrips (Nakayama and Yamaguchi 2002). Genotypic differences in outcrossing among varieties (Ahrent and Caviness 1994) and higher levels of outcrossing in wild soybean (up to 20 percent according to Fujita et al. 1997; Nakayama and Yamaguchi 2002; Ohara and Shimamoto 2002) suggest a partly genetic control in addition to environmental effects, principally the level of pollinating insects. *Thus, although soybean is predominantly selfing, insect pollination is a mode by which pharma transgenes will escape, if pollinators are present.*

In summary, pharma transgenes may escape via pollen in both corn and soybean, despite their different flower biologies.

SEED DISPERSAL AND MIXING

Seeds can also act as gene dispersal agents in two ways: they can be dispersed naturally—by

wind, animals, or humans—or they can be spilled during seed production, harvest, storage, and transportation, which may cause future contamination of crops. These seeds may then grow into plants (volunteers) in future crops or may grow in non-crop areas, which could lead to pollen flow. Other plant parts could be harvested with future crops if not completely covered in tillage operations.

Seed mixing is the inadvertent introduction of unwanted seeds or grains into a seed or grain product during the growing, harvesting, handling, storage, delivery, and processing of that product. In the broadest terms, seed mixing, as applied to grain, is the mixing of two different types (species) of grains, which, in grain industry terms, affects “other crop” purity. An example would be corn grains in a soybean crop sample. A more specific type would be mixing seeds of two different varieties within the same species, which, in seed industry terms, affects “genetic” purity. An example would be the presence of a small amount of variety B soybeans in a sample of variety A soybeans. In commercial seed, the offending contaminant might not be identified, other than as “off-type.”

Seed mixing occurs in both corn and soybean systems and for the same reason: the cropping methods and the equipment used for growing, harvesting, handling, and storage are very similar. The major difference between the two crops is the process of drying the corn grain after harvest. Soybean seeds usually reach storable moisture levels in the field, so there is no need for artificial drying. Corn, however, is harvested in a large part of its production area at moisture levels above those needed for proper storage, and requires drying with air in a grain dryer or in aerated storage bins. Seeds of corn and soybean, stored

under dry (less than 10 percent relative humidity) and cool (less than 10°C) conditions, remain viable for several years.

Currently, most of the sampling and testing of the seed mixtures described above involves obtaining a representative sample, making a visual inspection, or conducting more elaborate testing procedures involving enzyme or DNA analyses. Both the grain and seed industries provide tolerances for these types of mixtures. However, these were established to maintain seed purity and are less stringent than a virtually zero contamination standard.

Mixing of pharma crop and food crop seeds may occur at a number of points in seed production and in the grain production/handling/storage system—during the operation of equipment or the transfer of seed or crops between steps in the system. For example, pharma seed may lodge in equipment or facilities and not be found during the cleaning and inspection between pharma crop and food crop operations. Pharma seed remaining in a combine after harvesting could contaminate the next product harvested with this equipment. At a storage facility, grain spilled during dumping from transportation equipment into storage or processing facilities could become mixed with grain handled later in the same facility.

CONCLUSION

Whether by pollen or seed dispersal or seed mixing, there are many opportunities for the unwanted introduction of pharma genes into non-pharma crops, including food and feed crops. The next chapter will review the options available to block the contamination occurring by these routes.

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Chapter 3

CONFINEMENT OPTIONS

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As discussed in Chapter 2, there are two major routes by which pharma transgenes could move into non-pharma crops and eventually into the food or feed system: pollen dispersal and physical seed mixing. A number of confinement options are available to block these routes of contamination in corn and soybean systems; they can broadly be classified as follows:

- **Zoning**
Restricting the growth of pharma crops to areas of the country where corn and soybean are not usually produced
- **Spatial separation**
Growing pharma crops in fields separated from conventional crops by distances far enough that cross-pollination is unlikely
- **Temporal separation**
Planting pharma and conventional crops at different times to prevent overlapping flowering periods
- **Dedicated machinery/equipment/infrastructure**
Reserving farm machines and other infrastructure for use with pharma crops exclusively
- **Physical confinement: indoor production**
Growing pharma crops within physical structures

- **Biological confinement**

Employing various biological methods of reducing pollen or seed dispersal such as chloroplast engineering, male sterility, emasculation, seed sterility, cleistogamy, and apomixis

- **Disallowing food/feed crops**

Prohibiting the use of crops used for food or feed as pharma crops

Below we describe each of these confinement options and note their advantages and disadvantages when used as a single confinement measure within corn and soybean systems. Table 3-1 (p. 34) summarizes the advantages and disadvantages. A recent report from the National Research Council (NRC 2004) provides additional details on various methods of biological confinement.

While we analyze the options separately, we believe they would need to be integrated to achieve virtually zero contamination. In Chapter 8, we consider the use of two or more measures together.

Furthermore, these confinement options must be incorporated into special management systems to be effective. These systems are discussed in the latter part of this chapter.

In general, if a confinement measure or some combination of measures could completely block contamination during all three phases of corn and soybean production, it would be possible to achieve virtually zero contamination of the food/feed system when corn and soybean are used as pharma crops. On the other hand, if contamination cannot be completely blocked in any one of these three phases, achieving that goal would be impossible.

Table 3-1 **Confinement Options for Corn and Soybean Pharma Crops to Achieve Virtually Zero Contamination (VZC) of the Food/Feed Supply**

Confinement option	Effectiveness in achieving VZC		Cost	Ready for use?	Enforceability	Scalability
	Pollen dispersal	Physical seed mixing				
Zoning (isolation)	VZC unless fields at close distance are undetected	Not VZC by itself but does reduce probability of contamination	Moderate: costs associated with establishing the zone; some shipping costs	Ready now, but zones must be established	Reasonable; need to ensure and verify isolation	May run out of suitable areas
Spatial separation	Not VZC but reduces the probability of contamination; soybean probably will have higher confinement than corn at similar separation distances	Not VZC but does not preclude other actions	Moderate to high: costs associated with establishing and maintaining separation; potential costs associated with contaminating neighbors	Ready now, but size of buffer areas must be determined and these areas must be established with cooperation of neighbors	More difficult than zoning	Can scale up by consolidating areas of production
Temporal separation	Not VZC; ineffective alone for corn; may not help much for soybean; unpredictable from year to year; hard to predict for neighbors	Not VZC but does not preclude other actions	Moderate to high: costs associated with reduced crop yield; disruptive to management system in production	Ready now; used routinely in plant breeding	Potentially difficult	Can scale up by consolidating areas of production
Dedicated machinery/equipment/infrastructure	Not VZC but does not preclude other actions	Can reduce mixing to VZC for vulnerabilities related to machinery/equipment/ infrastructure	Machine costs are scalable; will need dedicated seed production facilities	Ready now	Design can ease moderate difficulties	Scalable
Physical confinement: indoor production	Not VZC but can be close to VZC (depending on the design and expense)	Not VZC but reduces the probability of mixing	High to very high: cost of structure can be greater than \$10 million per acre	Ready now; just have to be built or adapted	Reasonable	Cannot scale to large areas
Chloroplast engineering	Not VZC but has potential for substantially reducing escape by pollen dispersal; leakage rate unknown	Not VZC but does not preclude other actions	Prototypes available in soybean but not corn	Not ready in corn but available for soybean	Reasonable	Scalable
Male sterility: cytoplasmic	Not VZC but reduces escape by pollen in corn; leakage unknown in field; useful for corn, less so for soybean	Not VZC but does not preclude other actions	May constrain breeding options	Ready now; used routinely in plant breeding	Somewhat costly	Scalable
Male sterility: nuclear	Not VZC but potentially reduces escape by pollen; leakage rate unknown	Not VZC but does not preclude other actions	Uncertain; prototypes not yet available in corn and soybean	Not ready for use; needs development before it can be tested in corn or soybean	Potentially costly	Scalable
Emasculatation	Not VZC but reduces escape by pollen; possible only with corn	Not VZC but does not preclude other actions	High	Ready now; used routinely in plant breeding	Reasonable; need to monitor	100% emasculatation difficult, especially in large areas

Table 3-1 (CONTINUED)

Confinement option	Effectiveness in achieving VZC			Cost	Ready for use?	Enforceability	Scalability
	Pollen dispersal	Physical seed mixing					
Seed sterility	Not VZC but does not preclude other actions	Not VZC but potentially reduces seed dispersal; leakage rate unknown		Uncertain; prototypes not yet available in corn and soybean	Not ready for use; needs development before it can be tested in corn or soybean	Potentially costly to enforce	Scalable
Cleistogamy	Not VZC; will not reduce escape by pollen because expression is unreliable	Not VZC but does not preclude other actions		Low (once genes for cleistogamy have been identified)	Not ready for use	Not costly to enforce	Scalable
Apomixis	Not VZC in corn or soybean; will reduce escape only in a few species	Not VZC but does not preclude other actions		Low (once genes for apomixis have been identified)	Not ready for use	Not costly to enforce	Scalable
Disallowing food/feed crops	VZC	VZC, but would need to eliminate potential mixing of debris and seeds or volunteers with foods or feeds		Agronomic suitability may not be as good as corn and soybean	Tobacco ready for use and has no relatives on U.S. mainland; most other crops not ready for use; need to develop suitable alternatives that lack wild relatives, are transformable, are not used for food/feed, and for which sufficient molecular knowledge exists	Reasonably enforceable	Scalable
Management systems	Not VZC but necessary to ensure VZC	Not VZC but necessary to ensure VZC by reducing human error (in combination with other methods except the non-food/feed crop option)		Moderate: costs associated with record keeping and management	Ready soon; need to develop management and record-keeping capability	Moderate difficulties, but easier than most of the above	Scalable

ZONING (Paul Gepts)

Zoning is a confinement option that would restrict the growth of a transgenic pharma crop to areas outside the main production areas of the non-pharma food or feed crop. This option would mainly block contamination due to pollen dispersal but could also be implemented to reduce physical mixing.

Corn is grown principally in the eastern half of the United States (east of 104° west longitude) with two main exceptions: the central valley of California and a region where the borders of Idaho, Oregon, and Washington meet. In addition, there are areas in southern Arizona and New Mexico where white corn is grown for export to Mexico and other corn is grown for silage. American Indians throughout this western area may also grow corn on a small scale. If a zoning option were in place, producers in areas outside these production regions would be allowed to grow pharma corn. Some companies have already used this approach by locating pharma corn trials in western states.

The main growing region for soybean is similar to that for corn, except that soybean is not grown on a significant scale in the western states (Smith 1995).

Advantages

This approach virtually eliminates the escape of pharma transgenes via dispersal of pharma crop pollen. It would also virtually eliminate physical mixing provided there were neither other fields of the same crop nor stands of wild relatives growing in the vicinity of the pharma crop.¹⁶ Wild populations of a pharma crop could theoretically act as a relay population between successive growing seasons of the pharma crop. Gene flow in both directions (pharma to wild and wild to pharma)

could maintain the pharma gene in a certain area and could also lead to “stacking” of multiple pharma genes. This appears to be unlikely for corn, as the nearest wild-growing relatives are scattered populations in northern Mexico (Sánchez-González and Ruíz-Corral 1997), and is irrelevant for soybean given the absence of wild relatives in North America.

Although not common in such areas, corn and soybean may also be grown outside of the major production areas (for example, in home gardens or fields of sweet corn grown for local farmers’ markets). Pollen dispersal to those crops could be addressed if spatial separation complemented the zoning requirement.

The zoning approach would allow the continued use of well-known crops and cropping systems, reducing or eliminating the need to conduct research on cropping methods for new pharma crops. Except for the challenge of identifying and establishing cultivation zones, it is readily applicable and entails little additional cost except for the higher shipping costs. If combined with other measures, such as dedicated machinery and infrastructure, zoning may also address contamination by seed mixing. It can be easily overlaid with existing management approaches, including identity preservation.

Disadvantages

A major disadvantage of the zoning option is that the absence of other fields of the same crop within isolating distances would need to be verified before the planting of the pharma crop and would need to be monitored until the flowering period of the pharma crop ends. A permitting process tied to an Internet-based geographic information system might be needed to assist in siting pharma crop fields under a zoning option. Such a system would

¹⁶ For corn and soybean, there are no wild relatives in the United States. Scattered populations of teosinte (wild corn) have been described in the northern Mexico states of Chihuahua and Durango (Sánchez-González and Ruíz-Corral 1997).

have to be designed to function as a central source of information enabling growers to identify plots located at a sufficient distance to ensure spatial separation complementing the zoning isolation.

In addition, implementing this option would require the enactment of legal restrictions excluding pharma crops from some regions and, perhaps, setting aside zones for the exclusive cultivation of pharma crops in other regions. A zoning system may also be difficult to set up in practice because of the non-commercial production of food or feed crops within the zone. Certain crops such as corn, for example, are grown by American Indian communities in the Southwest not to sell but as part of their heritage. Furthermore, corn is also grown in home gardens. These situations would require careful monitoring and perhaps agreements with neighbors.

Another difficulty is the lack of optimal growing conditions outside the conventional growing regions. Pharma crop growers would need to find areas within permitted zones that provide appropriate soil and climate conditions for the crop involved, including proper length and timing of the growing period, water availability, and temperature. In areas of the country where corn and soybean have not traditionally been grown, such as the desert west, other facilities including irrigation, adequate and dedicated transportation, and seed storage facilities would have to be developed.

Thus, a zoning system may be difficult to set up in practice. Moreover, even if successful, implementation of this approach may soon exhaust the supply of land that satisfies the prerequisites for its application, depending on the scale at which the pharma crop is produced.

SPATIAL SEPARATION (Paul Gepts)

Spatial separation is a form of confinement that allows pharma crops to be grown in the major crop-growing areas but locates them far enough from food and feed crops to significantly

reduce pollen flow between crops. This option reduces contamination via pollen dispersal but has no impact on physical seed mixing.

Corn

In wind-pollinated plants such as corn, Tauber (1965, 1967) recognized three components in pollen dispersal, each associated with a different dispersal distance. The first is gravity, which acts over a very short distance. Basically, if gravity is the only process at work, pollen is deposited only on the parent plant or adjacent plants. The second, the local pollen component, depends on wind and shows a steep gradient in concentrations with distance downwind. This component is most likely to be affected by vegetation and other local physical barriers.

The third, the regional component, consists of pollen grains caught by upward air movements and transported by airflows above the height of vegetation and the local air current conditions created by surface features. Regional airflows may carry pollen considerable distances downwind. The relative amounts of pollen dispersed by these three basic mechanisms will differ with factors such as the type of plant, the prevailing weather, and the time of day of pollen release. Unlike seeds, however, pollen grains are short-lived (for example, corn pollen typically survives for less than two hours). This places a limit on the regional-scale distances over which cross-pollination can occur.

Factors that increase the dispersal of pollen include: a large plant population as the pollen source; the crop's reproductive system (a wind-pollinated plant such as corn often produces a high number of pollen grains, which are dry and airborne as opposed to predominantly selfing plants such as soybean, which have generally fewer, heavier pollen grains); the weather (sunny and dry days, strong winds); and the local environment (the absence of local vegetation and crop

barriers, the presence of insect pollinators) (Treu and Emberlin 2000).

Work by Jones and Brooks (1950; cited by Treu and Emberlin 2000) indicates that corn pollen has been observed at 800 meters (0.5 mile) from the source as measured by an outcrossing frequency of 0.2 percent. The most efficient physical barriers are hedges and woodlands, which are penetrable to air flow, as these encourage the removal of pollen from the wind by filtration and minimize the formation of strong downdrafts in the lee of the barriers, which can concentrate the pollen at ground level. Similarly, border rows¹⁷ on both the source and the receptor crops can be efficient at minimizing cross-pollination. It may be possible to reduce soybean cross-pollination with appropriate border plants (Treu and Emberlin 2000).

Although long-range pollen dispersal is a small fraction of total dispersal, it is a regular feature of plant reproduction and causes concern when pollen grains carry pharma genes. This is especially the case for corn, which is wind-pollinated and produces a very large amount of pollen per plant.

Setting isolation distances to eliminate long-distance travel of corn pollen will require much larger separation distances than those commonly used in certified seed production—on the order of several miles. Those standards were typically established to meet seed purity standards, most of which accept a relatively higher tolerance of contamination by other varieties of crops or even other crops. For example, certified soybean seed may contain up to 1.1 percent seed of other crops or other soybean varieties (AOSCA 2001). A standard of virtually zero contamination of the food system does not tolerate the levels of contamination set for certified seed production and needs far stricter standards.

Adopting the spatial separation option for pharma corn grown in corn-producing states could minimize, but cannot eliminate, cross-pollination even when combined with physical barriers and border rows. In these states, many miles of isolation would be needed around pharmaceutical-producing corn, including isolation from home gardens. Therefore, virtually zero contamination of the food supply by pharma corn cannot be achieved only by spatially separating pharma corn from food and feed corn in the major corn-producing states.

Soybean

For soybean, the spatial isolation distances recommended for commodity seed production are one to three meters (3 to 10 feet) and are set primarily to prevent mechanical mixtures of adjacent varieties or crops in the field. They are not intended to prevent occasional insect-vectored cross-pollination. Although this type of cross-pollination is rare in soybean, it can be a source of escape for crop genes, including pharma genes. Isolation distances to prevent this from occurring depend foremost on the maximum flight distances of insect pollinators.

The maximum measured flight distances of honeybees include 6.5 to 13.7 kilometers (4 to 8.5 miles) (Gary 1992), 4.3 to 6.2 kilometers (2.7 to 3.8 miles) (Moyes and Dale 1999; cited in Malone 2002), and 10 kilometers (6.2 miles) (Winston 1987). The largest distances are observed in settings without competing food sources. For leafcutter bees, a maximum distance of one kilometer (0.6 mile) was observed from alfalfa fields (St. Amand, Skinner, and Peaden 2000). Further experiments on individual plants led St. Amand, Skinner, and Peaden (2000) to recom-

¹⁷ Border rows are used to reduce the amount of pollen flowing from a particular source. In the case of engineered crops, rows of a conventional crop may be planted on the borders of a genetically modified (GM) crop plot to “capture” the GM pollen, reducing the amount moving off-site.

mend an isolation distance of some 1.6 kilometers (one mile).

Further research is needed to characterize pollinators and their flight distances in soybean. In addition, actual gene flow distances—which are typically shorter than pollinator distances—need to be characterized.

In conclusion, spatial separation on its own is not likely to ensure virtually zero contamination in soybean, even though isolation distances sufficient to prevent pollen dispersal are much shorter than in corn.

Advantages

The spatial separation confinement option has several advantages. This approach allows production of pharma corn and soybean in areas where corn and soybean grow the best and where farmers are expert in growing the crops. At the farmer level, the cost of adopting spatial separation may be minimal. This option can be readily instituted except for the problems of determining, implementing, and monitoring separation distances. It may be more effective for soybean than corn, given the shorter isolation distances needed.

Disadvantages

Used alone, spatial separation cannot achieve virtually zero contamination in either corn or soybean. It can be scaled up, but that will create additional problems of farmer adherence and cooperation, as well as enforcement.

TEMPORAL SEPARATION (Paul Gepts)

Temporal separation is meant to prevent an overlap in flowering times between pharma and non-pharma crops. It is an option that would affect pollen dispersal of pharma transgenes but would have no impact on physical mixing or seed dispersal of transgenes.

Implementing this option for corn requires information about other fields within pollinating distances, their planting dates, the varieties planted, the timing of male flower opening and silking, and the duration of male and female flowering for corn. For soybean, implementation requires information on a variety's sensitivity to day length and growth habit, both of which are important factors influencing the flowering time. Furthermore, in order to predict flowering time and determine when to plant other corn or soybean crops within isolation distance, intense monitoring of the weather (particularly in terms of temperature) is needed up until the end of the flowering time.

This option is difficult to implement because there is no control over the weather, which is a major factor in the timing of flowering in plants. For example, under warm springs and cool summers, two corn crops planted one month apart will overlap minimally in flowering, but under cool springs and hot summers, they could overlap substantially, depending on the specific planting time.

Advantage

The main, and perhaps sole, advantage of this option is that it can be implemented immediately.

Disadvantages

This option has several disadvantages. Used alone, temporal separation is ineffective in controlling pollen dispersal because it depends on the vagaries of year-to-year weather variation and the diversity of crop varieties. Each variety has its own characteristic growth pattern, which is also influenced by the weather, especially temperature and water availability. Thus, predicting the actual flowering time and duration for each variety is exceedingly difficult.

Furthermore, this option requires intense monitoring of fields in the region and knowledge of varieties grown by neighbors of pharma crop producers. Planting at dates other than the normal planting dates is disruptive to normal production schedules and often leads to yield decreases. Enforcement would be difficult because inspectors would be unable to observe whether or not farmers had achieved temporal separation (except during flowering periods).

DEDICATED MACHINERY/EQUIPMENT/ INFRASTRUCTURE (Dennis Strayer)

This option, requiring that certain equipment, machinery, and infrastructure be reserved for handling pharma crops exclusively, provides excellent protection against contamination by physical seed mixing, but does not affect pollen dispersal.

The descriptions below indicate which types of equipment, machinery, and infrastructure should be dedicated solely to pharma crops and which could also be used for other crops. For the latter, cleaning and other methods mentioned below should be sufficient to protect against mixing.

Dedicated

Planting equipment—planters or drills used to place seeds in the ground. Planting equipment must be dedicated to avoid seed mixing because planting errors are common, and an unrecognized planting error with pharma seeds could have disastrous consequences. Even though this equipment can usually be cleaned easily, the possibility remains that seeds could be missed. Since planting equipment is expensive, older and/or reconditioned machinery might be dedicated to small acreages of pharma crops.

Harvesting equipment—combines and other harvesting equipment used to remove the grain from plants in the field. Harvesting equipment

must be dedicated to avoid seed mixing. It is the most difficult equipment to clean with assurance that all seeds have been removed. Since this is the most expensive equipment in the production system, with new equipment costing approximately \$200,000, the same approach suggested above for planting equipment can be applied (i.e., older, reconditioned harvesting machinery might be dedicated to small acreages of pharma crops).

Handling and transporting equipment—implements used to move grain from harvesting equipment to a storage facility or to deliver grain to an end user. This equipment must be dedicated. Commodity grain production involves many handling and transporting steps, from harvesting the crop through its end use. Elaborate systems could include wagons, unloading augers, dump pits and elevator legs, conveyor belts, bins, and trucks. In addition, corn production would require a grain dryer using heated air and the equipment needed to move the grain in and out of the dryer. Since the best approach to minimizing mixing is to eliminate as many of the handling steps as possible, the most efficient dedicated system would dump crops from the harvesting equipment (combine) into a truck or container that would go directly to the end user.

Storage equipment (between harvest and end use)—bins or other containers used to store the crop and the machinery used to move the crop into and out of storage. Unless the crop is delivered directly from harvesting equipment to the end user, it would be stored either on the farm or by a handler until the end user needs it. Storage equipment must be dedicated. Storage containers include round grain bins with perforated aeration floors, hopper-bottom bins, and cement or glass-lined silos.

Delivery equipment (to the end user)—hopper-bottomed trailer trucks, railcars, or closed containers. This equipment must be

dedicated because commodity grain production involves many handling and transporting steps in the delivery system. The most efficient dedicated system would rely on a dedicated container system.

Not dedicated

Tillage equipment—implements used to disturb the soil and prepare a seed bed before planting. Tillage equipment need not be dedicated because it rarely moves seeds from one field to another, and can be easily cleaned to eliminate the seeds retained on those rare occasions. Seeds carried in soil adhering to the outside of the tillage equipment could be removed with a power washer.

Seed-handling equipment for planting—bulk handling wagons or boxes and augers or belts used to move seed from seed storage to the planting equipment. Rather than dedicate this equipment, growers could eliminate it by buying seed only in bags (50 to 100 pounds) or totes (1,500 to 2,000 pounds).

Cultivating equipment—implements used to mechanically control weeds. Cultivating equipment, like tillage equipment, need not be dedicated because it can be power- or steam-washed to remove adhering soil before use in food and feed crops.

Pesticide applicators—implements used to apply pesticides to crops. Application equipment need not be dedicated, except for machinery used during corn pollination, which might pick up pharma pollen from the air or plants and carry it to non-pharma corn. Soybeans do not shed pollen and would pose no problem in this regard.

Advantages

The advantage of a dedicated machinery/infrastructure system is that it nearly eliminates the potential contamination of food and feed supplies via the equipment and facilities used in

pharma crop production. Physical seed mixing from machinery, handling equipment, and storage and transfer equipment is probably very common in commercial grain production.

A second advantage is that it could be adapted immediately to pharma crop production. Currently, there is a surplus of seed-conditioning facilities in many parts of the United States that might be used as either dedicated pharma crop seed-conditioning facilities or dedicated commercial pharma crop-handling facilities.

For example, the Nebraska Foundation Seed Division (NFSD) has used a partially dedicated system for many years. Its growing, seed-conditioning, and storage facilities provide unusual opportunities in that they are located on a former World War II armament manufacturing and storage facility. NFSD has a lot of isolated land and many buildings that can be used for equipment and seed storage. It owns an older combine for each variety of soybean it will be producing, and that combine is dedicated to harvesting that one variety of soybean exclusively. NFSD may also use each combine for harvesting one variety of small grain that can be easily separated from soybean seeds. Other states may have similar, possibly underutilized handling systems that could be adapted to pharma crop production.

Disadvantages

One disadvantage of this option is that it ties up capital investment in equipment and facilities. Some of this equipment is very expensive when purchased new and represents a major investment for the producer. Decisions on how to implement a dedicated-machinery option would depend on the size of the pharma crop operation relative to the total farming operation. For small acreages, older, smaller equipment could be dedicated to pharma crop production and newer, larger equipment to

other production. In larger-scale pharma crop production, the entire farming operation, including all the equipment, may be dedicated.

Another disadvantage is the challenge of disposing of equipment and facilities dedicated to pharma crops. To allow equipment and facilities dedicated to pharma crops to be used for non-pharma crop production, it would be necessary to have certified equipment- and facility-cleaning processes.

PHYSICAL CONFINEMENT: INDOOR PRODUCTION (Emerson Nafziger)

Physical confinement of pharma crops sufficient to block pollen dispersal can be accomplished using indoor production systems, including opaque structures that require artificial lighting and temperature maintenance, greenhouses with translucent or transparent ceiling and wall panels (with or without supplemental lighting), and intermediate structures using a mixture of artificial and natural light.

Of these indoor systems, greenhouses are the best known—they are widely used around the world and the technology is well developed. They allow plants to be grown under close observation from seed production to planting to harvest, essentially completely isolated from other plants. With temperature control, plants can complete their life cycle within a relatively well-defined period, and yields are usually more predictable than when crops are grown under rain-fed conditions out in the open.

Water and nutrients are typically provided in indoor systems on an as-needed basis, and thus tend to be non-limiting. Adding carbon dioxide can increase seed yields of soybean but has less effect on corn. Corn, however, is a very light-responsive crop, and maintaining light intensities equivalent to those in an outdoor field requires transparent panels and/or supplemental lighting.

Management of pests and diseases in enclosed systems is usually accomplished by chemical, cultural, and biological methods. Airlocks and decontamination procedures upon entry and exit can prevent pest or pollen movement into or out of contained facilities. (For example, soybean rust, a potentially devastating plant disease not yet found in U.S. fields, is being investigated in a secure greenhouse at Fort Detrick, MD.) Electronic alarm and control systems can be used to help maintain isolation.

Indoor production facilities such as greenhouses are expensive, but the use of temporary, movable structures to isolate field-grown pharma corn during pollination would lower costs. Such structures are not in wide use now, but producing them using existing greenhouse technology is feasible. Devising ways to shed heat loads from inside the structure will require additional development, but it should be possible to use such structures to seal corn plants from the outside for the two- to three-week period when there is a possibility of pollen release. Blocking pollen dispersal could be supplemented in corn by detasseling before the movable structures are lifted off the pharma crops.

With plantings spread by one month or so, such structures could be used to isolate two crops in a season. Their use in soybean would also be possible, but because insect movement of pollen is the major dispersal mechanism in soybean, using mesh structures might be preferable to enclosures.

Advantages

Physical confinement of crops within structures is a very effective means for preventing pollen movement. Yields of pharma crops grown in enclosed structures would be more predictable and less variable than in the outdoors, and it should be possible to produce two or three crops per year, even in temperate climates. This option

could be implemented in the very short time needed to build and optimize the facilities.

Disadvantages

- Enclosed structures are expensive to build and maintain.
- Indoor crop production systems require large amounts of energy to maintain temperatures within an acceptable range.
- Failure of electric power could mean rapid loss of a crop due to temperature spikes.
- Maintaining adequate light for maximum yields of corn is difficult and energy-expensive.
- Pest management is often difficult, especially when crops are grown to maturity.
- Windstorms and hail can destroy structures and compromise isolation.
- Though largely preventable through electronic alarm and control systems, human error can result in loss of isolation.
- Because they are highly visible, sabotage of structures, with loss of isolation, would be a constant threat.
- Personnel costs per unit of pharmaceutical production would in most cases be higher than if such crops were grown outdoors.
- The use of structures will necessarily limit the scale of production.

BIOLOGICAL CONFINEMENT

1. Chloroplast Engineering (Henry Daniell)

One approach to restricting transgene dispersal via pollen is to place the genes in the DNA of

cellular structures that are not carried by pollen. One such structure is the chloroplast, which is responsible for turning light energy into chemical energy in plant cells. In most flowering plants, chloroplasts are inherited only through the female parent and are not carried in pollen grains.¹⁸ Transgenes inserted into the chloroplast DNA of most crop plants will not be carried by pollen to other plants (Daniell 2002).

Advantages

If chloroplast genetic engineering were developed to the point that it could ensure transgene-free pollen, it would be an elegant way to avoid the dispersal of pharma transgenes to other crops or wild plants. So far, engineering chloroplast DNA to keep transgenes out of pollen has been successfully demonstrated in several crops including tobacco (Daniell, Carmona-Sanchez, and Burns 2004), tomato (Ruf et al. 2001), cotton (Kumar, Dhingra, and Daniell 2004a), and soybean (Dufourmantel et al. 2004).

Although the chloroplast DNA of other crops, such as potato (Sidorov et al. 1999) and carrot (Kumar, Dhingra, and Daniell 2004b), has been engineered, the pollen of these plants has not been tested for the presence or absence of transgenes because of the difficulty in producing flowers under *in vitro* conditions. More than 40 transgenes have been stably integrated into chloroplast DNA to confer desired plant traits or produce pharmaceuticals, edible vaccines, and industrial chemicals (Daniell et al. 2001, 2004; Daniell, Carmona-Sanchez, and Burns 2004; Daniell and Dhingra 2002; Daniell, Khan, and Allison 2001; Devine and Daniell 2004).

In addition to its potential for confining pharma transgenes, chloroplast engineering offers other advantages over the more common nuclear

¹⁸ See Zhang, Liu, and Sodmergen (2003) for a list of plants that inherit chloroplast DNA through the female parent or both parents and Hagemann (2004) for more information on inheritance of non-nuclear DNA.

engineering. For example, restricting transgenes to chloroplasts means that transgene products including drugs and edible vaccines will be concentrated in tissues such as leaves and fruits where chloroplasts predominate (Daniell 2004; Daniell et al. 2004; Daniell, Carmona-Sanchez, and Burns 2004; Kumar, Dhingra, and Daniell 2004b).

It is also possible to engineer multiple genes into chloroplast DNA in a single transformation event (DeCosa et al. 2001) and to use antibiotic-free selectable markers (Daniell et al. 2001b) or eliminate marker genes (Daniell et al. 2004; Daniell, Carmona-Sanchez, and Burns 2004; Devine and Daniell 2004). Chloroplast genetic engineering is also free of the position effects and gene silencing often observed in nuclear engineering, as well as harmful transgene products that cause pleiotropic effects (Daniell et al. 2004; Daniell, Carmona-Sanchez, and Burns 2004; Devine and Daniell 2004; Lee, Byun, and Daniell 2003).

The NRC (2004) summarizes the strengths of chloroplast engineering as follows: chloroplast-specific transgenes would not be spread by the pollen of most cultivated plants, and this approach could prevent transgene dispersal in pollen while preventing some of the disadvantages of male sterility (e.g., a loss of pollen for cross-pollination).

Disadvantages

The disadvantages of chloroplast engineering are: the lack of success so far in moving transgenes into chloroplasts in some major crops, particularly corn and other cereal grains; the difficulty of establishing on a case-by-case basis and with certainty that pollen does not transmit engineered chloroplasts; and its inability to prevent transgene movement via seeds (NRC 2004). While the efficiency of chloroplast engineering is high in some crops, such as tobacco, cotton, soybean, and carrot (Dufourmantel et al. 2004; Kumar, Dhingra, and Daniell 2004a, b), studies are un-

der way in a number of crops, including potato (Sidorov et al. 1999) and tomato (Ruf et al. 2001) to improve efficiency and reliably exclude chloroplast DNA from pollen.

2. Male Sterility (Henry Daniell)

Male-sterile plants do not produce viable pollen capable of fertilizing eggs from the same or another plant. Male sterility occurs naturally in some plants, including corn and soybean (Ding et al. 2002; Sun, Zhao, and Huang 2001; Williams and Levings 1992), but can also be engineered. In conventionally bred crops, cytoplasmic male sterility—sterility controlled by non-nuclear genes—is used extensively to facilitate hybrid seed production. Engineered nuclear male sterility is also used in plant breeding; one example is transgenic herbicide-tolerant oilseed rape (Mariani et al. 1990), which comprises about 10 percent of the commercially cultivated crop in Canada.

Although male sterility was at one time used in commercial corn production, it was abandoned because of susceptibility to southern corn leaf blight. Alternative sources of male sterility genes could be used that do not have negative traits associated with them.

Advantages

Naturally occurring cytoplasmic male sterility already exists, is used in plant breeding, and could presumably be used to eliminate pollen dispersal of transgenes. Theoretically, the ability to engineer male sterility into crops, and therefore prevent pollen dispersal of transgenes, would allow a greater range of plants to be used for pharma production.

Disadvantages

Confinement systems based on male sterility have several disadvantages. First, male-sterile systems may be leaky (i.e., they would not completely eliminate gene dispersal via pollen). For example,

expression of naturally occurring male-sterile genes is known to be affected by weather conditions and the developmental stage of the plant. Leaky systems are sufficient for hybrid seed production but would not meet the virtually zero contamination standard for pharma crops in the food supply.

Second, neither naturally occurring cytoplasmic male sterility nor engineered nuclear male sterility has been developed for use in controlling transgene dispersal in major crops including corn and soybean. Third, while male sterility may be effective in preventing transgene dispersal in many cases, a crop engineered to be male-sterile could still be fertilized by pollen from wild relatives and serve as a female parent for hybrid seed. If such hybrid seed were to survive, germinate, grow, and reproduce, it would produce viable transgenic pollen that could cross-pollinate with weeds.

Fourth, if seed is the desired end product of a transgenic male-sterile crop, cross-pollination with pollen from another source would be required. Finally, like chloroplast engineering, male sterility does not prevent seed dispersal of transgenes nor does it affect seed mixing.

3. Emasculation (Henry Daniell)

Emasculation is the physical removal of male reproductive parts from a plant. As discussed in Chapter 2, corn and soybean have very different reproductive structures. Corn is easily emasculated to control pollen dispersal because male and female flowers are separated on the plant. Male reproductive structures are located in the tassel at the top of the plant, while the female reproductive structures are located in the ear on the side of the plant's main stem. The emasculation, or detasseling, process is accomplished by pulling or cutting the tassel off prior to pollen shedding. This process has been used for decades in the corn seed industry to control pollination

in the production of a hybrid from two different parental lines.

By contrast, soybean has totally enclosed flowers, containing both female and male parts. Emasculation in soybean is a time-consuming operation that is impractical on a commercial scale.

Emasculation might be used in pharma corn production as follows: the pharma gene would be engineered in the female (ear) parent, pollination would occur by a non-pharma corn line, and the female parent would be detasseled (emasculated) to prevent dispersal of pharma pollen to nearby crops.

Advantage

This method can eliminate pollen dispersal to surrounding corn crops if it is implemented effectively.

Disadvantages

Emasculation is not a practical method for soybean and most other crops because the male and female flower parts are too close together to allow easy physical removal of male parts.

In corn, the detasseling process is labor-intensive but used regularly in hybrid seed production. It must also be performed in a timely manner, regardless of weather conditions. Extreme weather, however, can compromise the process, allowing some pollen to escape (for example, if high winds blew through fields before detasseling was completed). Effective implementation would require a contingency plan and integration with other confinement measures such as spatial separation. Finally, emasculation, like chloroplast engineering and male sterility, does not prevent physical mixing or transgene dispersal via seeds.

4. Seed Sterility (Henry Daniell and Paul Gepts)

Seed sterility is a genetically engineered trait that leads to seeds that are formed normally on

the plant but are incapable of germinating. Used as a confinement option for pharma crops, seed sterility would aim to reduce seed dispersal of pharma transgenes.

Several seed sterility systems—variously called technology protection systems, gene use restriction technology, and “terminator” technology—have been proposed (Koivu, Kanerva, and Pehu 2001; Odell, Hoopes, and Vermerris 1994; Russell, Hoopes, and Odell 1992; Scherthaner et al. 2003; Tomes 1996). So far, however, the approach has been successful only in tobacco.

The lack of success reflects the fact that genetically engineered seed sterility systems are complex. For example, the mechanism proposed originally by Russell, Hoopes, and Odell (1992) and Odell, Hoopes, and Vermerris (1994) consists of a three-transgene system. This system is triggered by a specific external stimulus such as the antibiotic tetracycline, which initiates interactions between two transgenes—interactions that ultimately unblock the third transgene. The third transgene codes for a toxin that kills seeds at a late stage in their development. As long as the third transgene is blocked, no toxin is produced. Once it is activated, however, it produces the toxin to prevent an otherwise fully developed seed from germinating.

Advantage

A seed sterility mechanism successfully engineered into a pharma crop would, theoretically, substantially reduce dispersal of pharma transgenes via seeds.

Disadvantages

Seed sterility mechanisms have several disadvantages. As discussed above, they are complex and technically difficult to introduce into plants. In addition, the sterility trait may not function consistently. Two causes for failure might be the

inactivation of one or more transgenes or the separation of one transgene from the other two.

Seed sterility systems are also not ready for use in pharma crop production—none of the proposed mechanisms have been successfully introduced into crops other than tobacco. Finally, this technology raises political, social, and ethical issues (Lambrecht 2001). For example, “terminator” technology is generally considered unacceptable in areas where farmers save seeds for planting in subsequent growing seasons, as is the case in many developing countries (Cleveland and Soleri 2002; Zimmerer 1996).

Public access to data on the efficacy of transgenic reversible sterility will be essential. The technology should not be used in food crops for which growers need to save seeds for future planting or breeding (NRC 2004). Possible environmental concerns should be evaluated on a case-by-case basis. This technology will not prevent clonal propagation of many plants, such as some species of grasses, shrubs, and trees (NRC 2004).

5. Cleistogamy and Apomixis

(Henry Daniell and Paul Gepts)

Cleistogamy is a process by which self-pollination and fertilization occur within closed flowers. It has been suggested that crops engineered to exhibit cleistogamy could not disperse transgenes via pollen.

Another option would be to engineer crops that produce seeds without fertilization. This process, termed apomixis, occurs naturally in a small percentage of flowering plants. In apomictic plants, the embryo within the seed is not a product of sexual reproduction. Rather, it originates entirely from female flower parts.

There are two types of apomictic plants. In one, the seed tissue feeding the embryo and new seedling results from fertilization with pollen. If genetically engineered apomictic crops resembled

these plants, then apomixis would not alleviate the pollen dispersal concern as pollen is an integral part of the process. The second type of apomictic plants develops seed tissues without fertilization. If crops were genetically engineered to mimic these plants, apomixis could theoretically block pollen dispersal.

Although more than 400 apomictic plant species are known, apomixis is rare among crops and transfer of apomixis to crops by conventional breeding has been largely unsuccessful. Several methods for genetically engineering apomixis in crops have been proposed recently (Spillane, Curtis, and Grossniklaus 2004).

Advantages

Cleistogamy, if successfully engineered into pharma crops, may be an effective barrier to pollen dispersal of transgenes. Engineering apomixis into crops would be advantageous in reducing pollen dispersal of transgenes if fertilization were not required for seed production.

Disadvantages

Cleistogamy would appear to have limited efficacy, as it depends partially on uncontrollable and unpredictable environmental conditions. For example, in rice that exhibits cleistogamy, genes readily move between cultivated and wild forms of weedy rice, despite predominant self-pollination. Under cooler conditions (less than 20°C), soybean flowers remain closed and cleistogamy occurs. When temperatures rise above this threshold, flowers on the same plant open and fertilization occurs in an open flower. Thus, this option would not reduce pollen flow to virtually zero levels and does not reduce physical mixing.

To date, very little work has focused on this approach and knowledge of genes responsible for flower development remains rudimentary. Any application is a long way off. In addition, trans-

gene escape by seed or vegetative reproduction could still occur for plants with obligate cleistogamy (NRC 2004).

Engineering apomixis into crop plants may theoretically prevent pollen dispersal, but it would be effective only if pollen is not needed for seed development. Apomixis is known to occur only in a few cultivated plants and, thus far, the trait has not been introduced into any transgenic crops, including corn and soybean. Studies of naturally occurring apomixis suggest this method could be leaky. Given that even obligate apomicts still produce seeds, the method cannot be used for confinement if the goal is to prevent dispersal by seed. Also, it will be important to confirm that apomictic transgenic crops cannot establish invasive populations (NRC 2004).

DISALLOWING FOOD/FEED CROPS

(Paul Gepts)

Under this option, pharma genes could be engineered only into crops that are not used for food or feed. This option precludes both corn and soybean.

In the United States, corn and soybean are major feed crops and to a lesser extent food crops. (In other regions of the world, corn is principally a food crop.) The fact that corn and soybean are food and feed crops is the basis of concerns about pharma transgene dispersal by both pollen and seeds and physical mixing of pharma and food/feed seeds. A choice of non-food/feed crops would alleviate to a considerable extent those concerns and greatly facilitate the segregation of pharma and non-pharma crops.

Other crops besides corn and soybean being tested as pharma crops include alfalfa, canola, potato, rice, safflower, and tobacco. All of these crops are ingested in some way, and with the exception of tobacco, all are either food or feed crops.

Advantages

Use of non-food/feed pharma crops would completely block pollen dispersal and significantly reduce, but not eliminate, the risk of contamination by physical mixing into the food/feed system. For example, pharma seeds produced on stray (volunteer) plants that germinate and grow from pharma seeds left behind after the cultivation of the pharma crop may contaminate food or feed crops growing in that same field the next year.

This option can be scaled up once the expression of pharma traits and agronomic procedures for non-food/feed crops have been worked out. This approach would be more easily enforced and monitored than those using a food/feed plant to produce pharma products.

Disadvantages

Except for tobacco, this option is not ready to implement. Restricting pharma crop production to non-food/feed crops would halt work on most, if not all, products currently under commercial development and would mean a loss to companies that have invested in food and feed crops.

This approach requires identifying and developing suitable alternative plants, preferably crops, and implementing a breeding program to produce suitable varieties. Special field equipment to cultivate these crops may not be available or may need to be adapted from other crops.

MANAGEMENT SYSTEMS (Dennis Strayer)

While the options above are discussed separately and somewhat in isolation, we understand that the management of pharma corn and soybean must be considered in an overall management context. We strongly believe that the adoption of a comprehensive, structured management system focused on the potential pharma crop contamination of the food/feed system should be considered. Such management systems could either be

adapted from identity preservation systems currently used in the seed and specialty crops industries or be designed from the ground up to prevent pharma crop contamination.

1. Identity Preservation Management Systems

Identity preservation (IP) is a process or system of documenting the identity of a product and maintaining its segregation (Strayer 2002). An IP product has identifiable characteristics that have been maintained from the seed through all the steps of production and transportation to the end user.

This strict production and delivery method uses the procedures of an effective internal segregation system, including observations, inspections, sampling, and testing, to ensure the presence (or absence) of certain traits. IP systems encompass activities and procedures as well as infrastructure, equipment, and technologies. Growers must follow strict growing and handling practices, including segregation, inspections, and cleaning of equipment to prevent other varieties from mixing with or contaminating the IP variety. Other parties that handle, transport, condition, or process the IP product must also maintain and document a similar segregation system.

The key to an IP system is traceability. Each production, processing, and delivery step is documented so products can be traced from the store shelf back to the farmers' fields and every stage in between. IP must include a system of verified steps following the crop through the entire production and delivery system. Testing crop samples as a stand-alone procedure does *not* qualify as an IP system.

Advantages

IP systems are established management systems used in the seed and specialty crop industries

to maintain genetic purity of the product being produced. The companies and growers using these systems are well acquainted with the procedures and technologies required to maintain genetic purity within the crops being produced.

Disadvantages

IP systems have not yet been adapted to eliminate contamination of other crops and would need to be modified to be applied as a virtually zero contamination system. However, IP systems could easily incorporate confinement management procedures to eliminate or reduce potential contamination of crops or related wild species by pollen flow or physical mixing during growing and handling.

Even if modified to include effective confinement procedures, IP systems would still need to be used in conjunction with other confinement options to provide virtually zero contamination of food and feed crops. Most IP systems used in the seed and specialty crop industries tolerate some level of contamination depending on the requirements for a specific product.

2. Confinement Management Systems

These systems are not yet defined, but the following concept is in the early stages of development: forcing operators to document what processes are being used and how they are being conducted, then proving through records and audits that the processes, however described, are consistent.

This system would not itself require specific or high-quality standards, but would incorporate several strategies for minimizing any harmful effects on the environment or other plant materials caused by an organization's activities. Most

importantly, the system would address the way an organization goes about its work—not the result of this work. In other words, it is concerned with processes and not products, at least not directly.

Confinement management system standards would include requirements for a given organization to follow in managing those processes that have an impact on the environment or other products. For example, contamination of the food/feed supply by pharma products from either pollen dispersal or physical mixing could potentially occur during pharma crop production because of human error or lack of planning. Hence, a formalized confinement management system would address this possibility for all parties involved, including plant breeders, seed multiplication entities, seed companies, and pharma crop producers, handlers, and users.

The confinement management system envisioned would be structured similar to an ISO 9001:2000 quality management system or an ISO 14001:1996 environmental management system.¹⁹ It is possible that a confinement management system could be developed from or included as part of either of these systems. Whether such a system is completely new or part of an established system, a third party would be involved in approving and overseeing the compliance of pharma crop business entities.

Advantages

Requiring all parties to adhere to a formal confinement management system would tend to unify the management of pharma crops. The new system would include any government-mandated requirements in addition to its own structured confinement plans and would involve a third

19 An ISO system is a set of quality standards developed by the International Organization for Standardization (ISO) and is a model that is not specific to any product, service, or market but to the quality process itself. See <http://www.iso.org>. For more information on ISO 9001:2000 Quality Management Systems and ISO 14001:1996 Environmental Management Systems, see http://webstore.ansi.org/ansidocstore/dept.asp?dept_id=190 and http://webstore.ansi.org/ansidocstore/dept.asp?dept_id=230, respectively.

party outside the U.S. Department of Agriculture or the Food and Drug Administration. The uniformity provided by this system might be beneficial to those agencies in their assessments of pharma crop activities.

Disadvantages

Formal management systems such as the ISO systems require a large commitment of time and dedication by management and employees to develop and implement. They are not “off-the-shelf” systems; rather, they must be developed internally by the business entity, specific to its production processes and requirements. Developing a confinement management system as part of an already implemented quality or environmental management system would facilitate and shorten the process.

3. Industry-wide Marking Systems

Industry-wide adoption of a color scheme would facilitate the management of pharma crops. For example, bright pink might be designated as the marking color for pharma crop production systems exclusively, and would not be allowed in other agricultural uses. All planting seed could be delivered in bright pink bags or containers, and all dedicated equipment and facilities could be marked with bright pink paint at designated positions on the equipment. An equipment/facility

inventory control system would track this equipment so it could not be used for other purposes without authorized “decontamination.” Only after decontamination could the color marking be removed from this equipment.

This marking system could be extended to the pharma crops themselves. For example, a gene coding for a distinct color or morphological trait could be incorporated into the pharma varieties to clearly distinguish them from non-pharma varieties. Decisions of this type should be made by representatives of the seed and pharma crop industries, production agriculture, third-party consultants, and regulatory agencies, and should not be dictated only by government bodies.

CONCLUSION

Any single confinement method is unlikely to prevent the spread of pharma genes. Instead, a combination of these methods needs to be used in a well-integrated fashion with an acceptable management system that ensures tightly controlled supervision, traceability, and accountability.

At this time, confinement is not feasible for corn, soybean, or other crops, and total segregation of the seeds from commodity crops will be expensive and challenging. Further research in the various confinement methods, especially the biological ones, is needed to allow their application in pharma crop production.

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Chapter 4

SEED PRODUCTION IN CORN AND SOYBEAN

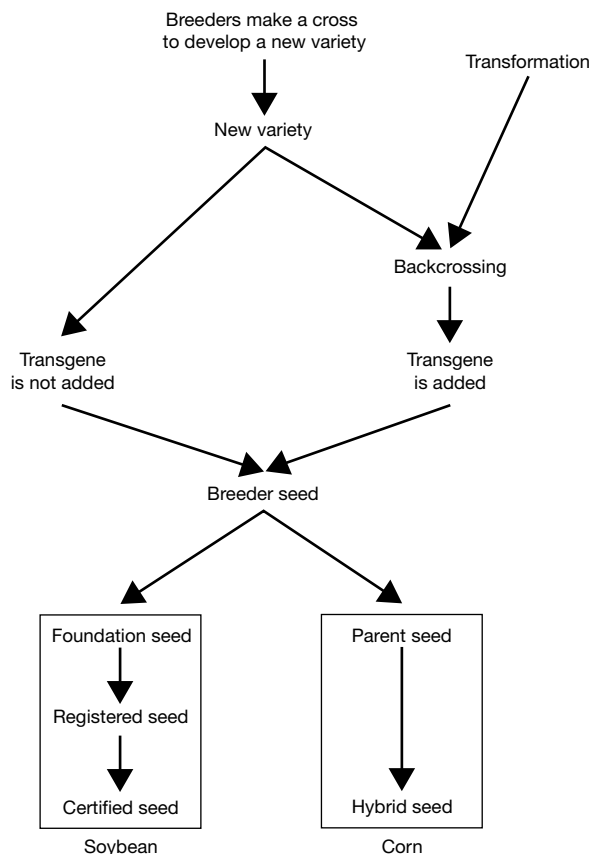
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Seed production is one of the least visible yet most important aspects of food and feed production. This part of the system is often taken for granted, even by the farmers who plant the seed. One of the reasons is that much of the seed in the United States is provided by the private sector, particularly for corn and soybean. Also, seed production is a technical process that requires in-depth knowledge of the reproductive mechanisms in plants.

For the purposes of this chapter, seed production has been defined broadly as the series of steps that begins with the breeding of a new variety and ends with seed that is sold to farmers (Figure 4-1). The seed production process is usually conducted by three or four specialized departments in a seed company. Plant breeders develop varieties²⁰ and produce breeder seed—the source seed from which all varieties are propagated.

Some companies now have separate departments that do all breeder seed production. In the case of corn, breeders will also be responsible for adding male sterility if needed. Parent or foundation seed production is usually done by a separate department. The production of hybrid or certified seed—the seed that will be sold to farmers—is done by yet another department.

Seed producers have many goals, but this chapter focuses on a detailed description and analysis of the steps depicted in Figure 4-1 with regard to maintaining genetic purity. Genetic

Figure 4-1 **The Seed Production Process**

purity is important because gardeners and farmers expect varieties with the same names to be identical from one year to the next.

We are concerned with two sources of contamination: impurity resulting from physical mixing of seed and impurity resulting from the movement of pollen. The seed production process is described in sufficient detail to identify points

²⁰ A variety is a subgroup of plants within a species whose genetic makeup and characteristics distinguish it from other varieties of the species. Crop varieties are often called cultivars, especially by agricultural scientists.

where such contamination may occur. The goal is to determine if seed of pharma crops can be produced in a way that ensures virtually zero contamination of the food system.

This chapter also makes recommendations for achieving virtually zero contamination of the food system by pharma crops.

PRODUCING COMMODITY SEED TO BE GROWN BY FARMERS

Seed production practices for corn and soybean have evolved to provide farmers with genetically pure varieties. The Association of Official Seed Certifying Agencies (AOSCA) has developed and published genetic purity standards, and many seed companies have developed best management practices for maintaining acceptable levels of genetic purity.²¹ The standards, however, do not specify or guarantee 100 percent genetic purity. It is assumed that most hybrids and varieties on the market contain some low level of contamination.

AOSCA consists of 44 state certification agencies in the United States and seven national agencies. Among other things, AOSCA is responsible for setting and monitoring genetic purity standards for the various classes of certified seed. AOSCA standards are at least partly responsible for the high seed quality that U.S. farmers have come to expect from seed suppliers.

Four classes of seed are officially recognized in the United States: breeder, foundation, registered, and certified. A brief description of each, as taken from the AOSCA genetic and crop standards handbook, follows. Understanding these classes is important to understanding the U.S. seed production system.

1. **Breeder seed** is seed directly controlled by the originator or sponsoring plant-breeding institution or person. This is the class of seed from which all other classes of seed are derived.
2. **Foundation seed** is developed from breeder or foundation seed produced under control of the originator or sponsoring plant-breeding institution or person. Foundation seed is a class of certified seed produced under procedures established by the certifying agency.
3. **Registered seed** is developed from breeder or foundation seed and is produced and handled under procedures acceptable to the certifying agency.
4. **Certified seed** is developed from breeder, foundation, or registered seed and is produced and handled under procedures acceptable to the certifying agency.

Not all classes of seed are used in all crops, and it should be noted that the United States has no laws or regulations requiring that only certified seed be sold to farmers. Certification of seed production is optional for seed sold in this country but is usually required for seed sold in other parts of the world, especially Europe. The requirements for each class of certified seed vary from crop to crop.

The AOSCA certification requirements for corn and soybeans are reproduced in Table 4-1 (p. 56). These are minimum standards and apply only to those segments of the flow chart in Figure 4-1 that are enclosed in boxes.

²¹ The Genetic and Crop Standards of AOSCA manual can be downloaded from the AOSCA website (<ftp://www.aosca.org/geneticstandards.pdf>), as can the Operational Procedures of AOSCA manual (<ftp://www.aosca.org/operationalprocedures.pdf>). These manuals outline the procedures that must be followed by the state and national agencies that certify seed.

Table 4-1 **Minimum Standards for Certification of Plant Materials under the AOSCA System**¹

Crop kind	Foundation				Registered				Certified			
	Land ²	Isolation ³	Field ⁴	Seed ⁵	Land ²	Isolation ³	Field ⁴	Seed ⁵	Land ²	Isolation ³	Field ⁴	Seed ⁵
Corn												
Inbred lines	0	660 ^{6,7}	1,000 ^{8,9}	0.1 ¹⁰								
Foundation												
Single-cross	0	660 ^{6,7}	1,000 ^{8,9}	0.1 ¹⁰								
Backcross	0	660 ^{6,7}	1,000 ^{8,9}	0.1 ¹⁰								
Hybrid									0	660 ^{7,11}	1,000	0.5
Open-pollinated									0	660 ^{7,11}	200	0.5
Sweet									0	660 ^{7,12}	---	0.5
Soybean	1 ¹³	0 ¹⁴	1,000	0.1	1 ¹³	0 ¹⁴	500	0.2	1 ¹³	0 ¹⁴	200	0.5

- 1 Extracted and reformatted from the Genetics and Crop Standards of AOSCA manual (<http://www.aosca.org/geneticstandards.pdf>).
- 2 Number of years that must elapse between the planting of different classes of seed. A certification agency may grant a variance in land cropping history in specific circumstances where cultural practices have proven adequate to maintain varietal purity.
- 3 Distance in feet from any contaminating source.
- 4 Minimum number of plants or heads in which one plant or head of another variety or off-type is permitted.
- 5 Maximum percentage of seed of other varieties or off-types permitted.
- 6 No isolation is required for the production of hand-pollinated seed.
- 7 When the contaminant is of the same color and texture, the isolation distance may be modified by adequate natural barriers or differential maturity dates, provided there are no receptive silks in the seed parent at the time the contaminant is shedding pollen. In addition, dent sterile popcorn requires no isolation from dent corn.
- 8 Refers to off-type plants in the pollen parent that have shed pollen, or to the off-type plants in the seed parent at the time of the last inspection.
- 9 Detasseling, cutting, or pulling of cytoplasmic male-sterile seed parent is permitted.
- 10 Refers to off-type ears. Ears with off-colored or different-textured kernels are limited to 0.5% or a total of 25 off-colored seeds or different-textured kernels per 1,000 ears.
- 11 Where the contaminating source is corn of the same color and texture as that of the field-inspected or white endosperm corn, optically sorted, the isolation distance is 410 feet and may be modified by the planting of pollen parent border rows according to the table below:

Minimum distance from contaminant (feet)	Minimum number of border rows required	
	Field size up to 20 acres	Field size 20 acres or more
410	0	0
370	2	1
330	4	2
290	6	3
245	8	4
205	10	5
165	12	6
125	14	7
85	16	8
0	Not permitted	10

- 12 The required minimum isolation distance for sweet corn is 660 feet from the contaminating source, plus 4 border rows when the field to be inspected is 10 acres or fewer in size. This distance may be decreased by 15 feet for each increment of 4 acres in the size of the field to a maximum of 40 acres, and further decreased 40 feet for each additional border row to a maximum of 16 rows. These border rows are for pollen-shedding purposes only.
- 13 Unless the preceding crop was another kind, or unless the preceding soybean crop was planted with a class of certified seed of the same variety, or unless the preceding soybean crop and the variety being planted have an identifiable character difference (in which case, no time need elapse).
- 14 Distance adequate to prevent mechanical mixture is necessary.

Variety Types

The type of variety grown in a crop is determined primarily by the crop’s mode of reproduction (self-pollinated in soybean versus cross-pollinated in corn). These are the major determinants of the steps involved in seed production. Seed production in corn is more complex than in soybean.

Corn

Of the many possible variety types, we will restrict ourselves to three: inbred lines, open-pollinated varieties (OPVs), and single-cross hybrids. An inbred (or pure) line is a strain that breeds true to type when individual plants of the strain pollinate themselves (self-pollination). An inbred line can be developed from repeated generations of self-pollination or from repeated generations of crossing to a common parent (backcrossing).

An OPV can be a landrace²² developed by farmers, landraces improved by breeders or farmers, or synthetics created by crossing landraces, synthetics, or inbred lines together. OPVs are genetically heterogeneous and are maintained by allowing individual plants to cross-pollinate in isolation. A single-cross hybrid is the first generation cross between two inbred lines.

22 A landrace is a variety developed and maintained locally by farmers.

OPVs were the dominant variety type in the United States before the introduction of hybrids in the mid-1930s. OPVs were gradually replaced by hybrids, and single-cross hybrids now account for at least 99 percent of the hybrid seed sold in this country (Wych 1988). OPVs are no longer grown on large acreages, but when they are, seed production is usually done on the farm by the farmer.

Soybean

The most popular variety type grown by farmers in soybean is a pure line. Pure lines of soybean are equivalent to inbred lines of corn. Soybean is predominantly self-pollinated, so inbred lines of soybean can be maintained by just planting and harvesting them. Seed mixtures (blends) of two or more soybean varieties are also a possible variety type (Fehr 1987). Hybrids have been proposed and have been evaluated extensively in soybean (Burton 1987), but they are not widely used by farmers because of the difficulty and expense in producing hybrid seed (Palmer et al. 2001).

Variety Development, Transformation, and Backcrossing

The variety development process in corn and soybean will not be described in detail because the conversion to a transgenic and/or pharma crop usually occurs after a new variety has been developed (though there are some exceptions in soybean that will be discussed). Since transgenic varieties are not usually crossed together to initiate the breeding process, there is a virtually zero chance of a pharma crop contaminating the food system during the breeding phase as outlined in Figure 4-1 (p. 54). We are therefore assuming that transgenes

producing pharma crop traits will be backcrossed into existing varieties and not used in the breeding process when developing new varieties.

Transformation consists of three main phases: introducing the gene into plant cells; regeneration, the process by which a plant develops from the cells into which the gene was introduced; and maturation, the process of inducing the regenerated plants to produce seed.²³ Backcrossing is the breeding procedure used to move the transgene from the regenerated plants into other more desirable plants. The maturation phase of transformation and backcrossing is of primary concern for contamination.

Corn

Before the seed of a commercial single-cross hybrid can be produced, the inbred lines used to produce the hybrid must be developed. The methodology for developing inbred lines varies widely from breeder to breeder and from company to company. Hallauer (1990) has outlined a standard inbred line and hybrid development program. During the entire developmental phase, controlled pollinations are made either by hand or by wind in isolated crossing blocks similar to what is done in commercial seed production fields. The final products are inbred lines that can be used to produce a commercial hybrid.

The first step in generating a transgenic plant is to introduce a transgene into plant cells and have it become integrated into a cell's DNA. This is most commonly done in corn using a procedure called particle bombardment. Once cells contain the transgene, a plant is regenerated from the cells in cell culture. Regenerated plants are transplanted to a greenhouse so that when they flower, they can either be self-pollinated or crossed to

23 Personal communication with Kan Wang, director, Center for Plant Transformation, Iowa State University, 2003.

another plant. (It is common to do both when possible.)

The most difficult step in transformation is regenerating plants from cell culture. Because not all varieties can be used for this purpose, cell culture is said to be genotype-dependent (Armstrong et al. 1991; Armstrong 1994). Most corn transformation labs use the same basic genetic material for plant regeneration (Armstrong 1994). This germplasm²⁴ from which plants are regenerated is not commercially viable, so a backcrossing procedure is initiated immediately after plant regeneration to move transgenes of interest into commercially viable inbred lines.

After plants containing transgenes (transformed plants) have been regenerated from tissue culture, molecular screens are conducted to identify individuals that carry only one or two copies of the transgene. Individual plant(s) meeting these criteria will usually be both self-pollinated and crossed to an elite line. These plants will be evaluated to determine if the transgene is inherited genetically and to verify that the transgene is producing the protein it was designed to produce.

Regenerated plants are self-pollinated, backcrossed to an elite inbred line, and crossed to a hybrid. The purpose of self-pollination is to obtain additional seed of the original plant that contains the transgene; the purpose of the backcross is to transfer the transgene into an elite inbred line. The subsequent cross to the hybrid enables the production of enough grain to begin preliminary protein extraction (in the case of pharma crops). All of these crosses occur in the greenhouse; all crosses in subsequent generations are made in the field.

The geographic area where these crosses are made is important. Breeding and backcrossing nurseries may be conducted on land rented or leased from farmers or on land owned by companies or universities. Some companies conduct their field breeding with experimental transgenes in dedicated off-season nurseries in other parts of the world. The use of such nurseries makes it easier to obtain isolation from other crops and minimizes the probability of transgenes entering non-transgenic products outside the nursery.²⁵

Backcrossing is a breeding scheme designed to move single transgenes from one inbred line into another inbred line (Figure 4-2). The inbred line that the transgene will be transferred to is called the recipient. The recipient is typically an elite inbred already used in commercial hybrids. The inbred line or plant donating the transgene is called the donor.

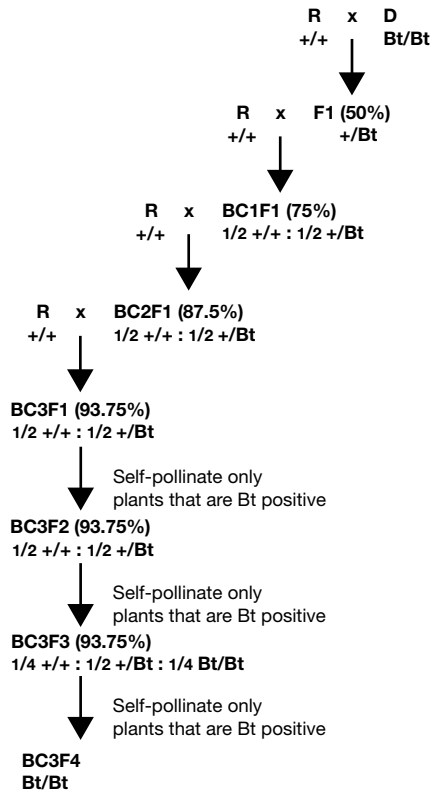
The goal of backcrossing is to transfer the gene of interest from the donor into the recipient without otherwise genetically changing the recipient. Backcrossing starts by making a cross between the recipient and donor. The progeny produced from this and later generations are repeatedly crossed with the recipient inbred line. With each generation of backcrossing, the amount of donor genome remaining is reduced by about one half. Each round is called a backcross.

The number of backcrosses used varies from two to seven with an average of about five. Because the recipient inbred line is already used to produce commercial hybrids in corn, there is typically no field testing for performance until the desired number of backcrosses has been completed. The decision to conduct field tests for performance

24 In general terms, germplasm refers to the genetic material that is the physical basis of heredity and is passed from one generation to the next. When applied to plants, germplasm refers to the seed or other structures by which plants are propagated.

25 The use of off-season nurseries varies from company to company and university to university. A cursory look at U.S. Department of Agriculture field testing permits for transgenic crops suggests that experimental events of corn are frequently grown in off-season nurseries, while soybean is grown in both off-season and summer season nurseries (ISB 2004).

Figure 4-2 **A Typical Backcrossing Scheme in Plants**



In this example, a gene called Bt is being backcrossed from a donor inbred (D) into a recipient inbred line (R). The genetic contribution of each generation is listed under the generation. The +/+ genotype is wildtype and the Bt/Bt genotype is homozygous for Bt. BC followed by a number is the backcross generation number. F followed by a number is the filial generation. For example, BC1F1 is the first backcross generation and the first generation cross. BC3F2 means the backcross 3F1 has been selfed once.

during the backcrossing procedure will depend on the amount of prior experience with the particular transgenic event.

After backcrossing is completed, the newly developed transgenic inbred line is crossed with another inbred to produce a hybrid for evaluation. The numbers of locations, replications per location, and years used for testing vary depend-

ing on prior knowledge of performance of the converted inbred, the quality of the conversion, and known problems with modifier genes associated with backcrossing a particular event.

Because a commercial hybrid receives extensive testing prior to commercialization, it is not necessary to re-prove the performance of the hybrid. Following backcrossing of a transgene it is necessary to demonstrate that the backcrossing process itself did not disrupt the performance of the hybrid. Breeders are most interested in the comparison of the transgenic hybrid with its non-transgenic counterpart.

The amount of testing required to do this will depend on the protocols in place at specific companies and the amount of risk they are willing to take. The time lag between the development of a new inbred line and its sale to farmers as a transgenic hybrid is three to four years, depending on how long it takes to backcross the transgene, to obtain adequate quantities of parent seed, and to produce the hybrid. Typical testing of a transgenic hybrid following backcrossing would involve 25 to 40 locations and one to three replications per location. The yield of pharma corn will not be such a major concern and less testing will need to be done.

Comparison of a transgenic hybrid with its non-transgenic counterpart would continue until a decision was made to either drop the hybrid or use it commercially. If the hybrid will be used commercially, up to three years of data would likely be obtained on the hybrid before it is actually planted by farmers.²⁶

The backcrossing procedure is conducted by making hand pollinations. If the transgene of interest (such as Roundup Ready™) has been approved (that is, allowed on the market by the federal government), the necessary crosses are

²⁶ The information and procedures in this paragraph are based on the author's conversations with private breeders who conduct backcrossing programs. What is done at a specific company may vary considerably from what has been described.

conducted in the field in summer or winter breeding nurseries (such as Hawaii or Puerto Rico) used by the companies. Most companies have extensive protocols in place to keep approved transgenes from entering their non-transgenic breeding germplasm. Corn breeders at most breeding companies are required to use separate nurseries for GMO (genetically modified organism) and non-GMO breeding activities. The author is unaware of any public sector corn breeding programs that use inbred lines containing approved transgenes to develop new breeding populations.

If the transgene is experimental and has not been approved, different procedures are used. Public sector scientists will conduct as much of the backcrossing as possible in the greenhouse, but it is also frequently done in the field using protocols developed by government regulators. Private sector scientists will usually do all of the backcrossing with experimental transgenes in a winter nursery. There are two advantages to this strategy: many winter nursery locations are tropical, enabling two or three breeding generations to be obtained in a year; and in many of these locations, such as Hawaii, it is easy to obtain long-distance (greater than one mile) isolation from other corn.²⁷

Breeder seed of both transgenic and non-transgenic inbreds is established and maintained by the originating breeder or breeding company by hand pollinations. Breeder seed of non-transgenic inbreds and inbreds that contain approved transgenes is maintained in summer or winter breeding nurseries as needed. It is the breeder's responsibility to ensure that the inbred is homozygous²⁸ for

the desired transgene, has uniform plant type, and adequately represents the genetic constitution of the inbred (Wych 1988).

This description of corn variety development, transformation, and backcrossing is a generic description. There are numerous major and minor variations in the execution of all three activities.

Soybean

Several breeding procedures are used to develop soybean varieties. Fehr (1987) lists five commonly used methods. The methods all involve self-pollination in every generation following the development of a breeding population. They differ primarily in the number of generations of self-pollination that are conducted before the lines are tested in replicated trials for their potential as new varieties. Single-seed descent is the most popular method of soybean variety development (Fehr 1987). Soybean is naturally self-fertilizing and hand pollinations are only used to produce hybrids for developing breeding populations.

The variety development phase for soybean, like corn, is not a source of contamination of the food supply by pharma crops. As in corn, the experimental transgenes and transgenes used in pharma crops are introduced into established varieties. Developing breeding populations that contain experimental or pharma crop transgenes would be too risky and difficult to control.

The transformation phase for soybean is similar to that used in corn except that a different protocol may be used to introduce the transgene.²⁹ If

27 The information in this paragraph was gleaned from informal conversations with commercial plant breeders and cannot be attributed to any single company. The author's impression is that most multinational seed companies practice good stewardship and do everything possible to minimize the escape of an experimental transgene into the food supply. There are many ways this could be accomplished, but restricting breeding activities for experimental transgenes to one location helps minimize the probability of escape.

28 Homozygous means that all sex cells of the inbred carry the transgene.

29 For more information on plant transformation, see the Iowa State University Plant Transformation Center website (<http://www.agron.iastate.edu/ptf/web/mainframe.htm>).

backcrossing is used to move the transgene into soybean inbred lines, the backcrossing procedure used would be nearly identical to that described above for corn (Figure 4-2, p. 59).

Commercial soybean breeders use a procedure called forward breeding to incorporate transgenes (usually herbicide tolerance) into new varieties. This basically involves initiating new breeding crosses with inbred line(s) that already contain the transgene. If both inbred lines contain the transgene, all progeny resulting from the cross will carry it. If only one inbred carries the transgene, then only some progeny will carry it, and the breeders will have to select for the trait to keep it in plants that are self-pollinated. For herbicide resistance, selection is easy. The breeder sprays the soybean with the herbicide and keeps those that survive.

There are three reasons why soybean breeders take this approach: 1) backcrossing is difficult in soybean because soybean is generally difficult to cross and backcrossing involves repeated rounds of hand crossing; 2) there is no time lag between the development of a superior variety and converting it to herbicide resistance; and 3) Roundup Ready™ soybean has been widely accepted and grown by farmers. No transgene has achieved such a wide acceptance in corn.

Since forward breeding is used primarily to incorporate herbicide tolerance into new soybean varieties, these breeding activities take place at standard soybean breeding facilities. Experimental transgenes are also often field tested in standard soybean production areas, judging by applications to the U.S. Department of Agriculture for field test releases (ISB 2004).³⁰ Many of these tests are conducted in Hawaii and Puerto Rico, but a number are also conducted in states where soybean is commonly grown.

Breeder seed is produced and maintained in a manner similar to that in corn. The primary differ-

ence is that in soybean, controlled pollinations are not used to produce seed. Fehr (1987) gives an excellent description of the production of breeder seed. Breeder seed is produced by planting the soybean inbred line in the field and allowing it to self-pollinate. Off-type plants, that is, plants that have different physical characteristics from the majority of the plants in the inbred line, are removed when they are identified.

Foundation Seed Production

Foundation seed increase is the next step in the process of developing a new variety (Figure 4-1, p. 54). Foundation seed production is also called parent seed production in corn because the foundation seeds of inbred lines of corn are used as parents to produce the hybrid corn seed sold to farmers.

Cytoplasmic male sterility (CMS) is a sterility mechanism frequently used in corn to reduce or eliminate the need to emasculate corn plants (remove the male part, or tassel) in the production of hybrid seed. Because CMS complicates the production of foundation seed, this section discusses male-fertile female parents and male-sterile female parents separately.

Corn

Male-fertile parents. Large quantities of seed are required of each inbred line (the male and female parents of the hybrid) to produce enough seed for sale to farmers (Table 4-2, p. 62). This phase of seed production is usually referred to as foundation seed production. Although procedures vary from company to company, Wych (1988) outlined the typical steps, the two most important of which for our purposes are establishing and maintaining a supply of breeder seed and producing foundation inbred seed.

³⁰ Field testing must follow protocols established by the U.S. Department of Agriculture and other regulatory agencies that oversee field trials of transgenic plants.

Table 4-2 Quantities of Production Required for Hybrid Corn Seed Production

Hybrid			Female Inbred Parent			Male Inbred Parent		
Final Hybrid Acreage	Units of Hybrid Seed Required ¹	Acres of Hybrid Seed Production ²	Number of Kernels of Foundation Female Seed Required ³	Acres of Female Parent Seed Production Needed ⁴	Number of Selfed Plants If Seed Is Produced by Hand ⁵	Number of Kernels of Foundation Male Seed Required ³	Acres of Male Parent Seed Production Needed ⁴	Number of Selfed Plants If Seed Is Produced by Hand ⁵
50	16	0.3	6,760	0.0017	27	1,690	0.0004	7
100	33	0.7	13,520	0.0034	54	3,380	0.0008	14
500	163	3.3	67,600	0.0169	270	16,900	0.0042	68
1,000	325	6.5	135,200	0.0338	541	33,800	0.0085	135
2,000	650	13.0	270,400	0.0676	1,082	67,600	0.0169	270
3,000	975	19.5	405,600	0.1014	1,622	101,400	0.0254	406
5,000	1,625	32.5	676,000	0.1690	2,704	169,000	0.0423	676
10,000	3,250	65.0	1,352,000	0.3380	5,408	338,000	0.0845	1,352
75,000,000	24,375,000	487,500.0	10,140,000,000	2,535.0000	40,560,000	2,535,000,000	633.7500	10,140,000

- 1 A commercial unit of hybrid seeds is assumed to contain 80,000 kernels and will plant approximately 3.1 acres, assuming a planting rate of 26,000 plants per acre.
- 2 The acres of hybrid seed production that need to be planted to produce a given quantity of hybrid seed, assuming the female yields 50 units of hybrid seed per acre of total production (including the acreage occupied by the males). The author assumed a planting ratio of 4 female to 1 male.
- 3 Number of kernels of foundation female or male seed required to plant the hybrid production field was calculated assuming a hybrid seed field planted in a ratio of 4 females to 1 male, and that the male and female parents were planted in the hybrid production field at the rate of 26,000 plants per acre.
- 4 Acres of female and male production required to produce a given number of kernels was calculated assuming the male and female parents yield 50 units of seed per acre and that each unit contains 80,000 kernels.
- 5 The number of plants selfed if seed is produced by hand, assuming that 250 kernels are produced with each self-pollination.

Foundation inbred seed production fields are planted with the initial supply of breeder seed. The foundation inbred seed increases are produced in isolation (via wind pollination) where the inbred line is allowed to sib-mate³¹ or open-pollinate. Since all plants in the inbred line are theoretically identical, sib-mating or open pollination is equivalent to self-pollination. This initial inbred increase produces the first crop of foundation seed, which is then used to plant subsequent inbred increases and produce larger quantities of foundation seed for hybrid seed production.

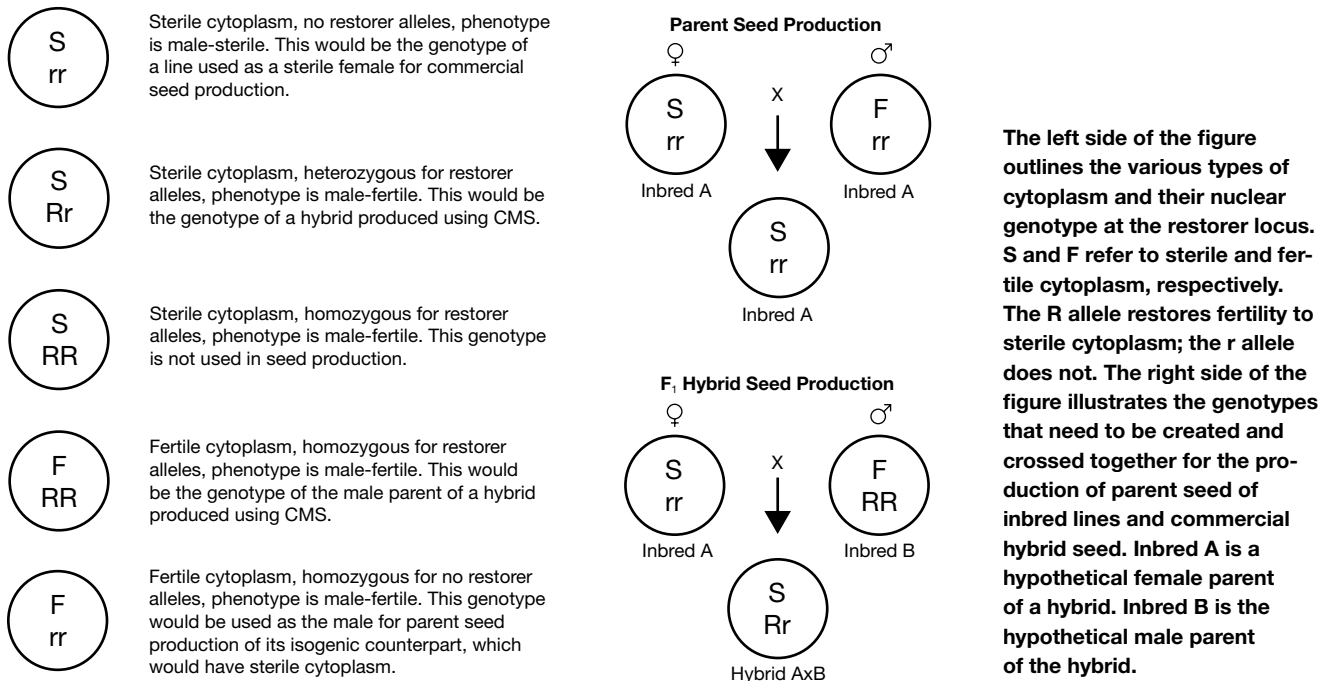
Foundation inbred seed increase fields are isolated from external pollen sources to maintain genetic purity. Only 1 in 1,000 off-type plants is allowed for certification of foundation inbred seed (Table 4-1, p. 56). Commercial companies certify most foundation seed that will be used for export or production of seed for export, but certification

is not required for foundation seed produced for use in the United States. There is no registered or certified class of seed for inbred lines because this seed is not sold directly to producers.

Although larger companies produce their own foundation seed of inbred lines, smaller companies may contract this production to another company or simply purchase their foundation seed from one of the industry's genetic suppliers. Foundation inbred seed production has typically occurred in the primary corn production areas on a contract basis with farmers or on land leased from farmers. To increase purity, foundation seed production has recently been moving to areas with no commercial corn production.

Male-sterile parents. If CMS is used to produce commercial hybrid seed, then parent seed production becomes slightly more complicated. The use of CMS involves an interaction between nuclear

31 Sib-mating is a term breeders use to describe the mating of individual plants. Sib-mating is usually done by hand and is similar to open pollination except that self-pollination is not allowed to occur.

Figure 4-3 **The CMS System in Corn and Its Use in Seed Production**

genes and genes inherited only through the cytoplasm. This system takes advantage of the fact that a plant can only inherit genes in the cytoplasm from the plant that served as its female parent.

There are two types of cytoplasm in a CMS system, which we will simply refer to as sterile (S) and fertile (F). There is also a dominant nuclear gene (R) that restores the male fertility of plants that contain sterile cytoplasm. This dominant gene is usually called the restorer gene, and one copy is enough to restore complete male fertility. Inbred lines are converted to CMS using the same backcrossing procedure used to incorporate transgenes into inbred lines. In the case of CMS conversion, however, the objective is to substitute the whole genome of an inbred line into the sterile cytoplasm.

The production of parent seed from a male-sterile inbred requires what is known as a maintainer line. A maintainer line is isogenic³² to the sterile inbred, carries non-restorer alleles, and has fertile cytoplasm. It is therefore male-fertile and will be used as the pollen parent in a seed production field similar to those used to produce hybrids, with the female being the sterile isogenic version of the same line (Figure 4-3). This is a slightly more complex process for producing parent seed than what is required if CMS is not used, but it must be done in isolation as well.

Soybean

Production of foundation seed to be grown by farmers is much simpler in soybean than in corn. Once breeder seed is available, foundation seed

³² Two inbred lines are said to be isogenic if they are genetically identical at all loci except one. In practice, breeders refer to these lines as near-isogenic lines because a block of genes around the gene of interest is moved, rather than a single gene (Fehr, 1991).

production can begin. Foundation seed is produced in the same manner as breeder seed—by letting plants self-pollinate. The major difference between producing foundation seed in soybean and corn is that there is no isolation requirement in soybean beyond that required to prevent physical mixing. Although there is a registered class of soybean seed, it is not widely used and not recognized in some states (Tekrony, Egli, and White 1987). Soybean foundation seed is usually produced near the area where the commercial seed is expected to be sold.

Commercial Seed Production

Although corn and soybean have very different modes of reproduction, commercial seed production involves many of the same steps. The basic steps are seed packaging, planting, crop maintenance, controlling pollen movement (corn only), harvesting, transporting, drying, shelling (corn only), seed conditioning, bagging, and storing.

Each of these steps often has several sub-steps and some of the processes differ slightly between corn and soybean. For example, there is no control for pollen movement in soybean, but isolation is used as insurance against physical mixing. Corn is harvested, transported, and dried on the ear, whereas soybean seed is removed from the pod by a combine in the field, then transported and dried. Corn seed production is technically more difficult and involves more steps.

Corn

Once the seed of a hybrid's inbred parents has been produced in adequate quantities, commercial production of the hybrid can begin. The first step is selecting the production area and the growers (Wych 1988). The majority of hybrid seed corn sold here is produced in the Corn Belt region of the United States, but the seed of new hybrids is also produced in the Southern Hemisphere. One of the most important factors in

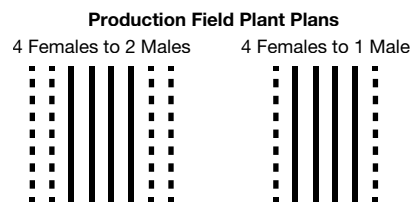
selecting the growing area and grower is isolation of the seed fields from other corn fields. The minimum isolation distances and contamination levels are shown in Table 4-1 (p. 56).

Once the fields have been selected, the next step is planting. Production fields are planted using a predetermined ratio of male to female rows (Figure 4-4). Depending on the ability of the male to produce pollen and the difference in maturity between the female and male inbred lines, either one or two rows of male parent are used for every four to six rows of female. The male and female parents may be planted at different times depending on the difference in their flowering times. In many production fields, once the male has finished shedding pollen it is mowed down to prevent accidental mixing at harvest and the theft of male inbred seed.

Standard equipment and production and pest control practices are used at this stage. Most cultural and management practices are designed to improve the yield of hybrid seed per acre.

The primary concern in a seed corn production field is pollen control. Female parents of hybrids are prevented from shedding pollen either by emasculation or CMS. CMS may or may not require emasculation depending on the cytoplasm

Figure 4-4 **Typical Planting Arrangements Used in Hybrid Seed Corn Production Fields**



The dashed lines represent male rows and the solid lines represent female rows. This is repeated across the entire field; the extra male rows in the figure are part of the repeated design.

used, the genotype of the female inbred, and the environmental conditions during flowering (Duvick 1959a, b, 1965). Neither emasculation nor CMS prevents contamination from pollen in nearby fields; this is accomplished entirely through spatial and sometimes temporal isolation. Ensuring an abundant supply of pollen from the male parent during the emergence of silks from the female also reduces contamination from nearby fields (Carcova et al. 2000).

Once the grain in a seed production field has reached physiological maturity, the seed crop will be harvested on the ear to minimize damage to the kernels. Harvesting is done with special machines that minimize ear damage. The seed is then hauled to a seed production facility where it is dried, shelled, cleaned, sized, treated, and placed into bags. These operations are accompanied by a series of quality assurance operations to determine the physical quality, purity, and germination of the seed. The seed is then stored until its distribution to dealers and farmers.

Soybean

Certified seed is the class of soybean seed sold directly to farmers. It is either produced from registered seed or, more commonly, from foundation seed, and is usually produced near the area where it is expected to be planted. AOSCA requirements for certified seed production are listed in Table 4-1 (p. 56), but certification is not mandatory for soybean seed in the United States and the use of certification agencies varies from company to company. The processing of soybean seed for shipment to farmers is similar to what is done with corn, though there are subtle differences.

VULNERABILITY OF SEED PRODUCTION TO PHARMA CROP CONTAMINATION

There are major differences in scale between seed production for commodity crops and phar-

ma crops. On average, corn and soybean are each planted on more than 70 million U.S. acres annually (USDA NASS 2004). Predicting expected production acreage for pharma crops would be conjecture, but seed production needs will be far less than for commodity crops. This difference in scale implies that standard production practices may not necessarily be used for pharma crop seed production, which would therefore more closely resemble commodity foundation seed production. All seed production, however, no matter what the scale, shares some common steps and points of vulnerability (Table 4-3, p. 66) that will be explored below.

The differences in scale are illustrated in Tables 4-2 and 4-4. Table 4-2 (p. 62) lists the seed production requirements for corn given an expected acreage to be planted with hybrids. For example, the planting of 1,000 acres of pharma crop would require about 325 bags of hybrid seed corn (the typical bag contains about 80,000 kernels), which would take 6.5 acres to produce. In turn, less than 0.1 acre would be required to produce enough seed of the male and female inbred parents to plant 6.5 acres of production. According to these calculations, the amount of seed needed to plant the entire U.S. commodity corn crop would require approximately 487,000 acres of hybrid seed production.

The situation is similar for soybean seed production, except that it generally takes more acres to produce enough seed to plant an acre of soybean. For example, planting 1,000 acres of soybeans would require 60,000 pounds of seed, which would take 25 acres to produce (Table 4-4, p. 67). Twenty-five acres of seed production would require about 0.6 acre of foundation seed production. In other words, producing enough seed to plant 1,000 acres requires about four times as much land for soybean as it does for corn.

Table 4-3 **Points of Vulnerability in the Seed Production Process**

<p>VARIETY DEVELOPMENT</p> <p>Seed packaging and preparation</p> <ul style="list-style-type: none"> <input type="checkbox"/> Spillage <input type="checkbox"/> Seed mixing <input type="checkbox"/> Mislabeling of seed <p>Planting breeding nursery</p> <p>Maintaining crop</p> <ul style="list-style-type: none"> <input type="checkbox"/> Cultivating <input type="checkbox"/> Spraying <p>Making controlled pollinations</p> <ul style="list-style-type: none"> <input type="checkbox"/> Pollinations made by hand <input type="checkbox"/> Pollinations made by wind <input type="checkbox"/> Pollen movement <p>Harvesting breeding nursery</p> <ul style="list-style-type: none"> <input type="checkbox"/> Seed on plants not harvested <input type="checkbox"/> Disposal of unwanted grain <input type="checkbox"/> Disposal of unwanted plants <input type="checkbox"/> Cleanout of machine used for gleaning field <input type="checkbox"/> Disposal of seed gleaned from field <input type="checkbox"/> Spilled grain <input type="checkbox"/> Volunteer plants emerge in field the following year <p>Transporting grain to shelling facility</p> <p>Shelling/threshing and seed processing</p> <ul style="list-style-type: none"> <input type="checkbox"/> Accidental mixing of seed <input type="checkbox"/> Mixing during shelling <input type="checkbox"/> Mislabeling of seed during seed processing <input type="checkbox"/> Improper discarding of seed <p>Field testing of new varieties</p> <ul style="list-style-type: none"> <input type="checkbox"/> Seed packaging and preparation <input type="checkbox"/> Planting field test <input type="checkbox"/> Crop maintenance <ul style="list-style-type: none"> • Cultivating • Spraying <input type="checkbox"/> Field testing on land rented from farmers <ul style="list-style-type: none"> • Farmers could accidentally harvest test plots • Seed may be spilled <input type="checkbox"/> Pollen movement <input type="checkbox"/> Harvest <ul style="list-style-type: none"> • Cleanout of machine used for harvesting • Disposal of harvested seed <input type="checkbox"/> Volunteer plants emerge the following year 	<p>Discarding seed of varieties that are not productive</p> <ul style="list-style-type: none"> <input type="checkbox"/> Seed may be mixed with other varieties <input type="checkbox"/> Seed may accidentally grow (resulting in pollen movement) <p>TRANSFORMATION</p> <p>Bombardment</p> <p>Regeneration</p> <p>Maturation</p> <ul style="list-style-type: none"> <input type="checkbox"/> Pollen movement <input type="checkbox"/> Physical mixing <p>BACKCROSSING</p> <p>Seed packaging and preparation</p> <ul style="list-style-type: none"> <input type="checkbox"/> Spillage <input type="checkbox"/> Seed mixing <input type="checkbox"/> Mislabeling of seed <p>Planting breeding nursery</p> <p>Maintaining crop</p> <ul style="list-style-type: none"> <input type="checkbox"/> Cultivating <input type="checkbox"/> Spraying <p>Making controlled pollinations</p> <ul style="list-style-type: none"> <input type="checkbox"/> Pollinations made by hand <input type="checkbox"/> Pollinations made by wind <input type="checkbox"/> Pollen movement <p>Harvesting breeding nursery</p> <ul style="list-style-type: none"> <input type="checkbox"/> Seed on plants not harvested <input type="checkbox"/> Disposal of unwanted grain <input type="checkbox"/> Disposal of unwanted plants <input type="checkbox"/> Cleanout of machine used for gleaning field <input type="checkbox"/> Disposal of seed gleaned from field <input type="checkbox"/> Spilled grain <input type="checkbox"/> Volunteer plants emerge in field the following year <p>Transporting grain to shelling facility</p> <p>Shelling/threshing and seed processing</p> <ul style="list-style-type: none"> <input type="checkbox"/> Accidental mixing of seed <input type="checkbox"/> Mixing during shelling <input type="checkbox"/> Mislabeling of seed during seed processing <input type="checkbox"/> Improper discarding of seed <p>Field testing new varieties</p> <ul style="list-style-type: none"> <input type="checkbox"/> Seed packaging and preparation <input type="checkbox"/> Planting field test <input type="checkbox"/> Crop maintenance <ul style="list-style-type: none"> • Cultivating • Spraying 	<ul style="list-style-type: none"> <input type="checkbox"/> Field testing on land rented from farmers <ul style="list-style-type: none"> • Farmers could accidentally harvest test plots • Seed may be spilled <input type="checkbox"/> Pollen movement <input type="checkbox"/> Harvest <ul style="list-style-type: none"> • Cleanout of machine used for harvesting • Disposal of harvested seed <input type="checkbox"/> Volunteer plants emerge the following year <p>Discarding seed of varieties that are not productive</p> <ul style="list-style-type: none"> <input type="checkbox"/> Seed may be mixed with other varieties <input type="checkbox"/> Seed may accidentally grow (resulting in pollen movement) <p>BREEDER SEED PRODUCTION</p> <p>Seed packaging and preparation</p> <p>Planting breeding nursery</p> <p>Maintaining crop</p> <p>Making controlled pollinations</p> <p>Harvesting breeding nursery</p> <p>Transporting grain to shelling facility</p> <p>Shelling/threshing</p> <p>Seed processing and conditioning</p> <p>FOUNDATION SEED PRODUCTION</p> <p>Seed packaging</p> <p>Seed planting</p> <p>Crop maintenance</p> <p>Pollen movement</p> <p>Harvest</p> <p>Transportation</p> <p>Drying</p> <p>Shelling</p> <p>Conditioning</p> <p>Storage</p> <p>COMMERCIAL SEED PRODUCTION</p> <p>Seed packaging</p> <p>Seed planting</p> <p>Crop maintenance</p> <p>Pollen movement</p> <p>Harvest</p> <p>Transportation</p> <p>Drying</p> <p>Shelling</p> <p>Conditioning</p> <p>Storage</p>
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The frequency of seed production can also be a problem. For example, if only one pharma crop is to be produced on 1,000 acres, then seed production is greatly simplified. If, however, 100 different pharma crops are to be planted on 1,000 acres each, then the frequency of production becomes a greater concern than the scale of production.

The major points of vulnerability to contamination in the food system are outlined in Table

4-3. The seed production system has been divided into six major steps (as shown in Figure 4-1, p. 54): variety development, transformation, backcrossing, breeder seed production, parent seed production, and commercial seed production. Each of these steps is then analyzed for points of vulnerability. Corn and soybean often share the same points, but the degree of vulnerability may differ.

Corn

Variety Development. As stated earlier, the variety development stage of seed production is not a point of vulnerability because pharma crop transgenes are currently introduced only into established varieties. If, however, pharma crop transgenes were introduced at the variety development stage, and if the program were conducted in parallel with conventional breeding programs, then avoiding contamination entirely would become highly improbable if not impossible. Because the points of vulnerability for variety development are the same as those for backcrossing, we will discuss the reasons for contamination in that section.

Transformation. Transformation is required to introduce all new transgenes into plants. The sources of potential contamination during bombardment and regeneration come from plant tissue. Most transformation labs destroy all unused biological material by autoclaving, and the biological material is confined to a laboratory or greenhouse. As long as this process is followed, contamination

of the food supply from biological material should not occur. The main concern with the transformation phase arises after a plant has been regenerated from cell culture and produces flowers.

The first plants after regeneration are grown and pollinated in the greenhouse, where, without appropriate precautions, contamination of other corn plants with the new transgene via pollen movement or seed mixing is likely to occur. The contaminated plants would most likely be other plants that already contain experimental transgenes. If the greenhouse is not a confined facility, pollen may escape into the atmosphere and contaminate plants outside the greenhouse.

Detection of a contaminant by an outside third party at this stage would be difficult because the transgene and its product are usually regarded as confidential business information, which means that only the transgene developer could identify the contaminant gene. Detecting compounds produced by the contaminant gene is less likely to involve confidential business information, but the ease with which that can be done will vary.

Backcrossing. The vulnerability of working with transgenes in the field is illustrated by backcrossing. The primary use of backcrossing is to move a transgene into a more desirable inbred line, but all field-breeding activities, no matter their objective, have points at which food crops are vulnerable to contamination.

The points of vulnerability are: seed packaging and preparation; planting the breeding nursery; making controlled pollinations; harvesting the breeding nursery; transporting, drying, shelling, and processing seed; field testing new varieties; and discarding the seed of unproductive varieties. Some of these activities occur simultaneously in a breeding program. For example, the planting of the 2005 breeding nursery will be done simultaneously with the planting of field tests of varieties developed in the 2004 breeding nursery.

Table 4-4 Quantities of Production Required for a Given Acreage of Soybean Production

Planted Acreage	Pounds of Soybean Seed Required	Acres of Soybean Seed Production Required	Acres of Foundation Seed Production
50	3,000	1	0.0
100	6,000	3	0.1
500	30,000	13	0.3
1,000	60,000	25	0.6
2,000	120,000	50	1.3
3,000	180,000	75	1.9
5,000	300,000	125	3.1
10,000	600,000	250	6.3
75,000,000	4,500,000,000	1,875,000	46,875.0

The calculations in this table assume an average planting rate of 150,000 seeds per acre, 2,500 seeds per pound, and a soybean yield of 40 bushels per acre. A bushel of soybeans weighs 60 pounds.

The main concerns for contamination during seed packaging are spilling and mixing, particularly if seed containing experimental transgenes is packaged in the same facilities with food/feed-grade seed. And there is always the risk of the planter not being properly cleaned before and after each use, especially if it is used for planting different types of corn.

The main problem during controlled pollinations, which are made either by hand or wind depending on the breeding procedure, is preventing pollen from moving to where it is not intended or wanted. Generally speaking, there are many more plants shedding pollen than are needed for use in backcrossing. The seed resulting from controlled pollinations in breeding nurseries is usually collected by hand and any seed left on the plants is harvested with machines.

Harvesting involves several points of vulnerability. There are always plants that produce grain that is not harvested for seed. The disposal of both this grain and the plants that produce the grain, as well as the cleanup of machines that glean the fields, poses special challenges. Seed may be spilled in the field during the harvest or during transportation to the shelling/threshing facility.

The shelling/threshing process generates a lot of loose seed, as does the associated handling of the seed and spillage. Seed from different lots, for example, can be easily mixed or improperly labeled after shelling by inexperienced personnel. If the shelling/threshing machines are not properly cleaned, they too may become a source of contamination.

One of the more serious problems during shelling is that there is frequently more seed than breeders need. This excess seed must be properly discarded so that it does not become mixed with other seed or grow the following year and produce pollen and more seeds. Volunteer plants emerging in the field the following year are always a prob-

lem in breeding nurseries, where the frequency of dropped ears and partially shelled ears is high because of the variability among plant types.

Field testing of new varieties poses many of the same vulnerabilities as described for variety development. The main difference is that field tests are more frequently conducted on land rented or leased from farmers. The field test may be located some distance from the breeding nursery, making daily or even weekly monitoring of the test site difficult. Otherwise, the vulnerabilities of field testing are almost identical to those encountered during the variety development phase.

Breeder Seed Production. Breeder seed is produced in breeding nurseries similar to those used for variety development. Therefore, the points of vulnerability are similar to those described above for backcrossing. The amount of breeder seed produced varies considerably depending on the circumstances, but a typical range would be 5 to 50 pounds per variety. Breeder seed is produced by making hand (controlled) pollinations.

Although the sources of contamination of breeder seed are the same as for backcrossing (Table 4-3, p. 66), the probability of detecting the contamination and its consequences are much different in breeder seed production using good practices (e.g., iterative self-pollination and observation). During the observation phase, mixing and outcrossing is nearly always detected before it can cause problems. Such a breeder seed production system is less vulnerable to contamination than backcrossing and other research operations.

Foundation Seed Production. Foundation seed production is the first large-scale seed increase that occurs in the seed production process. The amount of foundation (parent) seed of a corn inbred line produced will depend on the anticipated sales of the hybrid for which that line is a parent. For example, if the hybrid is expected to be grown on about 10,000 acres, then about

0.4 acre of foundation production will be needed. In practice, the acreage may be larger if a multiple-year supply of seed is desired, if the inbred line is used as the parent of more than one hybrid, or if there are facilities in which to store the seed.

The points of vulnerability for foundation seed production are similar to those described for breeding and field testing; the primary difference is scale and frequency. Foundation seed increases in corn are almost always done in isolation and pollination occurs via wind movement. Most companies use the standards listed in Table 4-1 (p. 56), which do not guarantee virtually zero contamination, and may need to produce the seed of 10 to 50 inbreds depending on the size of their product line, sales, and storage capacity. There is no easy way to contain corn pollen, and plants must produce pollen in order to produce seed.

Because of the need to produce foundation seed for a large number of inbred lines, the steps following pollen movement become even more important. Harvesting, transporting, drying, shelling, conditioning, and storing would all be problematic if the same equipment and facilities were used to process seed. If pharma corn were processed in the same manner and the same facility as commodity corn, the vulnerability to contamination due to seed mixing during these steps would be very high. The use of separate equipment and facilities is feasible for pharma corn.

Commercial Seed Production. Hybrid seed production poses some of the same vulnerabilities to contamination of the food system as foundation seed production. The most obvious source of potential contamination is pollen movement from the production field to a farmer's field or a field producing another hybrid. Physical mixing associated with harvesting equipment is another source. Hybrid seed production also has the same con-

tamination risks as on-farm production (Chapter 5) and risks similar to those for shipping and storage (Chapter 6).

Seed processing has several points of contamination, including the mixing of seed lots, imperfect cleaning of equipment in the processing plant, and mislabeling of bags. Although seed production plants are designed to maintain the purity of individual hybrids, virtually zero contamination is not necessary under normal circumstances and is never achieved. Separate equipment and facilities for pharma corn are feasible and could prevent cross-contamination with seed of varieties used for food.

Soybean

Pharma soybean has far less risk of contaminating the commodity crop via windborne pollen than corn. In other ways, however, soybean can pose greater risks than corn. For example, soybean is visited by insects that facilitate pollination (Palmer et al. 2001). Bees have the potential to travel long distances before depositing pollen, though the success of such long-distance pollination depends primarily on pollen longevity.

Otherwise, soybean has similar vulnerabilities to corn when it comes to contamination risks, including issues related to transformation, backcrossing, foundation and commercial seed production, and seed processing. Because a larger volume of seed is required to plant an acre of soybean than an acre of corn, there may be a greater risk of seed mixing with soybean than with corn.

ACHIEVING VIRTUALLY ZERO CONTAMINATION

As discussed, commodity corn and soybean share many of the same points of vulnerability. The major points are pollen movement, physical mixing of seed, and seed left in the field to become volunteers the following year.

Pollen Movement

The fact that soybean is predominantly self-pollinated has led many to believe that contamination from outcrossing in soybean is not a concern,³³ whereas the wind-pollinated nature of corn suggests that contamination from pollen movement cannot be eliminated. Surprisingly, some fundamental biological characteristics of corn make pollen control easier than in soybean production, particularly with regard to achieving the stringent goal of virtually zero contamination.

Soybean produces between 3,740 and 7,600 pollen grains per flower (Palmer et al. 2001). If the average soybean plant produces 100 flowers, then that plant produces between 374,000 and 760,000 pollen grains. Since soybean is typically planted at the rate of about 150,000 plants per acre, the number of pollen grains produced per acre is around 75 billion. This is less than that produced by corn, but obviously a large amount nevertheless.

Rates of outcrossing vary from less than one percent to more than 25 percent in soybean depending on the variety, environment, and availability of pollinators (Palmer et al. 2001). There is no published information on long-distance pollen movement in soybean, but there are many anecdotal accounts suggesting that soybean pollen can be carried long distances by insects under the right environmental conditions.³⁴ Because little is known about insect-mediated long-distance pollen movement in soybean, spatial barriers may not be effective. Temporal barriers are ineffective because soybean tends to flower over long periods of time.

Mechanical and biological barriers to pollen movement are also unavailable in soybean, which

is very difficult to emasculate manually and could never, therefore, be emasculated on a large scale. Biological sterility systems such as CMS only recently became available for soybean, and producing seed on male-sterile soybean plants is difficult (Palmer et al. 2001). For these reasons, the production of pharma crop soybean seed in areas where commodity soybean is grown cannot be recommended until more is known about insect-mediated pollen movement.

More tools are available to control pollen movement in corn than soybean. Though spatial and temporal barriers are not completely effective, there are good mechanical and biological barriers available. For example, corn can easily be emasculated on a large scale either manually or with special machines; the key is to start before the beginning of pollen shed. Excellent CMS systems, which have been used for commercial seed production, are also available for corn. In theory, combining these four barriers—spatial, temporal, mechanical, and biological—could effectively achieve virtually zero contamination from pollen movement in corn. This assumes, of course, no human errors and a 100 percent effective CMS system.

The ability to use all four barriers effectively to achieve virtually zero contamination from pollen movement depends on the size of the fields, the amount of time devoted to monitoring fields for potential problems, and the isolation distances. It is difficult to quantify the probability of a contamination event. There are, for example, no published data on the frequency of failure for emasculation or CMS—this is an area that needs additional research on both the plant side and the modeling and simulation side. Strong qualitative statements are also difficult to make because they

33 See, for example, the document on soybean available at the U.S. Department of Agriculture Animal and Plant Health Inspection Service (USDA APHIS) website (<http://www.aphis.usda.gov/brs/soybean.html>), accessed September 19, 2004.

34 Personal communication with R.G. Palmer, U.S. Department of Agriculture Agricultural Research Service, 2003.

require too many assumptions about processes under human control and thus depend on measurement of human error rates.

Another possible approach to achieve virtually zero contamination is for farmers to plant inbred lines rather than hybrids. The male-sterile inbred could then be pollinated with normal corn, and commercial production could proceed in much the same way it does for hybrids. The main disadvantage of this method is that larger seed production acres of the pharma inbred would probably be required, since inbreds yield substantially less than hybrids.

Growing inbred lines eliminates the hybrid seed production step but requires much larger increases of the inbred line carrying the transgene of interest. Since there is no easy way to produce this quantity of inbred seed other than by allowing it to open-pollinate in isolation, inbred seed production would require greater isolation distances than CMS production and may need to be conducted in areas where the commercial crop or a seed production crop is not grown. CMS could still be used, but it would require the creation of the appropriate sterile and maintainer lines as described earlier.

The type of hybrid corn seed produced for pharma crops is also important in preventing pollen movement. Assuming that the pharma transgenes are dominant, the hybrids to be grown by farmers might need to be 100 percent male-sterile. This can be accomplished in one of two ways. A male-sterile hybrid that is hemizygous³⁵ for the transgene could be produced as outlined in Figure 4-5 (p. 72, Option 1). The female inbred of the hybrid would be homozygous for the transgene and reside in sterile cytoplasm

without nuclear restorers. The male inbred of the hybrid would be produced with a normal inbred as the male that lacks both the transgene and restorer alleles. The resulting hybrid would be male-sterile and hemizygous for the transgene.

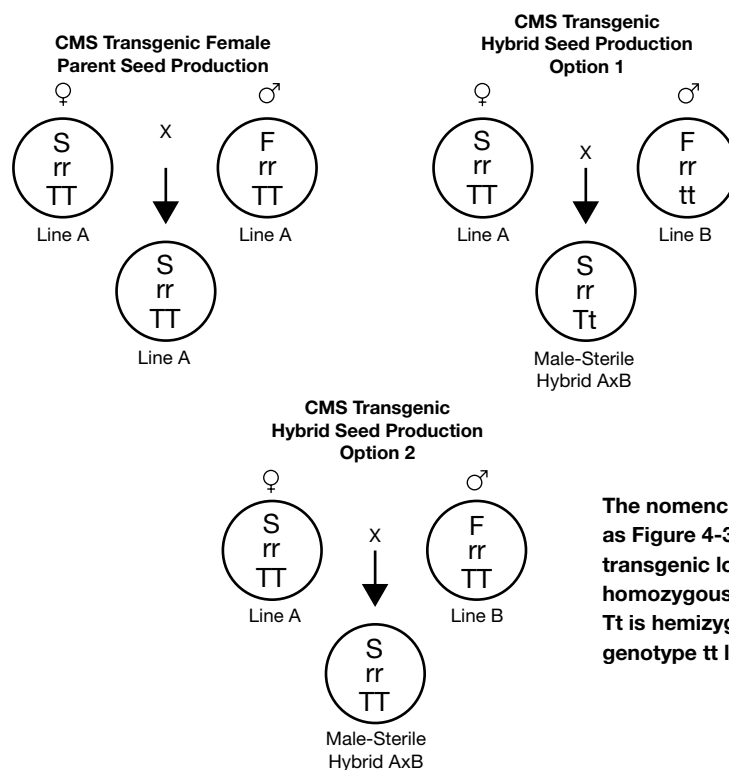
The farmer would plant the field in the same manner as a seed field with the male being a normal hybrid (Figure 4-4, p. 64). After pollination, the male rows in the field could be destroyed so they are not inadvertently harvested. The advantage of this system is that pollen would not be shed by transgenic plants. In case the CMS system failed or partially failed, the plants would also be emasculated as the tassels emerge.

Option 1 has an advantage during hybrid seed production as well, in that the only pollen shed in the field is from a non-transgenic inbred. The disadvantage of this option is that only 50 percent of the kernels on the ear will produce the pharma crop trait, a result that would presumably lower product yield at the extraction plant.

The second hybrid production option is to produce a CMS hybrid that is homozygous for the transgene. Seed is produced by using the same female inbred used in Option 1. The male inbred of the hybrid differs from Option 1 in that it is also homozygous for the transgene; otherwise, it has fertile cytoplasm and carries non-restorer alleles. The hybrid produced by Option 2 will be CMS and homozygous for the transgene. The farmer would plant the field as with Option 1. The primary advantage of producing hybrids with Option 2 is that 100 percent of the kernels harvested will carry the transgene; the disadvantage is that the transgene has to be backcrossed into two inbred lines instead of one, but this can occur simultaneously.

35 Hemizygous means each plant cell carries only one copy of the transgene.

Figure 4-5 **Using CMS to Create Male-Sterile Transgenic Commercial Hybrids**



The nomenclature in the figure is the same as Figure 4-3, except the genotype at the transgenic locus is shown. The genotype TT is homozygous for the transgene, the genotype Tt is hemizygous for the transgene, and the genotype tt lacks the transgene.

Physical Mixing

Preventing contamination of the food chain with pharma crops is primarily a function of keeping pharma crop seeds separate from commodity seeds during all phases of seed handling outlined in Table 4-3 (p. 66). Accomplishing this would require rigorous standard operating procedures (SOPs) to track the flow and quantity of seed and the use of dedicated machinery and infrastructure. The use of SOPs would ensure that employees were aware of the requirements, allow accidents or mistakes to be traced, and enable the process to be stopped or changed to prevent mistakes.

Volunteer Plants and Crop Residue

Volunteer plants are often a significant problem with regard to pharma crop contamination

of the food system. If, however, dedicated seed production facilities and locations are used and no commodity crops are grown in that location, volunteer plants, even if they occur, would not have opportunities to contaminate commodity crops. Crop residues are also an issue in that they can be moved from field to field by equipment and wind.

CONCLUSIONS AND RECOMMENDATIONS

Establishing effective isolation distances between pharma and other crops is difficult at this point. One strategy would be to determine distances as some function of the furthest distance that pollen of a given species has been found to travel. This would require conducting high-quality experiments to measure long-distance pollen movement. For example, pollen movement in corn can

be detected at 0.5 mile from the source when there is no temporal isolation (Halsey et al. 2002).

Another good option would be to grow the pharma crops in irrigated desert regions of the world where corn or soybean is not currently grown. This would reduce the likelihood of contamination by pollen movement, but the likelihood of contamination from seed mixing will depend on compliance with standard operating procedures, especially in the dedicated use and cleaning of harvest equipment and the use of sealed transport containers.

Because all seed essentially looks the same, one measure that should be adopted is the use of colored seed for all pharma crops at all stages of seed production. For example, almost all seed corn sold in the United States is treated with fungicides, and a colorant is added during the treatment process so that fungicide-treated seed can be identified and kept out of the food chain. A unique color could be assigned to pharma crop seed and required as a coating to be applied as soon as is practical following harvest. The color would identify this grain and help prevent pharma crop seeds from entering the food chain.

The use of natural color genes in corn and soybean has been suggested as another way of uniquely identifying pharma grain. The primary advantage of this system is that the color system would be genetic and always present. Depending on the genes used, this system could also help iden-

tify contamination events via pollen movement. The disadvantage of this system is its inherent complexity during breeding, backcrossing, and hybrid development. In addition, this system could impinge on those who sell naturally colored commodity crop seed as a specialty product (blue corn for example).

The only way to guarantee virtually zero contamination of the food supply by pharma crops is to maintain dedicated machines, facilities, and processes. Even though pollen movement in a crop such as corn can essentially be eliminated during seed production, seed can be moved long distances and can easily become mixed with commodity crop seed during harvest and transportation. For this reason, the author recommends that all pharma crop breeding and seed production activities be conducted in areas of the world where commodity crops and seed production crops of the same species are not grown.

Acknowledgments

The writing of this chapter required many informal conversations with scientists in both the public and private sector. I am grateful to all who contributed, but listing them by name would mean that I would inevitably leave someone out. I am especially grateful to Paul Christensen, who reviewed the entire chapter and offered numerous changes, some of which I used.

—Kendall Lamkey

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Chapter 5

ON-FARM PRODUCTION OF CORN AND SOYBEAN

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Among field crops grown in the United States, corn and soybean occupy the greatest acreage and produce the greatest total value. From 1993 through 2002, corn was harvested for grain on about 70 million acres annually in the United States, with an annual yield of 128 bushels per acre. Annual production was about nine billion bushels—worth some \$20 billion (USDA NASS 2004a). Over the same period, soybean occupied 68 million acres each year with an average yield of 38 bushels per acre, for total production of about 2.5 billion bushels—worth \$14 billion (USDA NASS 2004b).

The prominence of corn and soybean as commercial crops in the United States, the existence of an extensive body of genetic information on both crops, and the ability to genetically transform both crops make corn and soybean natural choices as pharma crops. Thousands of crop producers have experience with both crops and are knowledgeable about management techniques needed to optimize production. Corn can be stored for years with minimal deterioration, using structures that already exist. (Soybean is more vulnerable to deterioration.)

The climatic requirements of corn and soybean are similar, and they are mostly grown in the same areas of the American Midwest (often in rotation with one another). While there are some regional differences in production techniques based on differences in soils and climates, there is much commonality among production areas in the

states comprising the Corn Belt, and this chapter describes production processes typical for most producers of these two crops.

While their occupation of so many acres in the United States and their familiarity to crop producers and processors make corn and soybean leading crops to be considered for pharmaceutical production, it is clear that commingling pharma crops with regular commercial production fields brings serious challenges in avoiding genetic cross-contamination. It should not be assumed that the midwestern United States, despite its ideal growing conditions, should be the primary locus for pharma corn and soybean production.

The ubiquity of non-pharma corn and soybean, the fact that corn in particular (and soybean to a much smaller degree) naturally cross-pollinates, and the inability to distinguish contamination either visually or by other practical means are reasons not to produce pharma crops in the U.S. Corn Belt. If such production is pursued, novel and far-reaching modifications of on-farm practices will be needed to achieve virtually zero contamination of the commercial crop by pharmaceutical genes.

The nine states that comprise the Corn Belt in the north central United States³⁶ account for more than three-fourths of the country's corn and soybean production. Given the concentration of corn and soybean production in the U.S. Corn Belt, this chapter will describe production systems typical of the upper Midwest. Illinois, which occupies a central position in the Corn Belt, is

³⁶ Illinois, Indiana, Iowa, Kansas, Minnesota, Missouri, Nebraska, Ohio, and South Dakota.

used as a “median” example of the timing of operations and the time course followed by the developing crops. In general, planting and harvest occur earlier as one moves south, and later as one moves north, but other operations and principles of production are not different enough to warrant separate description.

While there are differences in the crop mix produced in different areas, such differences have little bearing on this chapter’s conclusions. For example, while the two-year corn-soybean rotation is more common in Illinois than in, say, Georgia or North Dakota, its existence is not mandated, nor are alternatives appreciably more or less feasible in any of these places. Except with regard to cropping intensity as it affects the likelihood of gene movement to non-pharma crops of the same species, issues of pharma corn and soybean production are largely location-neutral.

COMMODITY CORN AND SOYBEAN PRODUCTION CYCLES

The production cycle for corn and soybean in the midwestern United States begins following the harvest of the preceding crop. For the majority of crop acres, corn and soybean are rotated in a two-year cycle that carries yield benefits for both crops in comparison to either crop following itself in the same field. There is also a substantial acreage of corn that follows corn, and, in live-stock-producing areas, of corn that follows a forage crop such as alfalfa or a grass-legume mixture.

Corn Production

Figure 5-1 provides a timeline to indicate when different production procedures are used during the corn growing season. Points of vulnerability to gene flow from pharma to normal crops are also indicated.

Previous (Soybean) Crop Harvest, Tillage, and Fertilizer Application

When a corn crop follows soybean, the soybean stubble following the September or October harvest is sometimes left undisturbed over the fall and winter. Alternatively, fields can be tilled in the fall using primary tillage implements, though this can reduce the amount of surface residue to a level below what is necessary to maintain desired soil stability.

Depending on the fall weather, climate, and soil, nitrogen for the following corn crop is sometimes applied in the fall, usually using anhydrous ammonia applied beneath the soil surface using narrow “knives” that disturb only 10 to 20 percent of the soybean residue. Dry fertilizers (mostly phosphorous and potassium) are often broadcast-applied in the fall after soybean harvest, usually in amounts adequate for two succeeding crop years (corn and soybean).

The following spring, nitrogen fertilizer is usually applied in fields where it was not applied the previous fall, and soybean stubble is typically tilled once with a relatively shallow-running tillage tool prior to planting.

Seed Delivery to the Farm

Seed supplies are usually ordered in the fall, and delivery takes place over the winter and early spring, as seed is processed and put into containers by seed companies. Commercial corn seed is usually delivered to producers in plastic-lined paper bags, which are directly emptied into seed boxes on the planter. Such bags typically contain 80,000 kernels and are sold by seed number, not weight. At normal planting rates of 28,000 to 32,000 seeds per acre, such a unit plants about 2.5 to 2.8 acres. Seed is also graded, meaning separated to size and shape categories, for better distribution by planter units.

Figure 5-1 **Timeline of Corn Production Operations**

Symbols (*) indicate points of vulnerability to contamination through transfer of pollen or other plant material.

Month												
Sep	Oct	Nov	Dec-Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov
Soybean Harvest*												
	Fertilizer Applied											
	Fall Tillage											
			Seed Delivered to Farms*									
			Tillage and Fertilizer Application									
					Planting*							
						Weed Control						
								Pollination*				
										Corn Harvest*		
										Grain Storage*		
Grain Storage (duration variable)												

There is increasing use of bulk-handled seed, utilizing containers that hold 1,000 pounds of seed or more and are usually lined with plastic fabric that can be sealed. Bulk containers are delivered to producers, who have the equipment needed to manipulate such containers and transfer seed directly from the containers to the planter. These save time in handling and filling planters, and are reusable and cost-effective, but because they are designed for multiple use, could present a slightly higher risk of seed mixing than when seed is packaged in smaller, single-use bags.

POINT OF VULNERABILITY:

Human error is the main cause of problems in delivering and keeping stored corn seed separate and in delivering seed to the field for planting. While inadvertent seed mixing in the planter is rarely reported, differ-

ent hybrids from the same company are usually in bags of similar size, and the hybrid may be designated only by stamped information on one end of the bag. Stacking and handling bags of the same hybrid together help minimize the chances of mixing but do not prevent it.

The placement of special seed such as pharma seed in bags of distinctly different size, shape, and (especially) color than those commonly used would greatly reduce the chance for inadvertent mixing due to human error. As mentioned earlier, an agreed-upon “pharma color” that would be recognized instantly and universally associated with pharma crop production, say bright pink, would help prevent pharma crop contamination through human error.

The potential also exists for rodents to remove seeds from storage containers and move them to places where they might be inadvertently used as seed of the wrong variety. Normal sanitation and rodent-proof containers at facilities for pharma seed will help to minimize the potential for such contamination.

Planting

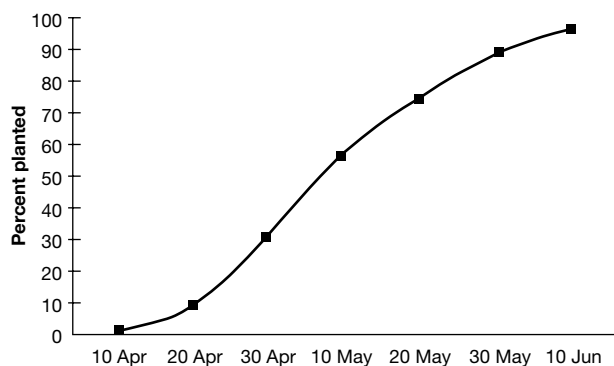
Corn is usually planted in April or May, as the weather allows, with yield losses mounting as planting is delayed past mid-May. Expectations for corn yield decrease to about 50 percent of normal by mid- to late June (or earlier in northern areas). Wet weather is the primary reason for delay, and planting progress thus differs considerably among years. Figure 5-2 shows the percentages of Illinois corn acreage planted by the indicated date, averaged over 10 years from 1993 to 2002.

Virtually all corn seed planted by producers in the United States, with the exception of open-pollinated types produced for special markets, is hybrid seed purchased from commercial seed companies.

POINT OF VULNERABILITY:

One of the key danger points for unintended seed mixing comes with the changeover of the planter from one hybrid to another. Most producers have no particular need to be fastidious about this, as in most instances there is no penalty for having a few seeds carry over to the next planting. In fact, it is common practice to simply load different seed into the seed boxes atop small quantities of the previous seed, such that different planter units change over at different places in the field, with considerable intermixing before the change is complete.

Figure 5-2 **Average Corn Planting Progress in Illinois (1993–2002)**



SOURCE: IASS 2003a.

With common planters now capable of holding 12 or 16 units, and some up to 24 or even more, it can be quite laborious to remove, carefully empty, and replace each seed box in order to change to the next seed. There is a trend toward central seed tanks that can not only be filled mechanically, often from bulk seed containers, but also distribute seed out to the units as the planter is operating. This trend makes it more difficult to clean all seed from the planter, especially if individual planter units can still contain leftover seed. The size and high mounting of such seed tanks also make it difficult to assess whether some seed remains. Therefore, the use of planters dedicated to particular pharma crops is essential to eliminate the chances of cross-contamination by seed.

Weed Control and Crop Monitoring

Most producers apply herbicides before or just after planting. Herbicides applied this early are soil-active, meaning they have been formulated to prevent weed establishment as the crop emerges and grows. Other herbicides are active on growing weeds, and these are applied post-emergence (after the corn crop and weeds are actively growing). Row cultivation for weed control is practiced in some fields but has decreased in use recently.

Except for the application of post-emergence herbicides, which is usually done before corn plants reach 24 inches in height, most fields grown under rain-fed conditions are not entered again with equipment until harvest time. Many producers spend some time scouting for insects and diseases or hire someone to do this, but because such scouting tends to be general rather than thorough in coverage, the presence of off-types usually goes undetected (unless they occur frequently and are easily recognized). The most visible occurrence in the field—tassel appearance—is usually noted easily, but other events such as the onset and duration of pollen shed among fields are not typically noted with much precision.

POINT OF VULNERABILITY:

Heavy rains after planting can cause soil and seeds to wash into adjoining fields, which could result in pharma plants growing in unintended places, including non-pharma fields. In rare cases, rodents might also move seed to other places, where such seed could germinate and emerge. Spatial separation of only a few hundred yards should keep pharma corn from establishing in non-pharma corn, but any pharma plants growing outside the field where they were planted need to be located and destroyed in order to prevent them from shedding pollen outside the pharma field. This will require close monitoring of fields and the surrounding area.

POINT OF VULNERABILITY:

While its occurrence is infrequent, soybean has been observed growing as a weed in corn fields. In cases where the previous crop was pharma soybean, this could be a source of contamination in corn. As with all crops, some soybean seed is left in the field after the harvest, though the amount varies greatly depending on pre-harvest and harvest conditions. If such seed germinates in the fall, plants are almost always killed by freezing temperatures, but some plants might survive in areas with warmer winters. Seed that germinates in the early spring is usually killed by freezing, mechanical cultivation, or the herbicide used on corn.

Those few plants that might survive are usually shaded by faster-growing corn plants, so they usually set little or no seed. Even vegetative pharma soybean plant material, however, could contaminate corn during the corn harvest. The chance of such plants setting seed that will survive until the next crop is very small, but would not be zero, especially if the corn stand were thin enough in some places to allow soybean “weeds” to thrive. The best defense against soybean as a contaminating pharma crop in the next year’s corn crop would be tillage before the corn planting, using herbicides that kill soybean, and scouting and hand removal of any surviving soybean plants.

POINT OF VULNERABILITY:

It is possible (though no cases have been documented) that a person scouting fields at the time of pollination could carry pharma corn pollen to a non-pharma field, where pollination could result in kernels contain-

ing pharmaceuticals. This potential problem should be eliminated by wearing complete-cover clothing to visit pharma fields once pollination starts, and leaving this clothing in the field for subsequent visits.

Pollination

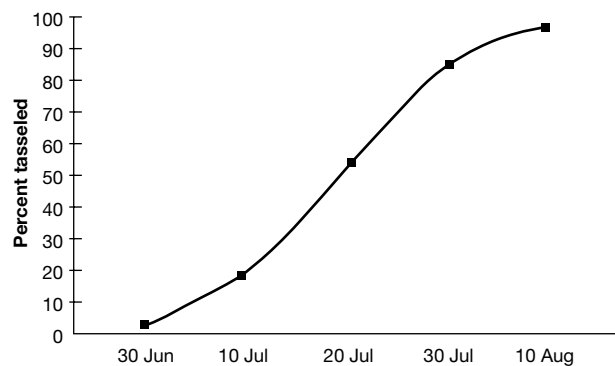
Hybrids of different maturity tend to require different numbers of days from planting to pollination but relatively similar number of days from pollination to maturity. For example, an earlier-maturing hybrid may require 60 days from planting to pollination and 55 days from pollination to maturity, while a late-maturing hybrid may need 65 days from planting to pollination and 57 or 58 days from pollination to maturity.

Later-planted fields also pollinate later, but corn plant development follows thermal accumulations (measured as growing degree days, or the average daily temperature minus the base temperature of 50°F) much more closely than the number of days elapsed. Therefore, planting 10 days later when temperatures are cool may only delay the onset of pollination by two or three days.

The warm temperatures that typically hold during July when most of this takes place tend to compress the duration of pollen shedding and silking both within and among fields; it is not unusual for most fields in an area to show tassels within the space of about a week (except for fields that might have been planted very late). Figure 5-3 (p. 80) shows tassel appearance in Illinois averaged over 10 years from 1993 to 2002.

Dry weather and inadequate soil moisture during the critical pollination period (essentially during July) usually decrease the success of pollination, resulting in lower numbers of kernels and lower yield potential. The relationship between late pollination and low yields can often be alleviated by adequate rainfall and warm weather extending into late September.

Figure 5-3 **Average Progress of Corn Tassel Appearance (1993–2002)**



SOURCE: IASS 2003b.

POINT OF VULNERABILITY:

The time during which pollen is released into the air from (male) corn tassels and drifts until it lands on (female) silks represents the most vulnerable point of potential genetic contamination. In one study in Minnesota, Westgate, Lizaso, and Batchelor (2003) reported 4.3 million to 5.2 million pollen grains shed per plant and up to 128 billion pollen grains shed per acre of corn when all plants were male-fertile.

Actual pollen numbers in commercial fields are often lower than those reported by Westgate due to the common practice of using some proportion (perhaps 30 to 50 percent) of male-sterile (non-pollen-producing) plants in production fields. Such plants are used because they produce more grain than male-fertile plants. There are rarely, however, fewer than 50 billion pollen grains per acre. Assuming normal inheritance, each pollen grain from a pharma corn plant carries the potential to generate a pharma-producing corn kernel, whether in the field of origin or another (non-pharma) field.

Spatial and temporal isolation can be used to keep nearly all such pollen from reaching non-pharma corn plants when they have receptive silks, but it is impossible to ensure that all non-pharma corn plants within a mile of a pharma corn field have completed pollination when the pharma pollen is first released. Examples of non-pharma temporal or spatial “escapes” might include tillers of corn forming ears well after damage to the main plant has already occurred, areas of corn that are replanted after damage to the first planting has already occurred, and volunteer plants that germinate and emerge in nearby soybean fields.

Maturation and Harvest

Corn completes its grain-filling process at some point between early September and mid-October depending on planting date, hybrid maturity, and seasonal temperatures. Kernel moisture at this point is 30 to 35 percent, and the crop is usually harvested several weeks after physiological maturity, once kernel moisture has dropped to less than 25 to 27 percent.

The success of the harvest in removing all grain from the field is sometimes decreased by extensive stalk breakage and plant lodging, usually brought on by diseases that invade stalk tissue during the grain-filling process, weakening it significantly. Lodging tends to be worse under drought conditions, especially when pollination has been successful and plants have used up their carbohydrate reserves to fill kernels rather than help maintain stalk quality. Ears can also sometimes drop from the plant before the harvest. All of these problems increase harvest losses.

POINT OF VULNERABILITY:

Ears that fall to the ground because of stalk breakage or breakage of the shank (the short branch that holds the ear), as well as kernels shelled onto the ground or moved through the combine, all result in kernels left in the field that can potentially sprout and grow as volunteer plants in the succeeding year. The percentage of kernels left in the field that survive winter freezing is variable and usually small (less than one percent), but because harvest losses of 100,000 kernels per acre would be considered acceptably small, the potential number of volunteer plants the following year could be hundreds or thousands per acre.

Corn kernels typically do not survive for two years after the crop is grown, but volunteer plants can produce seed that can establish plants, thus keeping the original genetics in the field or in nearby fields for several years. If soybean follows corn, volunteer corn plants can usually be controlled effectively by herbicide.

POINT OF VULNERABILITY:

Experience has shown that it is almost impossible to clean every kernel or piece of kernel from a combine, or at least to do this on a routine basis. The only practical solution to this problem is to dedicate a combine to a particular pharma crop and not use it for non-pharma crops under any circumstances.

POINT OF VULNERABILITY:

Residue (leaves, stalks, roots, husks, cobs) left after pharma corn harvesting would likely contain the pharma gene of interest, though ideally the level of gene expression in such residue would be minimal. Corn residue following the harvest is essentially dead, so there is virtually no possibility that it could give rise to new plants, but the possible presence of a pharma product in the residue raises other concerns.

Most corn residue left in the field deteriorates over the course of two years or more, so much of the residue on the soil surface during the succeeding season remains recognizable. And depending on the pharma crop of interest, deterioration could be slowed by the presence of the pharma product in the residue. Therefore, allowing livestock to graze on residue after the harvest (though not common in much of the Corn Belt) would need to be strictly prohibited for pharma corn residue. Furthermore, if the pharma product is stable and soluble, it could leach out of the residue and run off the field during rainfall, perhaps moving into ground or surface waters.

Residue can also blow away in high winds. If a pharma product were allergenic, such windborne particles could become a public health problem. To help keep pharma corn residue in the field, it would be best to incorporate it into the soil, using a tillage implement that covers at least 80 percent of the residue with soil. The moldboard plow, set to cover almost all the residue, would be ideal, but in sloping fields the use of such an implement increases the chance of soil loss during rainfall. Removing pharma corn residue from the field after harvesting is not feasible; the large volume of residue would be difficult to manage, chances of unintended movement would increase, and a new disposal problem would be created once the residue is stored elsewhere.

Grain Drying and Storage

Most corn is harvested at 18 to 25 percent kernel moisture, and the grain needs to be dried to about 14 percent for safe storage. One method involves using a grain dryer, which moves heated air through the grain; if the weather is warm and dry and grain moisture is less than 20 percent, unheated air can sometimes be used. Grain dryers are either continuous-flow, with wet grain constantly being added and dried grain flowing out, or batch-type, where a quantity of grain is placed in the dryer and removed after it has dried. Most dryers keep the grain moving in order to dry it uniformly.

The other common method of grain drying is in-bin drying, in which a slotted floor in the grain bin holds the grain up and allows air (heated or unheated) to be pumped through it. Such systems typically have a lower drying capacity, which is matched to the quantity of grain that can be stored in the bin. If the grain is relatively wet, the bin might be only partially filled so the grain can dry faster and avoid spoilage.

In the Corn Belt, roughly half of the corn harvested for grain is stored on the farm, and the other half moves directly to an elevator or other collection point. Some producers store none; others store the entire crop in their own facilities. Most on-farm storage takes the form of cylindrical metal bins with conical tops and slotted floors as described above. A fan pumps air through these bins not only to dry the stored grain but also to help prevent temperature buildup and grain deterioration. The grain is usually moved using grain augers, and it is common (though not universal) for the grain to be passed over a rotating screen to remove weed seeds and broken pieces of kernels before storage.

Bins are usually monitored to see if the grain is staying free from mold and insect infestations.

Liquid insecticides are often used on interior surfaces before the bins are filled as a preventative measure, but if insects have already infested the grain, fumigants may be used to control their spread. The grain industry has standards regarding insects, mold, and foreign material, and failure to meet these standards results in price reduction when the grain is sold.

POINT OF VULNERABILITY:

The entire system of transporting grain to the dryer or bin, drying the grain, and storing it in previously used storage structures presents numerous points where cross-contamination between pharma corn and non-pharma corn could occur. Corn kernels or pieces of kernels can lodge in trucks, wagons, dryers, augers, and grain bins, thus carrying over to the next crop handled in the system. The only practical means available that would completely prevent this from happening would entail dedicating all grain-handling equipment and storage structures to a particular pharma crop, with zero tolerance for using such equipment with any other crop, especially non-pharma corn.

Soybean Production

In the American Midwest, soybean most often follows corn in the crop sequence. Some soybean follows wheat, either in the same year that fall-seeded (or winter) wheat is harvested, or planted the next spring. Some soybean also follows grain sorghum. Soybean following soybean usually suffers substantial yield penalties, in part because of a buildup of diseases and nematodes in the soil, so this practice is relatively rare unless weather prevents the timely planting of corn in the year following soybean. In such cases, soybean may be the crop of choice because its yield is decreased less than corn when planting is delayed.

Figure 5-4 depicts a timeline for soybean production operations in the U.S. Corn Belt, as well as points during the production process when the crop is vulnerable to cross-contamination between varieties (in this case, from pharma to non-

pharma soybean crops). Many of these operations and points of vulnerability are similar to those in corn, with the key difference being that soybean is almost completely self-pollinated, so large amounts of pollen are not released into the environment and dispersed to other soybean plants. While this biological difference decreases the overall vulnerability of non-pharma soybean to contamination by pharma soybean, it does not eliminate it.

Tillage

Corn residue left after the fall harvest is sometimes tilled using primary tillage equipment, and sometimes left undisturbed. No-tillage techniques have been found to work well in soybean, so more than one-third of soybean acres are now planted using no-till (CTIC 2002). To qualify as no-till, less than one-third of the soil surface can be disturbed prior to planting. In the spring, fields tilled in the fall are tilled again, while those left undisturbed are often planted directly, using a planter or drill equipped to plant through the heavy crop residue (as much as five to six tons per acre) left by a high-yielding corn crop.

POINT OF VULNERABILITY:

Tillage equipment used to till corn residue in the fall preceding soybean planting could move residue from pharma to non-pharma fields. Thorough steam cleaning of such equipment between fields should prevent such movement. Tillage associated with soybean residue is less problematic because it is not normally plowed in the fall and normally does not adhere to tillage implements the way corn residue does.

Seed Delivery and Storage

Most soybean seed is purchased from commercial seed companies, though it is possible for producers to keep seed from their own operations. However, soybean seed carrying transgenes (e.g., Roundup Ready™) is patent-protected and requires an agreement that the seed will not be kept.

Figure 5-4 **Timeline of Soybean Production Operations**

Symbols (*) indicate points of vulnerability to contamination through transfer of pollen or other plant material.

Month												
Sep	Oct	Nov	Dec-Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov
Corn Harvest*												
	Fall Tillage*											
			Seed Delivered to Farms*									
					Tillage*							
					Planting*							
						Weed Control						
								Pollination*				
										Soybean Harvest*		
										Grain Storage*		
Grain Storage (duration variable)												

Some companies are even moving to prohibit the keeping of seed of non-transgenic varieties, citing patent protection. In light of this development and the fact that only about 20 percent of the U.S. soybean crop is currently “conventional” (non-transgenic), within a few years there may be few soybean producers able to keep seed for their own production. Those who do often have it cleaned and germination-tested by third parties.

POINT OF VULNERABILITY:

Keeping and using pharma seed to plant regular production fields would be disastrous. Pharma soybean varieties would certainly carry patents for the pharma gene, and saving or selling such seed is already prevented by law (and often by specific, producer-signed agreements). This prohibition would need to be strictly enforced in order to prevent the planting of non-pharma seed in regular production fields, which could magnify any undetected contamination with pharma genes in

the parent seed. It will also be critically important to dispose of unused pharma seed using methods that render it impossible to use the seed for planting.

Like corn seed, commercial soybean seed is sold either in bags or bulk containers, though the three- to four-fold greater weight of seed required to plant an acre of soybean compared with corn has increased the use of bulk handling in soybean. Unlike corn, soybean seed is usually sold by weight rather than seed number—a typical unit of soybean seed is a 50-pound lined paper bag—but it has become more common for seed bags to include estimated seed counts (per pound, usually) to help producers plant by seed number. Most producers try to plant 180,000 to 200,000 seeds per acre, and at typical seed counts of 2,600 to 3,000 per pound, it takes 60 to 80 pounds of seed to plant one acre of soybean.

Soybean seed processed and sold by commercial companies is delivered to producers in the winter and early spring. Because soybean seed is considerably more vulnerable to quality deterioration (i.e., loss of germinability and vigor) during storage than corn, storage conditions must be appropriate. It is highly unusual for soybean seed to be stored more than one winter since it normally loses quality quickly within a year of its being harvested (at least when stored under ambient conditions).

POINT OF VULNERABILITY:

Soybean seed is seldom used as food by rodents due to its taste and anti-nutritional factors that inhibit digestion. Hence the danger of movement by rodents is low, and exposed or partially eaten seeds seldom germinate. Movement by rodents could be completely prevented by storing seed in rodent-proof containers until planting time.

To reduce the chances of human error, keeping pharma soybean seed stored in distinctly colored bags and a dedicated facility could reduce errors to zero. Bulk containers should probably not be used for pharma soybean seed due to the fact that they are not sealed as well as bags and can be reused, with the potential for a few unused seeds to carry over to the next seed placed in such containers.

Planting and Weed Control

Because soybean is less affected by planting delays than corn, it is almost always planted after corn planting is completed by an individual producer. As a result, soybean planting typically lags corn planting by about 10 days in the Corn Belt, starting in late April and usually ending by early or mid-June. Soybean plant development is affected by day length, so planting delays usually have less effect on the time of flowering and seed development—and hence on yield—than in corn.

More than 80 percent of the soybeans in Illinois are grown in rows less than 18 inches apart, whereas corn is grown in rows 30 inches apart

(IASS 2003b). These narrower soybean rows are about equally split between rows seven to eight inches apart, which are planted with a drill that is not also used for corn, and rows 15 inches apart, which are planted using the same planter as is used for corn. Soybean rows tend to be narrower than corn rows not only because soybean responds better to this arrangement but also because effective herbicides have relieved the need to cultivate soybean rows for weed control. Herbicides are often applied to soybean after emergence, and the crop is sometimes scouted for insects and disease (including nematode) incidence, but other mechanical operations between planting and harvesting are rare.

POINT OF VULNERABILITY:

With the recent increase in soybean planting using the same machine as corn planting, there is a slight increase in the risk of mixing corn seed with soybean. Such corn would act like volunteer corn except that it would come up in the row and relatively early, so it would be more easily seen and controlled.

Human error (e.g., failure to clean out the planter completely when changing the crop or variety, putting the wrong seed in one or more of the seed containers on the planter) would be a greater danger than mixing seed. As with corn, the use of dedicated equipment for pharma soybean production should completely prevent such errors.

POINT OF VULNERABILITY:

Corn is a common volunteer weed in soybean, usually growing from corn seed that was left in the field after the previous year's harvest. If such corn produces seed in a soybean field, that seed can emerge in the next year's corn crop, where it could cause genetic contamination. This occurrence would be rare due to the care that must be taken to remove volunteer pharma corn plants from soybean, but the spread of pharma corn pollen to a non-pharma volunteer corn plant growing in a soybean field would result in the introduction of the pharma gene into seed produced by that plant.

More commonly, moving tillage equipment from pharma fields to regular production fields could bring seeds and plant material as potential contaminants. Most tillage equipment can be carefully cleaned (usually

with steam) to eliminate any such carryover of plant material from one field to another.

In addition, if the previous corn crop was a pharma crop, corn volunteers in soybean might escape removal if they are inside the soybean canopy. The vegetative material from such volunteers could contaminate the harvested soybean crop.

Flowering

The U.S. soybean crop generally begins to flower as day length decreases following the summer solstice and, in the Midwest, it is common for the first flowers to appear sometime during July depending on temperature and cultivar maturity. On average, half the Illinois crop has reached first flower by mid-July, though this varies considerably by year. Most of the U.S. soybean crop is produced using indeterminate varieties, meaning that vegetative development and flowering continue concurrently for several weeks, and pods begin to develop on the lower stems before the last flowers appear at the upper nodes.

POINT OF VULNERABILITY:

Even though soybean is considered to be a self-pollinated crop, insect-mediated cross-pollination does occur. Caviness (1966) found “natural” percentages of insect-pollinated soybean as high as 7.7 percent, though pollen movement beyond five meters (5.5 yards) was uncommon. Boerma and Moradshahi (1975) used male-sterile soybean and found cross-pollination decreased to less than one percent at distances of 15 to 20 meters (16 to 22 yards) from the pollen source, and to about 0.4 percent beyond those distances.

Bees are known to visit soybean flowers (Jaycox 1970), however, which suggests that pollen can be carried as far as bees fly—a distance estimated at up to 10 kilometers (6.2 miles) (Visscher and Seely 1982). The absence of hives and wooded areas in which to live likely reduces the presence of honeybees in most soybean fields. While there is no known model of soybean pollination by insects, isolating pharma soybean from non-pharma soybean by a distance of one-quarter mile should come close to completely preventing pollen flow.

The flowering period is triggered by day length and lasts for several weeks within a field, compared with only about one week within a cornfield, so attempting temporal separation by planting pharma soybean at dates different from non-pharma soybean is not practical. A redundant safeguard of spraying pharma soybean fields with an insecticide that kills pollinator insects would help, but would be more disruptive environmentally than increasing spatial separation distances.

Harvest and Storage

Most seed growth occurs during August and early September, and physiological maturity, the dropping of leaves, and the drying of seed to the appropriate combine-harvest moisture level (13 percent or so) occur within the space of two to three weeks. In the central Corn Belt, corn and soybean are usually harvested with the same equipment and often at about the same time. If soybean seed becomes too dry, it can be easily damaged during or even before the harvest, reducing seed germination but not utility for processing. Most soybean seed can be stored without drying; storage structures and transport equipment are typically the same as those used for corn.

POINT OF VULNERABILITY:

Volunteer pharma corn plants can carry pharma genes into the soybean crop. This was the source of soybean contamination in the 2002 ProdiGene case in Nebraska. While corn plants that emerge early in the season can usually be seen and removed using herbicides or hand removal, volunteer corn plants can also emerge late and grow shorter than the soybean crop, thus escaping detection prior to harvest. Such corn plants do not produce seed, but if they are from pharma corn or corn pollinated by pharma corn, they will usually contain the pharma trait in their vegetative tissue.

Except in the unlikely event that corn and soybean would both be used to produce the same pharma product, pharma soybean should not be grown on land used in the past season to produce pharma corn. Growing any soybean at all on land used the previous season for pharma corn carries the risk of contamination by pharma

corn genes, as described above. Use of soil-applied, long-lasting herbicides to prevent corn from growing in soybean crops, coupled with a system of intensive, monthly monitoring during the soybean season to detect and remove any corn plants should reduce contamination by this route. Growing soybean in rows spaced 20 inches or more apart would also aid in this effort by making other plant species easier to see.

A more drastic solution would be not using the field at all the year following pharma crop production, instead keeping it as tilled or chemical (nonselective herbicide-treated) fallow in order to control any volunteer crops. In most foreseeable cases, such a drastic measure should not be necessary.

POINT OF VULNERABILITY:

As with corn, the use of harvest, handling, and storage equipment dedicated to pharma soybean production will be critical to preventing the contamination of production fields by pharma crops. Trucks and wagons used for transport could likely be cleaned adequately to use with other crops and non-pharma soybean, but inexpensive wagons reserved for pharma soybean could constitute a useful redundancy.

SUMMARY

Lack of wild or domesticated botanical relatives of corn and soybean within the main corn and soybean producing areas of the United States is a great advantage of using these two crops for pharma production. On the other hand, the very large and concentrated acreage of these crops in the American Midwest means that any pharma corn or soybean field is almost certain to be in close proximity to a non-pharma crop of the same species.

From a close study of the corn and soybean production systems used in the Midwest, the following conclusions are offered.

Reducing the contamination of commodity corn to virtually zero during the production phase within the U.S. Corn Belt is possible but would require both a large investment in dedicated equipment and coordination within a

large area, up to the size of an average county. Within such a zone, fastidious sanitation, coordination of planting times, and thorough and continuous monitoring of all corn fields (pharma and non-pharma) would be required to ensure no movement of pollen or seeds from pharma to non-pharma crops. Separate efforts of this magnitude would be required for each class of pharma products developed.

The expense of such an intensive program, along with the need to impose monitoring and coordination of practices on those who are not involved in pharma corn production (and do not share in the proceeds), are barriers of sufficient size to suggest that pharma corn production would be more efficiently carried out in naturally isolated zones. In the United States, these zones—where corn is (or could be) produced in very small areas, isolated by miles of arid or mountainous terrain—are located primarily in the west, in small pockets of irrigated land in the valleys of California, Colorado, New Mexico, Oregon, Washington, and Wyoming, and the Sandhills of Nebraska.

Where corn is already grown in such areas, yields tend to be high due to abundant sunlight and adequate irrigation. Crops other than corn (alfalfa, especially) are common in such areas now, and the absence of other non-pharma corn would be an inherent advantage. The use of equipment dedicated to pharma corn production would be necessary, even in isolated production zones. Ideally, though, pharma corn would be the only corn in the entire area, within at least 10 miles.

Under such a production scheme, growing the same pharma crop year after year would make sense and would relieve the need to fallow or otherwise try to manage crop residue, at least until a changeover to a novel pharma crop. Loss of yield expected from such continuous cropping can be minimized with irrigation.

Reducing the contamination of commodity soybean to virtually zero during the production phase is possible in the midwestern United States, even in areas of intensive soybean production, if multiple independent and redundant methods to restrict pollen movement and seed mixing are used. As with corn, marked and dedicated production, processing, and storage equipment would be needed for each class of pharma products, and continuous cropping of

the same pharma soybean varieties would be recommended. But the very limited natural cross-pollination in soybean means that spatial separation of pharma fields from non-pharma fields (research to determine this distance is needed, but it will probably be at least one-quarter mile) and the use of an insecticide at first flower to eliminate pollinating insects should be adequate to ensure virtually zero contamination of non-pharma soybean.

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Chapter 6

POST-HARVEST GRAIN HANDLING, STORAGE, AND SHIPPING IN CORN AND SOYBEAN

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As discussed briefly in Chapter 2, conventional post-harvest handling, storage, and shipping methods for commodity crops have been developed over many decades to enhance large-scale efficiency—not to ensure strict confinement. This chapter will describe these activities (which can take place either on the farm or at facilities further into the value chain) in detail, and systematically assess the points at which commodity corn and soybean are vulnerable to contamination by pharma crops.

According to our analysis, the conventional system of post-harvest handling, transport, and storage is vulnerable to contamination at so many points that it cannot be simply modified for use with pharma crops. Instead, we argue that a totally different system is needed to ensure against the contamination of our food and feed systems.

The implication of this analysis is that implementing a new system such as the one described below may be able to completely prevent contamination of commodity corn and soybean during handling, transport, and storage. We hope that recognition of the shortcomings in the conventional system—emphasized by the endemic nature of post-harvest mixing in corn and soybean production—will prompt the pharma crop industry to embrace a stand-alone system designed to achieve virtually zero contamination of the U.S. food/feed supply.

POST-HARVEST SYSTEMS, EQUIPMENT, AND FACILITIES

Conventional Corn/Soybean Systems

Before proceeding, it may be useful to define the three terms used in the title of this chapter.

Handling describes the moving or transfer of seed and grain from one piece of equipment to another (e.g., from a combine to a truck, from a truck into a storage facility, within a facility). Short-term transportation by truck between harvesting and on-farm storage is usually considered “handling” as opposed to “shipping.”

Storage refers to the long-term holding of seed and grain in a facility prior to its use for feed, food, or industrial purposes. Storage facilities include holding structures such as bins and silos that may have perforated floors to provide aeration of the grain in storage. Grain may be stored more than once between harvest and use.

Shipping refers to long-distance movement of grain. Transportation equipment used for shipping includes trucks, rail cars, barges, and ocean vessels. Shipping of grain is often the step between two different parties in a supply chain.

Before discussing potential pharma crop production and delivery systems, the following descriptions will help visualize systems currently in place.

Differentiation of Grains or Seeds in Agricultural Systems

The establishment of different grain and seed purity standards to meet end-user requirements has led to different grain-handling systems with

varying capacity for separation and segregation. Three broad categories exist in U.S. agriculture today: commodity grains, identity-preserved grains, and seed.

The **commodity grains** category is used when there are no requirements for differentiation among crop varieties. Commingling varieties from many different growers is common practice in commodity grain systems. Standards for commodity grains are defined by the U.S. Grain Standards Act (USGSA), administered under the U.S. Department of Agriculture Grain Inspection, Packers and Stockyards Administration (USDA GIPSA),³⁷ but within the commodity grain system, some grain intended for specific needs is processed according to more definitive standards than those set by the USGSA.

Identity-preserved (IP) grains are destined for food and feed products that require specific grain characteristics. Purchasers either sign contracts that dictate the production of individual varieties or groups of varieties with similar characteristics, or at the very least require some level of traceability to identified varietal sources. The USGSA standards form the basis of this kind of production but additional quality and varietal purity standards are applied by individual contracts.

There is a range of quality standards within the IP grain system, which are usually determined by specific agreements between end users and their suppliers. Some may be set with very high genetic purity requirements that may approach those that are standard in the seed industry.

Seed is used for planting in the production of commodity or IP grains. As described earlier, seed is grown and handled under strict segregation systems where complete traceability and quality standards are the norm. Depending on its pollination method, the seed crop is planted with some

degree of isolation from other sources of potentially contaminating pollen. Physical mixing of non-conforming seed is minimized by cleaning equipment between uses. Standards for seed purity and quality are set by the Association of Official Seed Certifying Agencies; not all seed is certified, but the seed industry uses these standards as a basis for both domestic and international trade.

The seed industry has the highest genetic purity and quality standards of the three systems, but even within that industry there is a range of company standards set to meet particular market niches. However, as we have already established, even these seed standards allow some level of cross-contamination.

Agricultural Crop Production and Delivery Systems

Most farmers grow two or more crops and more than one variety or hybrid of each crop. Planting, harvesting, handling, and storage equipment is usually used with more than one crop or crop variety during each growing season. Though some equipment is fairly simple, offering little opportunity for physical mixing of grains, other equipment is more complex and offers many such opportunities.

In the conventional grain-handling, storage, and shipping system, grain buyers and handlers, local and terminal elevators, and truck, rail, river barge, and ocean vessel transporting machinery all could be involved in moving a farmer's harvest to the final end user.

A value chain is a differentiated supply chain comprising a string of companies or collaborating players that work together to produce specific products or services. In crop agriculture, a value chain might include business entities such as seed or genetic supply companies and their representa-

³⁷ Additional information is available on the USDA GIPSA website (<http://www.usda.gov/gipsa/reference-library/standards/standards.htm>).

tives, farmers or growers, buyers and handlers of grain, and end users. This value chain requires teamwork governed by contractual arrangements between the various parties in the chain. A pharma crop production system also involves parties that form a value chain, but would need to be very restrictive in ownership control of seed and the resulting crop.

The link in the value chain formed by buyers and handlers has evolved over the last 10 to 15 years toward a more condensed system. Since this part of the chain is not involved in growing crops, potential contamination can only come from physical mixing.

Grain harvested on the farm might be delivered directly from the field at harvest time, or at some later time from on-farm storage. The first buyer could be a local elevator or cooperative that might specify delivery to a local facility or terminal facility (the second buyer). Corn and soybean grown in the temperate climates of the United States are planted in the spring and harvested in the fall, resulting in only one crop per year. The storage and delivery system serves the purpose of maintaining a year-round supply for end users.

Systems where traceability and quality assurance are important, such as the seed and specialty crops industries, may use equipment and facilities similar to the commodity grain industry. In these cases a strict management system is in place to control commingling and provide the traceability required.

Terminal elevators that receive grain from local elevators or directly from producers either supply end users nearby or river or rail transportation systems that ship the grain for distant use in the United States or for export. River terminals on the Mississippi, Missouri, Illinois, and Ohio Rivers

load barges destined for New Orleans, where the grain is transferred to ships for export. Great Lakes terminal elevators at Buffalo, Chicago, Duluth, Milwaukee, and Toledo serve markets through the St. Lawrence River. There is also increasing use of terminal grain facilities in the Pacific Northwest (at Portland, Seattle, and Vancouver) for corn and soybean destined for Asian markets. Most corn and soybean produced in the eastern and southeastern United States is used locally, but there are some minor exporting facilities in the Delaware/Maryland/Virginia area.

Certain facilities in this commodity crop system might be dedicated to pharma crops, but they would need to be stand-alone facilities. The production and movement of pharma crops will require changes in facilities, but more importantly will require changes in the thought processes and management programs applied to the systems.

IP products, such as seed and crops with specialty traits (other than pharma crops), are handled through systems designed to eliminate or minimize contamination of the product by outside genetic material (Hurburgh 1994). Pharma crop production and delivery systems may need to maintain genetic purity in the same way as IP products, but will also need to prevent the product from contaminating food and feed products.

Quality management systems have been developed in the seed and IP specialty crops industries to reduce or eliminate genetic contamination of the product being handled. Quality management systems for pharma crop products, on the other hand, must prevent contamination of both the product itself and other non-pharma crop (i.e., food/feed) products. The management strategies needed to achieve these goals will be different.³⁸

³⁸ The potential contamination of other products by the crop being handled has surfaced with the advent of genetically engineered crops. Concerns about contamination of the environment and food/feed products by DNA from genetically engineered products have been raised by scientists, environmentalists, and consumers following the introduction of such products. Even though the potential routes of contamination are similar, the methods of confinement would differ depending on the particular operation involved.

A Typical Elevator Facility

Elevator facilities (so named because of their extensive use of bucket elevators to move grain) are generally of two types: local and terminal. Local elevators are scattered throughout grain-growing areas around the world; in the United States, almost any town in grain-growing areas will have one or more. These facilities are usually the first buyer of grain in the value chain.

In the past, most local elevators had railroad access and much of the grain moved by rail. Many of the smaller U.S. rail lines, however, have closed within the last 20 years, leaving a large percentage of local elevators without rail access. Grain is now moved by truck to nearby elevators with rail access or to terminal elevators.

Terminal elevators are usually larger than local elevators and located at some sort of terminus such as a railroad spur, river or seaport, or nearby processing plant. Almost all terminal elevators have rail access for both incoming and outgoing grain. Ocean terminals are often huge facilities equipped to handle large quantities of grain rapidly—the ocean vessels loaded at these terminals are capable of carrying up to 55,000 metric tons (60,500 tons) of grain.

Most elevator facilities, whether local or terminal, have similar handling and storage systems (Berruto and Maier 2001; Herman, Baker, and Fairchild 2001) even though the layout of equipment and storage bins or silos may be different. (See Table 6-1 for descriptions of specific equipment.) It should be noted that elevator facilities, including all equipment and bins, require maintenance to remain in their proper working state. In addition to the mechanical wear on this equipment, grain is abrasive to all surfaces it contacts.

The flow of grain through an elevator, including points of vulnerability to contamination by pharma crops, is described below.

(* = point of vulnerability where physical mixing or escape of seed might occur)

1. As grain enters an elevator facility it is weighed, sampled, and tested for quality and grading*. The devices used for these procedures vary with the mode of transportation bringing grain to the facility and the volume being handled, but they are standardized and regulated by USDA GIPSA (1995). “Official” samples are obtained and graded by GIPSA-designated personnel.
2. Grain arriving by truck is dumped into a pit over which the truck drives*. Hopper-bottomed trailers dump their grain by opening slide gates in the bottom of the hoppers*. Flat-bottom trucks dump their cargo from the rear of the grain box with help from onboard hydraulics that tilt the grain box, or the entire truck (including the tractor) is tilted by a hydraulic platform inside the facility*.
3. Grain arriving by rail car is handled similarly, with slightly different equipment. Hopper-bottom cars dump their cargo into pits similar to a truck dump pit*, while flat-bottom cars are turned on their side so they can dump their load into a pit*.
4. The pit into which the grain flows has smooth, sloping steel sides that are virtually self-cleaning*. In the bottom of the pit is a flat-belt conveyor, auger, or chain-and-paddle mechanism for moving the grain from the pit to other conveyance equipment*.
5. Bucket elevators are used to elevate the grain* so it can flow by gravity into storage bins* or other transportation equipment. A distributor* that receives grain from a bucket elevator has a mechanism for selecting one of several round

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Table 6-1 **Descriptions of Seed- and Grain-Handling Equipment and Recommendations (*in italics*) for Removing Contaminating Grain**

TRANSPORTATION EQUIPMENT

Grain trailer (flat): a semi trailer that has a flat floor, sides four to six feet high, and folding doors at the back for unloading. Unloading is facilitated by either a hydraulic hoist on the trailer that raises the grain box, or a hydraulic platform in the grain facility that raises the entire truck (tractor and trailer). The top is open but covered with a tarp during transporting. *All joints, corners, crevices, and seams need to be inspected and cleaned. The tarp may need extra attention to remove DNA dust.*

Hopper-bottom grain trailer: a semi trailer with a floor sloped to either two or three sliding gates in the bottom for unloading by gravity flow. The top is open but covered with a tarp during transporting. A hopper-bottom grain trailer will hold 800 to 1,100 bushels of grain. *The corner joints, any riveted or welded seams, and sliding doors need to be inspected and cleaned after unloading to remove lodged grains.*

Hopper-bottom rail car: a rail car designed for transporting bulk materials including grain; it has a floor sloped to either two or three sliding gates in the bottom for unloading by gravity flow. The top is covered with large hatches that are opened for filling. A typical hopper-bottom rail car will hold 3,500 bushels of grain. *The corner joints, any riveted or welded seams, and sliding doors need to be inspected and cleaned after unloading to remove lodged grains.*

Ocean vessel (bulk): a ship or vessel with individual compartments called holds designed to transport bulk materials including grain. With proper separation, individual holds may be filled with different materials. Hold size generally ranges from 5,000 to 10,000 metric tons (5,500 to 11,000 tons). *At this point, bulk ocean vessels are not expected to be used for pharma crop transportation.*

River barge: a flat-bottom river vessel for transporting bulk materials including grain in groups called tows. Depending on the depth and width of the river channel, 9 to 15 barges will be lashed together to form a tow. Each barge holds about 52,500 bushels (1,500 metric tons or 1,700 tons). *At this point, barges are not expected to be used for transporting pharma crops. If they were to be used, the same inspection and cleaning procedures would be needed as with other transportation equipment.*

GRAIN-HANDLING EQUIPMENT

Auger (grain auger): a shaft with an attached flighting (a spiral steel or plastic appendage, or “fins”) that rotates within a tube and moves grain, either horizontally or at an angle, from a truck to a bin. Augers are used extensively in a combine to move the harvested grain from one position to another during the various operations within the combine, and are also used to move the grain from the combine grain tank to transporting equipment. *Augers are difficult to inspect and clean. This equipment would either need to be totally dedicated to pharma crop use or disassembled for inspection and cleaning.*

Chain and paddle: a mechanism utilizing a chain or cable on which steel, hard rubber, or plastic paddles are mounted. The chain or cable is a continuous loop with pulleys at each end; it is drawn through the bottom of a long hopper (commonly an elevator dump pit), which drags the grain out of the hopper, into a spout, and then into an elevator leg. *Depending on the design of this equipment, some disassembly may be required for inspection and cleaning.*

Charge bin: a bin used to help control grain flow rather than grain storage. Charge bins are always hopper-bottom bins, with a control slide gate in the bottom. Charge bins are commonly located overhead throughout a grain-handling facility in order to accumulate grain and then quickly discharge it into a transportation vehicle or evenly feed it into other grain equipment. *Charge bins have no moving parts (with the exception of slide gates), so all joints, seams, and corners, whether riveted, bolted, or welded, would need to be inspected and cleaned.*

Dump pit: usually a smooth steel hopper, either in or on top of the ground, that facilitates the transfer of grain from a wagon or truck into an auger or elevator leg. The grain is dumped by gravity into the pit and then moved from the pit horizontally into other conveying or elevating equipment. The unloading mechanism could be a “U-trough” auger, a flat-belt conveyor, or a chain-and-paddle system. *The corner joints and unloading mechanism need to be inspected and cleaned after unloading to remove lodged grains.*

Elevator leg: a vertical mechanism that moves grain in small containers (cups) attached to a continuous-loop flat belt. The belt is contained in two square tubes so that the filled cups move up one tube to dump their contents, then return down in the other tube. The two tubes are connected at the top and bottom with belt pulleys, which move the belt. The bottom connection contains a filling hopper for loading the cups, while the top connection contains an emptying hopper that transfers the grain from the moving cups to storage bins or other conveying equipment. *The filling and emptying hoppers as well as the cups attached to the belt must be inspected and cleaned of lodged grains after use.*

Table 6-1 **Descriptions of Seed- and Grain-Handling Equipment and Recommendations (*in italics*) for Removing Contaminating Grain** (CONTINUED)

Flat-belt conveyor: a continuous-loop flat belt that moves grain horizontally or at a slight incline. The belt runs in a shallow pan. *Only slight cleaning effort is required at the fill/distribution hopper and the discharge hopper.*

Grain distributor: a device located in a flow of grain, either at the top of an elevator leg or the end of a grain spout, that has the mechanical ability to direct the grain from one elevator leg or grain spout to a choice of several locations. These devices can usually be controlled remotely. *The grain distributor will need to be inspected and usually requires a minor cleaning as well.*

Grain dryer: a device designed to remove moisture from grain with artificially heated air. Many different types of grain dryers can be divided into two general categories: continuous flow and batch. The continuous-flow type dries a steady flow of grain as it moves through the unit, while the batch dryer dries a fixed quantity of grain, then is emptied and refilled with another batch. *Both types present similar problems with small amounts of grain potentially lodging or sticking in the dryer. Wet grain is prone to sticking to the perforated metal in the drying chamber. Some dryers allow easy access to the chamber for inspection and cleaning, while others have obstructions blocking access to the chamber.*

Grain spout: a round steel spout that directs the flow of grain moving by gravity from one piece of equipment to another (or to a storage bin). Since the process of moving grain is abrasive, spouts are commonly lined with a durable material such as glass, dense plastic, or rubber. *Spouts are generally self-cleaning, but the transfer points into and out of the spout may need to be checked or cleaned.*

Hopper bottom: the bottom of bins or hauling equipment designed on a slope rather than flat. The sloping bottom of a cylinder would be conical, while a square or rectangular shape would have four sloping sides converging on a slide gate in the center. The slide gate holds the grain in the vessel or controls the flow during the emptying process. *The hopper bottom, any joints, and the slide gate need to be inspected and cleaned.*

Slide gate: a steel gate, sliding in grooves on either side of the opening and supported by rollers, used to control the flow of grain from a bin or hopper bottom. When the gate is closed there is no flow through the opening; the gate can be opened incrementally to match the flow of other equipment such as elevator legs or processing equipment. Slide gates are used in hopper-bottom grain trailers and hopper-bottom rail cars as well as stationary equipment and bins in a grain facility. Small gates may be opened and closed by hand crank-operated ratchets, while large gates are usually moved by hydraulic power. Some may be controlled remotely. *The slide grooves need to be inspected and cleaned.*

GRAIN STORAGE FACILITIES AND STRUCTURES

Concrete silo: a large, cylindrical concrete structure with one end mounted on a concrete base and the other covered by a conical roof. The sides of the bin are reinforced with steel rods embedded in the concrete to add structural strength. In grain elevator facilities, concrete silos are built in clusters with distribution systems designed to fill the silos at the top of the cluster and unloading mechanisms in tunnels underneath the silos. (Also see **grain bin or silo**.) *All joints, walls (grain tends to stick to concrete walls more than steel), and any handling equipment will need to be inspected and cleaned.*

Elevator facility: a grain-handling facility that uses a combination of equipment to move, transfer, and store grain. The facility may perform several tasks including the transfer of grain from one mode of transportation to another, long- or short-term storage of grain, and the merchandising of grain. *The individual components of an elevator facility would need to be inspected and cleaned as indicated for those components.*

Flat storage building: a large, flat building used for storing grain. These buildings look like any warehouse building from the outside. They may be filled and emptied by portable grain-moving equipment, usually when filled once a year. More sophisticated systems may include spouting from higher elevator facilities, overhead flat-belt conveyors for filling, and flat-belt conveyors mounted in tunnels under the building floor for emptying the storage space. *All individual components of the system would need to be inspected and cleaned.*

Grain bin or silo: a storage structure designed to hold grain and protect it from weather for a period of time. There are many types of bins constructed of various materials. A common type is a round, cylindrical corrugated-steel structure, which may have a perforated floor to facilitate aeration of the grain during storage. The roof at the top of the cylinder is conical and has weatherproof air vents to allow air to enter or exit, and a fan assists in the aeration process. *The floor and walls of the bin must be inspected and cleaned to ensure that no grain has lodged in cracks between the steel sheets of the walls or flooring.*

Steel bin: a large, cylindrical steel structure with one end mounted on a concrete base and the other end covered by a conical roof. The steel sides of the bin are usually corrugated to add structural strength. (For recommendations for removing contaminating grain, see **grain bin or silo**.)

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steel spouts, which deliver grain, by gravity, to a specific location.

6. There are several types and designs of storage bins*; large, cylindrical steel bins are most commonly used at local elevators. Large, round concrete silos, built in clusters, are common at large local elevators and terminal elevators. Flat storage buildings, which are more difficult to fill and empty, are used for long-term storage at any of these facilities. Any bin type might have a hopper bottom to facilitate the emptying of grain. “Charge bins,” for example, are hopper-bottom bins located overhead throughout a grain-handling facility* to accumulate grain and quickly discharge it into a transportation vehicle or to provide a continuous flow of grain to a specific piece of equipment. Export facilities refer to these bins as “shipping bins.”
7. Bin-unloading equipment is usually a combination of augers, flat-belt conveyors, elevators, and spouts designed to move grain from the storage bin to the next step*.
8. Truck, rail car, river barge, or ocean vessel loading also involves a combination of such handling equipment, which moves the grain into the outgoing mode of transportation*.
9. The outgoing grain is again weighed, sampled, and tested to ensure that specifications are met.
10. The above equipment and the flow of grain throughout the system are often controlled by push buttons that start and stop equipment and move deflection gates. Sensing devices tell the operator that equipment is functioning, grain is flowing, and bins are filled to certain levels.

A grain elevator facility is designed to efficiently move and handle grain so that little physical

effort is required of elevator employees (other than pushing control buttons and observing the process). The facility is designed to allow flexibility in terms of the source and destination of the grain, and to permit the blending of different qualities—and sometimes even different types—of grain in order to make the product needed for the next phase in the supply chain (Berruto and Maier 1999).

POINTS OF VULNERABILITY TO PHARMA CROP CONTAMINATION

Every point of transfer from one piece of equipment to another provides an opportunity for seeds to escape confinement. In a conventional grain system as described above, there are innumerable places where this might happen. These systems were designed for the efficient handling of grain without concern for how small amounts of spillage or seeds lodged in the equipment could contaminate other grain handled by the same equipment in the future.

Table 6-2 (p. 96) lists the steps in the post-harvest components of a grain industry value chain, along with potential points of vulnerability to contamination.

The handling of bulk grain differs from moving a liquid through a system of pipes and vessels. A liquid can be pumped and totally contained within the transport system, and its movement can be controlled by completely enclosed valves. Such a system can be “flushed” with an appropriate cleaning liquid between uses and effectively sanitized.

Bulk grains, on the other hand, must be moved by some physical means of pushing or lifting (e.g., augers, elevator buckets, conveyor belts, paddles on a chain or cable). Since all of these moving parts require maintenance, they must be accessible. Depending on the specific piece of equipment, its physical surfaces may provide places for individual grains to become

Table 6-2 **A Typical Value Chain in the Grain Industry**

Symbols (*) represent points of vulnerability to contamination through dispersal of seeds or other plant material.

Production Phase ¹	Steps Involved ²	Equipment/Facilities ³	Transfer Points ⁴	Possible Steps to Eliminate ⁵
Seed production	Crop breeder	The equipment used in the seed multiplication and production steps is very similar to the field production process, with the addition of conditioning plant facilities. The considerations would be the same.		
	Foundation seed producer			
	Commercial seed producer			
Field production (production agriculture)	Field isolation planning	No exposure at this point		
	Seed procurement	Seed bags	Broken bags must be repaired and cleaned up*	
	Planting	Planting equipment	From seed container to planter*	
	Growing		Washouts must be observed and corrected*	
	Harvesting	Harvesting equipment	Spillage during harvest* From combine to hauling equipment*	
	Delivery to storage	Trucks or wagons	From hauling equipment to handling equipment*	■
	Storing (on farm)	Transfer equipment Bins or silos	Dumping from hauling equipment to transfer* From transfer equipment to bin*	■ ■
Delivery	Transfer equipment	Dumping from storage to transfer*	■	
Transportation	Pickup	Transportation equipment	Transfer to transportation*	
	Transport	Truck or railcar	Spillage during transport*	
Intermediary handling & storage	Receiving	Dump pit or other Elevator leg or other Conveyor or spout	From transportation to receiving pit* From pit to elevator leg* From elevator leg to conveyor or spout*	■ ■ ■
	Storage	Storage bin or silo	From conveyor or spout to bin*	■
	Remove from storage	Conveyor or auger Elevator leg or other	From bin to conveyor or auger* From conveyor to elevator leg*	■ ■
	Conditioning	Conditioning equipment	Complex handling and conditioning equipment*	■
Processor	Receiving	Dump pit or other Elevator leg or other Conveyor or spout	From transportation to receiving pit* From pit to elevator leg* From elevator leg to conveyor or spout*	
	Storage	Storage bin or silo	From conveyor or spout to bin*	
	Remove from storage	Conveyor or auger Elevator leg or other	From bin to conveyor or auger* From conveyor to elevator leg*	
	Processing	Processing equipment	Complex handling and processing equipment*	

1 The major phases in the value chain of pharma crop production, including seed development and production, on-farm production, handling/storage/shipping, and pharmaceutical processing. In many cases, each phase will be performed by a different party or business entity.

2 The potential steps involved; in some cases, one party might perform several of the steps shown.

3 The equipment or facilities that might be utilized in each step.

4 Points where the seed or pharma crop product might be transferred from one piece of equipment to another, or other points of vulnerability.

5 Steps that might be eliminated in a pharma crop production and delivery scheme.

lodged. To clean the equipment sufficiently between uses requires that it be at least partially dismantled, then cleaned and inspected.

Similar equipment used in the seed and IP industries has either been designed to minimize or eliminate spillage and be self-cleaning, or has been modified to provide these features. These modifications, while providing more precise handling with less spillage and easier cleanup between batches, do not totally eliminate the potential for physical mixing. Even the seed and IP industries' minute tolerances for mixture would not be acceptable under a virtually zero contamination standard for pharma crop production and delivery.

The vulnerability of grain-handling systems to contamination is a result of inherent equipment and facility design weaknesses, the potential for human error in operating the facilities, and inadequate infrastructure management systems. A study at the Manhattan, Kansas, elevator facility of the United States Department of Agriculture's Agricultural Research Service Grain Marketing and Production Research Center (Ingles, Casada, and Maghirang 2002) found there was considerable commingling of two different types (colors) of corn for a period of time following the change (without cleaning) to the other type.

This study did not attempt to determine the degree of commingling if the facility had been cleaned between the two types of corn. The point is that "flushing" the old grain with the new grain is not sufficient to maintain genetic purity.

A NEW HANDLING, STORAGE, AND TRANSPORT SYSTEM FOR PHARMA CROPS

Two strategies must be pursued to achieve virtually zero contamination in post-harvest corn and soybean systems. First, the equipment used for storage, shipping, and handling must be dedicated so different types of grain remain separated.

Second, management systems must be modified substantially to ensure that virtually zero contamination is attained and maintained in routine operations.

Equipment and Facilities

The discussion in this chapter has shown that the current commodity corn and soybean handling, storage, and shipping system cannot be used as a pharma crop system because of the large number of points of vulnerability and the difficulty in managing such a system. But a new system based on equipment and/or facilities exclusively dedicated to the processing of pharma crops may have the potential for attaining virtually zero contamination if operated under proper management systems.

Using facilities that are currently part of commodity grain systems or seed and IP crop systems for pharma crop production and delivery would require one or more of the following:

- Dedication of equipment and facilities to pharma crop use exclusively
- A comprehensive sanitation system for dismantling, cleaning, and inspecting equipment and facilities
- A management system that establishes protocols for total confinement methods

To eliminate points of vulnerability, the supply chain should have as few steps as possible. Ideally, a pharma crop system would deliver the grain directly from the harvesting operation to the pharma crop processing facility using dedicated handling and transportation equipment. In small-scale pharma crop systems, this would probably be the method used.

In large-scale production, where many acres of production and possibly many contract growers could make this method impractical, a grain

handling and storage facility might be dedicated to strictly long-term pharma crop use, with the pharma crop processing plant built on the same site or nearby. The pharma crop would again be delivered directly from the harvest to the dedicated handling, storage, and processing facility.

Using on-farm storage facilities for the pharma crop would require dedicated handling systems and bins on the farm. Ideally, the pharma crop handling and storage system would be a stand-alone system located a specific distance from other on-farm grain-handling facilities.

Innovative ideas to reduce points of vulnerability such as using modified export containers for grain drying, storage, and transportation could eliminate several steps in a value chain. Export containers, in either 20- or 40-foot lengths, are easily sealed to provide security and could be modified with perforated floors to dry and aerate the grain. These containers are similar to semi trailers (without chassis and wheels) and could each be loaded with 20 to 40 metric tons (22 to 44 tons) of grain. Grain could be loaded into the containers directly from the harvest combine and, with aeration/drying capability, could remain in the container until delivered to the end-use facility.

Management Systems

The successful management of a pharma crop confinement system will require a completely different way of thinking about grain handling, storage, and shipping than is customary with commodity crop systems. A formal, structured management system would be appropriate, but a system specific to the requirements of pharma

crops is as yet undeveloped. Several models that could form the basis of such a confinement management system are discussed briefly below.

Quality management systems such as the International Organization for Standardization (ISO) 9001:2000³⁹ and the USDA GIPSA Process Verification Program⁴⁰ are well established. The ISO9000 family of standards, originally adopted in 1987, was revised in 1994 and again in 2000. The ISO9001:2000 standards provide guidance on quality management for a broad range of businesses, and for those businesses that become “registered,” the standards provide third-party oversight and auditing through accreditation organizations. The USDA GIPSA Process Verification Program is based on ISO9001:2000, but participants are USDA GIPSA-certified rather than ISO-registered.

Environmental management systems are currently characterized by ISO14001:1996, part of the ISO14000 family that evolved following a 1992 United Nations conference on the environment. The management of an organization’s environmental activities, or what the organization does to minimize its harmful effects on the environment, can be handled with a stand-alone ISO14001:1996 system or incorporated into an ISO9001:2000 quality management system that encompasses both quality and environmental management.

Food safety management systems were formalized with the Hazard Analysis Critical Control Points (HACCP) program, which was initiated in the 1960s to provide systematic food safety checkpoints for providers to the U.S. military. Though

³⁹ The International Organization for Standardization (ISO) is a worldwide federation of national standards bodies, currently comprising 140 members (each from a different country). ISO promotes the worldwide development of standardization and related activities to facilitate the international exchange of goods and services and develop cooperation in intellectual, scientific, technological, and economic spheres. The results of ISO technical work are published as International Standards. For more information, see <http://www.iso.org>.

⁴⁰ USDA GIPSA offers a Process Verification Program to meet the grain industry’s evolving needs. For more information, see <http://www.usda.gov/gipsa/programs/gis/inspwgh/processver/processv.pdf>.

this system is currently being adopted into the ISO family of standards as ISO22000 (draft form), it had already been used to identify points of vulnerability both as voluntary industry practice and as a mandatory process in some cases for many years.

Designing a Confinement Management System

The broad ISO family of standards represents an international consensus on good management practices that will ensure an organization can repeatedly deliver products and services or meet specified requirements. These practices have been distilled into sets of standardized requirements for management systems applicable to any organization.

ISO management systems can provide a model for the development of a pharma crop confinement management system. Such a system would provide strict protocols for managing the *processes* involved in pharma crop production, not the product itself. The system would be certified or registered by a third party and audited regularly.

The Hazard Analysis Critical Control Points (HACCP) system might be adapted as follows:

Confinement Analysis Critical Control Points⁴¹

- Principle I: Conduct a confinement analysis
 - A. Physical—physical mixing
 - B. Biological—pollen and/or gene flow
- Principle II: Identify critical control points
- Principle III: Establish critical limits for each critical control point
- Principle IV: Establish monitoring procedures
- Principle V: Establish corrective actions

Principle VI: Establish record-keeping procedures

Principle VII: Establish verification procedures

The design of a confinement management system will require innovation and creativity, as the goal of virtually zero contamination is somewhat outside quality management system or HACCP protocols. Once such a system is developed, it should be emphasized that it provides a structure from which individual organizations can develop systems that fit their needs exactly; it is not intended to be a “one-size-fits-all” document.

Keeping outside contaminants from entering the system is a different matter than preventing a product from contaminating other products. A system designed to achieve the latter goal might be similar to what a hospital uses to ensure that disease is not spread. Therefore, the development of a confinement management system that offers protocols necessary for this task will be considerably different than one designed to maintain a product’s purity.

SUMMARY

The conventional post-harvest handling, storage, and shipping systems for corn and soybean, if used together as a pharma crop system, are inadequate to achieve virtually zero contamination of the food/feed systems by pharma versions of corn and soybean.

The conventional post-harvest systems for seed, IP crops, and commodity crops are primarily concerned with contamination of those products from the outside, but pharma crop systems must also be concerned that seed, IP crop, and

⁴¹ The Council for Agricultural Science and Technology (CAST) provides updates on the status of agricultural science and technology programs. According to an article (Cline 2003) on the CAST website, a Plant-Made-Pharmaceuticals Industry Working Group, coordinated by the Biotechnology Industry Organization, has developed an industry reference document on confinement.

commodity production not be contaminated by the pharma crop. Thus, conventional and pharma crop supply chains must be totally separated. A new system for pharma crop production and delivery is needed.

The requirements of a new post-harvest handling, storage, and shipping system for pharma crops can be summed up in three statements:

- Eliminate as many steps as possible.
- Dedicate equipment and facilities.
- Implement a structured management system to guide long-term decisions and day-to-day operations.

The problems inherent in the conventional commodity system should not cloud the design of a streamlined system that eliminates as many points of vulnerability as possible. Management system design for pharma crop production will require thinking “outside the box,” not just modifying the commodity system for this application. In other words, a management system for the production of pharma corn or soybean needs to be designed from the ground up.

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*Chapter 7***ALTERNATIVE PHARMA CROPS**

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The major concerns about the use of corn and soybean as pharma crops derive from their wide use for food and feed. This report has detailed the numerous points in the commodity grain system at which pharma versions of these crops could contaminate food and feed crops and the substantial effort that would be required to block that contamination. Thus, the question arises whether there are alternative crops that could be used in pharma crop production.

While the topic is beyond the scope of this report, this chapter addresses it in a preliminary way.

DESIRABLE CHARACTERISTICS OF PHARMA CROPS

1. The paramount characteristic is that the crop should have little use as a food or feed crop; an ideal pharma crop would have no role as either. Crops not used for food or feed would present few opportunities for contamination of the food and feed supply. Unfortunately, few crops are produced solely for non-food/feed purposes. All five of the world's major commodity crops, for example, are substantially or primarily used for human food.

Wheat and rice are used mostly for food in all parts of the world. Corn is used primarily as a food crop in the developing world, but in the United States, it is predominantly a feed crop with some important food (e.g., high-fructose corn syrup) uses. Soybean is primarily a source of oil (food) and protein (feed), but it also has other

food uses. Cotton is grown primarily for industrial (fiber) purposes but also has feed (protein) and food (oil) uses. Thus, pharma crops will have to be found among those relatively rare crops used primarily for industrial purposes or among plants not yet adapted to agricultural use.

2. The crop should lack sexual reproductive organs or be amenable to processes that restrict pollen and seed dispersal. Even where pharma crops are not food crops, the dispersal of genes through pollen and seeds to other crops or wild plants is undesirable. The best pharma crop candidates would be plants that are entirely propagated vegetatively, or which produce pharma proteins in vegetative organs (e.g., leaves) that can be harvested before the appearance of any reproductive structures.

Biological barriers to dispersal by pollen or seed would enhance the attractiveness of candidate plants. A self-pollinated reproductive system is preferable to a cross-pollinated system (though not sufficient). The availability of male sterility mechanisms, such as cytoplasmic male sterility, is also desirable, as is the absence of interfertile wild or weedy relatives.

3. The organ or tissue in which the pharmaceutical or industrial compound is produced should be easily stored and amenable to drug purification. The pharma compounds should be easily extractable without interference or contamination by other, natural metabolites in the organ or tissue in which the compound is produced. In addition, a plant tissue or organ that can be stored gives manufacturers flexibility. The availability of tissue-specific promoters to direct production in

tissues that are not harvested for food or feed and not involved in reproduction (i.e., pollen, fruits, and seeds) would also be advantageous. For example, one could envision the production of pharma compounds in the leaves of potato plants but not in their tubers.

4. Appropriate production infrastructure should be available. The ready availability not only of the necessary equipment for planting and harvesting but also knowledge of the best production practices would shorten the time needed to develop new pharma crops.

5. The molecular information and tools needed to direct the production of pharma compounds at desired levels in the intended tissue should be available. This includes the availability of a transformation system to create transgenic plants, information about sequences necessary to direct tissue-specific expression, and knowledge of codon usage to ensure efficient expression by the cellular machinery. Maximizing gene expression can increase yields and minimize the land area necessary for pharma crop production.

The following paragraphs discuss three possible alternative pharma crops in the context of

these five characteristics. Table 7-1 summarizes the extent to which each crop possesses the five characteristics.

Tobacco (*Nicotiana tabacum*, Solanaceae)

Use as a food crop. Tobacco is not used for food or feed, but is used in various products that humans inhale or inadvertently ingest.

Restriction of reproductive structures.

The feasibility of leaf production reduces dispersal by seeds and pollen (i.e., plants can be harvested before flowering). Gene flow could be further reduced if expression of pharma transgenes were excluded from the seeds. Tobacco is a self-pollinating crop with no known sexually compatible wild relatives in the United States. It does not readily establish free-living populations, although it may sometimes—as in Hawaii—escape cultivation (Cramer, Boothe, and Oishi 1999; Keeler, Turner, and Bolick 1996). Male sterility can be introduced via sexual crosses with wild *Nicotiana* species (for example, Nikova and Vladova 2002) and has been genetically engineered via the nuclear genome (Mariani et al. 1990).

Table 7-1 **Three Potential Alternative Pharma Crops**

Potential Alternative Crop	Non-Food/Non-Feed	Potential Pharma Compound Production Organ	Naturally Occurring Bioconfinement		Production Infrastructure	Molecular Information		Minimum Time to Pharma Production
			Reproductive System	Crossable Relatives		Gene Expression	Engineered Nuclear/Chloroplast DNA	
Tobacco	Yes/Yes (but ingested by smokers, other tobacco users)	Leaves	Selfing and maternal inheritance of chloroplast	Not in the United States, except escapes from cultivation (e.g., Hawaii)	Well developed	Extensive	Yes/Yes	Immediate
Guayule	Yes/Yes	Stem/leaves	Partial apomict	Yes	Some development*	Limited	Yes/No	5–10 years
Jojoba	No/Yes	Seeds Stem/leaves	No: male and female flowers on different plants	No	Some development*	Limited	No/No	More than 10 years

*Guayule has only been produced experimentally under contract from the United States Department of Agriculture for subsidized rubber and resin extraction. Jojoba was grown extensively by private farmers in southern California and southern Arizona as a liquid-wax seed crop, but the market was not developed for anything other than cosmetics. It is still grown commercially to some extent. (Personal communication with J.G. Waines, professor of genetics and Director of Botanic Gardens, Department of Botany and Plant Sciences, University of California, Riverside, October 11, 2004.)

Ease of drug purification. Pharma production in tobacco would likely take place in the leaves because the seeds are very small. This may or may not be a disadvantage, depending on whether the pharma compound can be stored in dried leaves. Although many tobacco varieties produce high levels of alkaloids (potential contaminants), there are low-alkaloid varieties that can be used for the synthesis of pharmaceutical proteins. Moreover, alkaloids are easily separable from proteins during purification.

Availability of production infrastructure. Tobacco is an excellent biomass producer (in excess of 40 tons of leaf fresh weight per acre based on multiple harvests per season) and a prolific seed producer (up to one million seeds per plant), thus hastening the time in which a product can be scaled up and brought to market (Cramer, Boothe, and Oishi 1999). The existence of large-scale processing infrastructure is yet another advantage for tobacco.⁴²

Availability of molecular tools. Tobacco is easy to genetically engineer and is widely used as a model system to test the suitability of plant-based expression systems for producing therapeutic proteins and other transgene products. In fact, more transgenes have been introduced into the tobacco chloroplast or nuclear genomes than all other crop species combined. Fischer and Schillberg (2004) provide a recent list of pharma products produced in transgenic tobacco plants.

Both nuclear and chloroplast genomes have been transformed with very high efficiency, and several methods of genetic modification are readily available (Daniell 2002; Daniell, Khan, and Allison 2001). Because chloroplast genomes are inherited predominantly through the female parent (Daniell 2002), the ability to splice pharma transgenes into chloroplasts limits the spread of the trans-

genes by pollen. The high levels of transgene expression via the chloroplast genome also minimizes acreage. For example, it has been recently shown that one acre of chloroplast transgenic tobacco plants could produce 400 million doses of anthrax vaccine (Watson et al. 2004). Seed sterility has also been developed in tobacco (Odell, Hoopes, and Vermerris 1994; Russell, Hoopes, and Odell 1992).

Overall, tobacco is the best prospect for an alternative pharma crop.

Guayule (*Parthenium argentatum*, Asteraceae, pictured on back cover)

Use as a food crop. There are no known food or feed uses for this crop, which is the only crop other than the rubber tree that has been grown successfully on a commercial scale for the production of rubber (Estilai, Naqvi, and Waines 1988; Mooibroek and Cornish 2000). Like the rubber tree, latex is extracted from the bark of guayule stems (Kuruvadi and Jasso de Rodríguez 1993).

Although commercial guayule operations have not had long-term success, the plant has recently received new attention because its latex may be less allergenic than latex from the rubber tree (Cornish and Siler 1996). Additional uses for guayule have also been recently identified; its fibers, for example, have been found to have insecticidal and fungicidal properties. The composite wood made from the residues remaining after latex extraction resists termite and wood-rot damage.

Restriction of reproductive structures. This plant is a small perennial shrub adapted to the hot and dry conditions typical of the Chihuahua desert on both sides of the U.S./Mexico border (University of Arizona 2004). Although guayule exists as both diploids and polyploids within the

⁴² See, for example, Large Scale Biology Corporation's website (<http://www.lsb.com/cgi-bin/content.cgi?p=agriculture&n=business>).

species, tetraploids ($2n=72$) are the most common and usually the largest and most productive form. Guayule is partially apomictic (see Chapter 3) and can have both sexually and asexually formed seeds on the same plant. The type of reproduction may be under environmental control.

There are some 15 related species, several of which may hybridize with guayule (Rollins 1946; West and Waines 1988). Latex content of the stem varies from 1 to 10 percent.

Ease of drug purification. There is no information on the ease of purifying pharmaceuticals from the guayule plant.

Availability of production infrastructure. The agronomic characteristics of guayule need to be improved. For example, seed shattering at maturity is still a common occurrence. There are no commercial varieties available, but improved interspecific germplasm with increased above-ground biomass yield has been developed (Estilai 1991; Estilai et al. 1992; Ray et al. 1999). Several agronomic aspects have been investigated, such as regrowth capability following harvest (Estilai and Waines 1987), oil and rubber production (Estilai 1993), and response to irrigation (Rodríguez-García, Jasso de Rodriguez, and Angulo-Sanchez 2002). Although production infrastructure is limited, there is interest in and experience with growing this crop (Purdue University 2004).

Availability of molecular tools. Guayule can be transformed by *Agrobacterium* (Pan et al. 1996).

Adoption of guayule as a pharma crop would probably require at least 5 to 10 years before full production.

Jojoba (*Simmondsia chinensis*, Simmondsiaceae, pictured on back cover)

The jojoba plant is a shrub reaching up to 15 feet in height, native to the Sonoran Desert, and

adapted to dry and hot conditions. Individual plants have a lifespan of 100 to 200 years.

Jojoba is an oilseed crop with up to 50 percent of its seed weight consisting of vegetable oil with unusual properties. Specifically, jojoba oil is a polyunsaturated liquid wax of a type not easily synthesized commercially. The only other source for this kind of oil is the sperm whale, which was once killed in great numbers for its oil. A ban on the importation of sperm whale oil led to the discovery that jojoba oil is in many ways superior (Stephens 1994; Undersander et al. 2000)—it has high viscosity, a high flash and fire point, high stability, low volatility, and is non-toxic, biodegradable, and resistant to rancidity.

Use as a food crop. Jojoba has a few food uses; it is primarily an industrial and feed crop. Its oil has been formulated into lubricants, cosmetics, pharmaceuticals, waxes, animal feed supplement (20 to 30 percent protein content of oil-less meal), and animal browse food. A small percentage of commercial production is used for salad oil, vegetable oil, and shortening. American Indians have long eaten soft-skinned jojoba nuts; the roasted nuts smell and taste like roasted coffee beans (Stephens 1994).

Restriction of reproductive structures. Pharma compounds would most likely be produced in seeds, although pollarded,⁴³ aboveground biomass is a possibility. Confinement may be problematic for this species because it is cross-pollinated. Individuals are either female or male, the pollen is distributed by wind, and only 8 to 10 percent of the plants need to be male for sufficient pollination. On the other hand, natural distribution is restricted to parts of southern California, southern Arizona, and northwestern Mexico.

⁴³ A pollarded plant is one whose branches have been cut back to promote a dense growth of new shoots.

Ease of drug purification. There is no information on the ease of purifying pharmaceuticals from the jojoba plant.

Availability of production infrastructure. Selection of jojoba clones with high yields and early seed production has been performed in several countries. Frost-resistant clones have been selected in Australia and the United States. Clones with different chilling requirements have been selected in Israel. Since seedlings are heterozygotes, the genetic variability is vast, and selection for desirable agronomic traits can be done in seeded plantations if necessary (Benzioni 1997; Milthorpe 1998). Increase of desirable genotypes by vegetative propagation is easy. However, production infrastructure may be limited.

Availability of molecular tools. There is limited molecular information available for jojoba.

Overall adoption of this crop for pharma production would require more than 10 years of research and development.

FINAL CONSIDERATIONS

The three crops discussed here were not chosen based on a comprehensive analysis and

should not be considered the only crops potentially useful as pharma crops. A thorough search would undoubtedly turn up a number of additional candidates. This discussion was simply intended to illustrate the fact that non-food and non-feed crops are available as candidates for pharma crops and to suggest the complexity of selecting crops for further development.

It is clear that some of the selection criteria can be mutually contradictory. For example, the use of seeds as a pharma production organ conflicts with the need to decrease dispersal by seeds.

Finally, to the extent that pharma crops are sought among non-domesticated or wild plants, it is important to note that such plants may have their own disadvantages. Compared with domesticated crops, for example, wild plants are usually better able to distribute their seeds. Wild plants also generally have lower seed yields than their domesticated counterparts.

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Chapter 8

SYNTHESIS, CONCLUSIONS, AND RECOMMENDATIONS

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Transgenic pharmaceutical crops produce compounds intended for use as pharmaceuticals and transgenic industrial crops produce compounds for use in industrial manufacturing processes. Some of these industrial compounds have pharmacological properties and can be used to produce pharmaceuticals. In this report, we have referred to both pharmaceutical and industrial crops as “pharma” crops.

There is a broad consensus that the transgene products of pharma crops must be kept out of the human food and animal feed systems. Although we have concentrated our analysis on these systems, similar principles and parallel issues will be needed to protect the forage supply.

Several approaches to protecting the food and feed supplies from contamination by pharma crops have been suggested (e.g., a ban on using food and feed crops to create pharma crops, a case-by-case assessment of the risks of particular pharma crops in particular contexts). In this chapter, we summarize our arguments about the advantages and disadvantages of these approaches, and highlight our key findings and recommendations.

Conclusion #1

There is a broad consensus that the transgene products of pharma crops must be kept out of human food and animal feed systems. At the present time, it is difficult to prevent the commingling of these systems in the United States.

Recommendation #1

It is essential to protect simultaneously our food and feed supplies from contamination by pharma crops. Comprehensive systems must be devised that will ensure this protection.

Rationale

Current corn and soybean production systems overlap considerably between the human food and animal feed supplies, and it will be important that any new protection systems be comprehensive enough to cover these systems in their entirety.

Both corn and soybean are among the crops currently being considered and used for commercial production of pharma crops, with corn the most common by far. These crops are widely used in both the human food and animal feed systems. Despite current systems to segregate transgenic and non-transgenic soybean, there continues to be considerable admixture of transgenic soybean, even at high tolerance levels of parts per thousand. As we discuss below, a more rigorous production and management system will need to be developed if corn and soybean are to be used as pharma crops.

Any oversight system will need to consider the risk of contamination by pharma crops of all systems simultaneously to ensure that commingling among them does not create additional contamination risks. The consensus of the authors is that performance standards governing the production and processing of pharma crops should meet a virtually zero contamination goal.

Conclusion #2

A virtually zero contamination standard will be beneficial for protecting the food and feed supplies from contamination by pharma crops and will facilitate the development of useful pharma crops.

Recommendation #2

A virtually zero contamination standard acceptable to the pharma crop industry, the food and feed industries, and regulatory bodies should be developed and implemented.

Rationale

Zero contamination is an absolute standard. Because any observed contamination violates this standard, it would be possible to determine unambiguously that contamination of the food or feed supply has occurred. In practice, this standard would be impossibly rigorous to attain. Events of minuscule effect or vanishingly small probability would violate this standard. For example, one seed of a pharma crop would contaminate an entire truckload of non-pharma crop according to this standard.

Instead, we advocate the development and implementation of a “virtually” zero contamination standard. We acknowledge that this standard does not yet have a legally defensible definition, but the plain and simple essence of this idea is that no contamination is tolerated; the likelihood of intentional occurrence is so remote as to be nearly zero, and any contamination that inadvertently occurs is so small as to be nearly zero.

In contrast, a standard based on detectable contamination will depend on the sensitivity of the detection method. As increasingly sensitive detection methods are developed, the standard would become more stringent and reveal exposure

that had previously been unknown—exposure that people may decide is unacceptable. Moreover, a standard based on detectability is based on the principle of technical feasibility, not the principle of safety. Protection of the human food and animal feed supplies should be based on the principle of safety.

On the other hand, a standard based on acceptable or tolerable risk necessarily leads to case-by-case risk assessment. Such an approach is necessarily regulatory and requires the development of a regulatory agency—one that must assess the risks and decide if they are low enough to be considered safe. A regulatory procedure is time-consuming and likely to be quite costly, both in monetary terms and in terms of the expertise needed to conduct sufficiently rigorous risk evaluations.

A system that requires significant costs for each product evaluated will have the effect of limiting the development of pharma crops to those producers that are sufficiently profitable to recover these costs. This would mean that pharma crops would be unlikely to reduce the “orphan drug” problem,⁴⁴ might not reduce the costs of producing medications, would be difficult for small companies to develop, and would be controlled by those companies that have the financial, human, legal, and scientific resources to negotiate a complex regulatory landscape. Moreover, regulating the occurrence of pharma products that are not supposed to enter the food or feed supplies in the first place seems unwise.

The virtually zero contamination standard would prevent contamination of the food and feed supplies through performance standards for each stage of the production process. Such standards could be viewed as best management

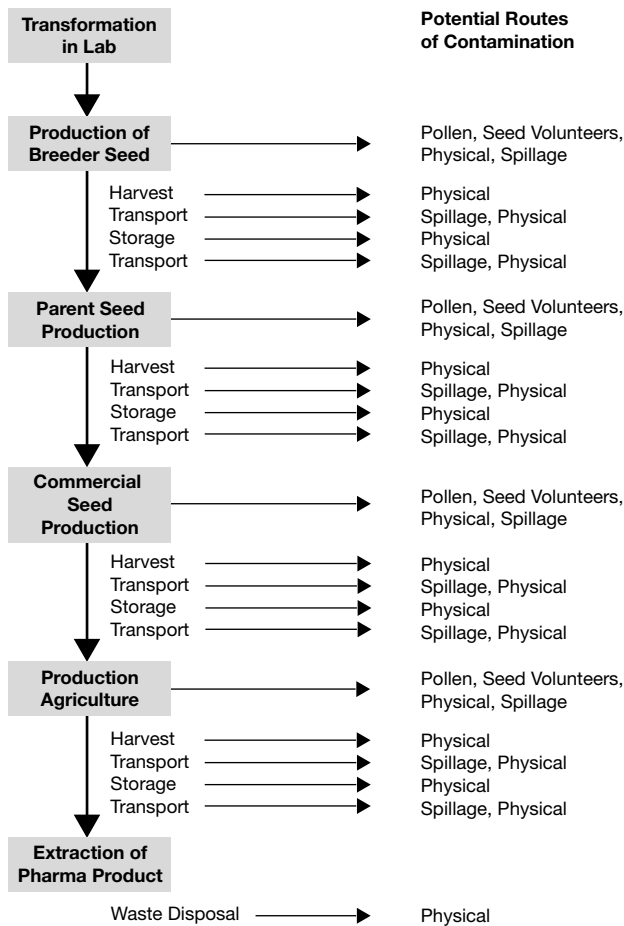
⁴⁴ An orphan drug is a pharmaceutical that is technically feasible to produce and effective in treating a disease, but is not commercially released because it is not profitable enough. This situation can occur because the disease is rare or the drug is too expensive for most people to afford.

practices for maintaining a food and feed supply system uncontaminated by pharma crops. We describe several strategies by which the virtually zero contamination standard can be achieved, based on our analysis of the production process and scientific literature associated with crop production.

CURRENT CORN AND SOYBEAN PRODUCTION PROCESSES

Existing corn and soybean production processes are a complex series of steps. And as depicted in Figure 8-1, there are vulnerabilities within each

Figure 8-1 **Routes of Contamination from Pharma Crops (under Standard U.S. Production Practices)**



step that could result in contamination of the human food or animal feed supplies. These steps include: the transformation of a crop in the laboratory; a series of laboratory and field growing seasons to produce breeder seed; production of parent seed, commercial seed, and the actual pharma crop; and finally, extraction of the transgene product from the pharma crop.

In the field, each step begins with planting and ends with harvesting. After harvesting comes a series of operations; the seed or plants must be transported from the field, cleaned, and stored in a facility until they are needed for the next step, when they will be transported back to the field from the storage facility. These operations are essentially the same for each stage, but vary significantly in scale.

Conclusion #3

The current production process and production areas for corn and soybean cannot be used without substantial modification to ensure virtually zero contamination of the human food and animal feed supplies.

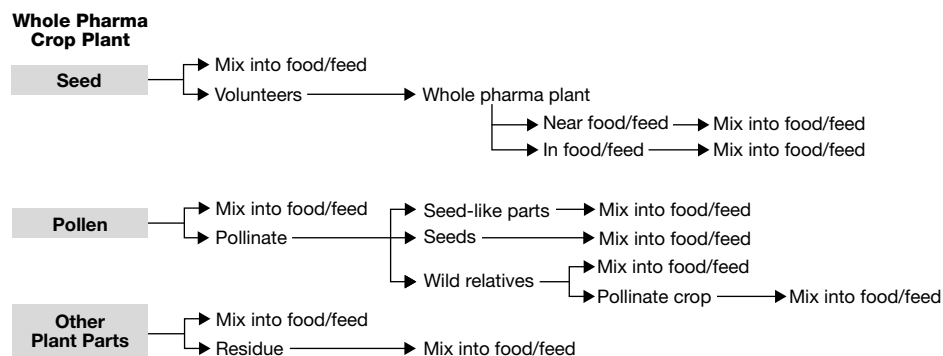
Recommendation #3

Systems designed to ensure virtually zero contamination by pharma corn and/or soybean production need to eliminate as many steps as possible in each of the seed development, seed production, crop production, and handling, storage, and delivery operations.

Rationale

Each crop production step has associated with it many possible pathways and events that could lead to contamination of the human food or animal feed supplies (Figure 8-2, p. 112). These can occur either through physical mixing of seeds, pollen, or other plant parts and plant residue, or through gene flow associated with the movement of seeds or pollen. The actual mixing could occur

Figure 8-2 **Contamination of the Food/Feed Supply by Pharma Crops and Pharma Crop Products**



during the year in which the pharma crop plants were produced, or in subsequent years (due to contamination via plant residues or volunteer plants arising from pharma seed left in the field after harvest). Management of volunteers growing in a food or feed crop may differ from management of volunteers growing near such crops.

Pollination may result in the production of viable seeds (which would repeat the pathways associated with seed movement) or nonviable seeds (which could still express the pharma transgene product and contaminate the food or feed supply). Pollination with wild relatives could result in contamination if the wild relative itself is a contaminant, or the wild relative can act as a bridge back to the crop, leading back to contamination pathways associated with the whole plant. However, corn and soybean in the United States have no wild relatives with which they can cross-pollinate.

Between each crop production cycle is a series of activities associated with harvesting, cleaning, storage, and transportation. Sometimes there are additional operations, such as grain drying after the corn harvest, or multiple storage operations, such as might occur when a crop is moved to successively larger storage facilities. Associated with each of these operations is the possibility that pharma crops might contaminate food or feed via shared

equipment, operator error, or inadvertent spillage.

The scale of production varies substantially among the various production steps. Producing breeder seed for pharma crops, for example, requires growing the crop in the environment to ensure high-quality seed production, uniformity of genetic background, that the transgene is present, and that the transgene product is expressed at high enough and uniform enough levels. However, the quantity of seed produced is always small, often not exceeding a few hundred plants and a few thousand seeds. The breeder is interested in maintaining the purity of the breeder seed and retaining as much of it as possible. If gene flow occurs, it is more likely to lead to the contamination of other breeder seed or seed that breeders will not harvest rather than contamination of the food or feed supply. But because of the small quantities involved, both are unlikely.

It is also unlikely that pharma transgene products would enter the food or feed supply directly from breeder seed or breeder operations because these operations typically take place in the midst of a breeding nursery, usually far enough away from commercial production fields to prevent contamination. It is possible, however, that experiments conducted near the breeding nurseries could be contaminated by pharma crops, and

if experimenters used these crops for food or feed, people or animals could be exposed to pharma crop products.

Harvesting is usually done by hand, seeds are hand-cleaned, and lines are stored separately. Extra care is taken not to lose seed inadvertently and to avoid seed mixing in equipment. Accidents, however, can happen during handling and storage, leading to unintended mixing of the breeder seed. Under normal operations, such mixtures (if and when detected) are disposed of and do not enter the food or feed supply.

While the small scale of breeder seed production makes it easier to ensure no direct contamination of the food or feed supply, this should not lead to a false sense of safety. Inadvertent contamination of breeder seed could result in the transgene being reproduced unknowingly in an otherwise non-transgenic line, resulting in widespread contamination.

Seed production takes place in two steps: production of the parents of the commercial seed, followed by production of the commercial seed itself. For hybrid corn, the parents are two different inbred lines, which are crossed to produce the commercial seed. For soybean, the steps are not as distinct because the parent and commercial seed are genetically the same.

As described earlier, these two seed production steps are scale-dependent. For example, 100 acres of a pharma corn crop require 0.7 acre of seed production, which requires 0.0042 acre (68 plants) of parent seed production. Even 10,000 acres of pharma corn crop production requires only 65 acres of seed production and 0.42 acre of parent production. For pharma soybean production, 100 acres of production require three acres of seed production and 0.1 acre of foundation seed production; 10,000 acres of pharma soybean production require 250 acres of seed production and six acres of foundation seed.

At any scale of production, more soybean seed must be produced compared with corn, so the propensity for human error may be higher with pharma soybean production. If the scale of pharma crop production is small (e.g., less than 10 acres), the probability of contamination associated with field production may be similar to normal seed production practices. If the scale of production is larger, the probability of contamination may be similar to production agriculture practices. Similarly, the probability of contamination during the harvesting, transportation, and storage processes may range between these two scales.

Large-scale production agriculture has the highest probabilities for contamination among all the production steps. If management practices can be implemented to ensure virtually zero contamination from production agriculture, the same practices should also be capable of ensuring virtually zero contamination from the other production steps. This would make it possible to safely use corn or soybean to produce pharma crops.

Typically, production agriculture is conducted without close attention to the kinds or proximity of surrounding plants. In addition, volunteers are common, and little care is taken to keep varieties separated during production operations. Standard post-harvest practices associated with transportation and storage encourage the mixing of crops from different fields. Hence, existing production processes for corn and soybean in the United States cannot ensure virtually zero contamination of the food and feed supplies. To accomplish this goal, it will be necessary to make substantial changes to normal production practices.

CORN AND SOYBEAN PHARMA CROPS

Corn and soybean are currently used as pharma crops in the United States. They were chosen for this purpose because they are readily transformed

and easily grown, their seeds store for long periods of time, and the extraction of pharma products from their seeds is readily accomplished.

Corn and soybean are two of the most widely grown crops in the world. In the United States, about 70 million to 80 million acres of each crop are grown annually, making these the two largest agronomic crops in terms of area. Although soybean is predominantly self-pollinating, corn is highly outcrossing and gene flow is widespread.

Conclusion #4

As they are currently produced, stored, and transported, corn and soybean cannot be used as pharma crops in the United States while ensuring virtually zero contamination of the food and feed supplies. Theoretically, a virtually zero contamination goal could be achieved, but this would require such substantial changes in production practices, management systems, and oversight that a major effort would be required to achieve this goal.

Recommendation #4

Corn and soybean production and management systems that will ensure virtually zero contamination of the food and feed supplies should be developed through collaboration between industry, academia, and regulatory bodies. If a broad-based consensus cannot be reached, it would be inadvisable to initiate further use of corn and soybean as pharma crops.

Rationale

Substantial changes are needed in seed production processes and in farm production, harvest operations, and post-harvest handling, transportation, and storage of both corn and soybean. Slightly fewer changes may be needed in soybean processes since soybean is predominantly self-pollinating. These changes are needed to create an independent pharma crop production and han-

dling system that would parallel but not intersect normal commodity production.

In addition, fail-safe mechanisms that anticipate and guard against human error and potential sabotage need to be developed. Redundancy in safety measures needs to be built into production and management processes. Finally, verifiable and independent oversight systems need to be designed in a way that ensures all needed precautions are implemented uniformly and effectively.

The 2002 ProdiGene contamination incident demonstrated that production and management systems have not yet been developed that will achieve virtually zero contamination without significant regulatory intervention. The 2000 StarLink incident demonstrated that once contamination occurs, it will be very difficult to remove. The development of well-planned protocols and oversight strategies is imperative if corn and soybean are to be used as pharma crops.

FUTURE PROSPECTS FOR PHARMA CORN AND SOYBEAN

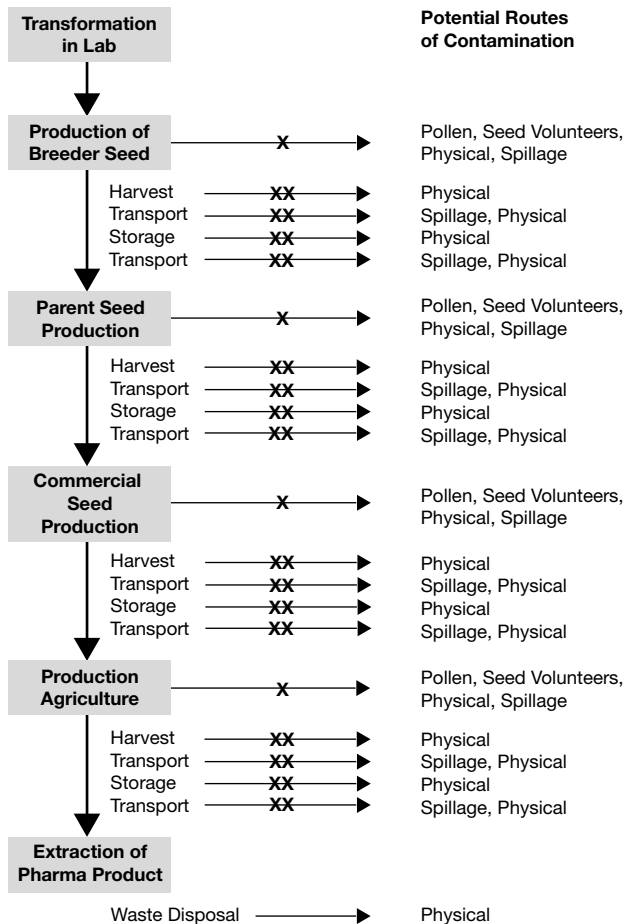
In this section, we outline strategies by which corn and soybean production systems might be modified in ways that would allow these important crops to be used as pharma crops while maintaining virtually zero contamination of the food and feed supply.

Geographic Isolation from Commodity Crop Production

Geographic zoning would entail the restriction of corn and soybean pharma crop production to areas far removed from commercial corn and soybean production. If corn or soybean had wild relatives with which they were interfertile in the United States, pharma crop production would also have to be isolated from these wild relatives. Zoning distances ensure virtually zero contamination from gene flow. Zoning can also reduce

Figure 8-3 **Effect of Geographic Zoning and Dedicated Infrastructure on Routes of Contamination**

X = Pathways reduced because of geographic isolation.
 XX = Pathways reduced because of dedicated infrastructure. (Though waste disposal was not discussed in this analysis, this route of contamination could be reduced by dedicated infrastructure.)



potential contamination from physical mixing, spillage, and operator error to virtually zero because of distance; the use of marked seed and marked and dedicated machinery, storage, and transport containers; and appropriate management systems and oversight (Figure 8-3).

Conclusion #5

If geographic isolation zones and the necessary management and oversight can be established

and maintained, pharma crops can be produced with virtually zero contamination of the food and feed supplies.

Recommendation #5

Studies of pollen flow, isolation, and crop production areas should be synthesized to determine whether further research is needed to establish the scientific basis for geographic isolation zones.

Rationale

We do not here propose a quantitative standard for determining an adequate degree of isolation. Instead, we suggest that spatial isolation distances will need to be several times greater than scientifically credible gene flow distances. For example, soybeans are cross-pollinated by insects such as bees. Since bees are able to forage for several kilometers, isolation distances of around 50 to 100 kilometers (31 to 62 miles) may be sufficiently far to ensure virtually no contamination by pollinators without additional measures. Shorter distances may also be sufficient, especially when the area of production is small (as with most pharma seed production) and other measures to reduce potential pollen movement can be used easily. Specific data are needed to justify this or any other suggested isolation distance.

Maintaining such isolation zones would likely be relatively easy for seed production, but as the scale of production increases under commercial operations, it will become more difficult. For corn zones, private garden production would need to be monitored and controlled. Some possible locations for corn isolation zones include the small pockets of irrigated land in isolated valleys of the western United States, but these sites could become in short supply should pharma crop production increase, putting an upper limit on the production capacity of U.S. corn and soybean pharma crops.

If isolation zones are successfully established, it becomes more likely that dedicated machinery would be used in all farm operations and that dedicated containers would be used to hold and transport the harvest. Still, it will be essential to mark pharma crop seed and dedicated machinery and containers to minimize operator errors. In addition, isolation zones could make it easier to monitor pharma crop production, ensure that farmers are using appropriate management practices, and ensure that operator errors are being reported in a timely fashion. Nevertheless, it will be necessary to implement specialized management systems (such as an ISO system) to ensure virtually zero contamination.

Embedding in Commodity Crop Production Areas

An integrated system for local confinement of corn or soybean pharma crops does not yet exist. It would involve developing, implementing, and monitoring integrated management systems so that corn and soybean pharma crops could be grown in the normal geographic areas of commercial commodity production while ensuring virtually zero contamination of the food and feed supplies.

This strategy resembles systems that have been implemented for identity-preserved (IP) corn and soybean products, particularly in the central role of traceability, but with a fundamental difference. Where IP systems are oriented toward maintaining product purity, virtually zero contamination strategies must keep the product from contaminating other products.

A local confinement system can ensure virtually zero contamination by creating a system of production, handling, and transport that isolates pharma production practices from normal commodity production of corn and soybean. It might work by having (1) dedicated machinery and

infrastructure; (2) an industry-wide marking system; (3) a confinement management system; (4) spatial separation from conventional commodity production; (5) varieties with sterile pollen (corn) or cleistogamous, determinant flowers (soybean) and additional means of biological pollen confinement; (6) emasculation (of corn); and (7) varieties producing sterile seeds.

Components 1, 2, and 3 could reduce potential contamination from physical mixing, spillage, and operator error; components 4, 5, and 6 could reduce potential contamination from gene flow by pollen; and components 1, 3, 4, and 7 could reduce potential contamination from gene flow by seeds to virtually zero. Appropriate management that provides redundant safeguards and fail-safe mechanisms is essential to the success of this strategy.

Conclusion #6

If appropriate management, spatial separation, and biological confinement can be developed, implemented, and enforced, it might be possible to grow corn and soybean pharma crops embedded in the same geographic areas as corn and soybean commodity production and still attain virtually zero contamination of the food and feed supply.

An appropriate management and oversight system would require considerable discipline and reproducibility in the production process, predetermined performance standards, documentation and auditing, and third-party monitoring and approval. Furthermore, this system and any associated biological confinement must include redundancy and fail-safe mechanisms to safeguard the food and feed supply.

Recommendation #6

Strategies should be developed that would allow individual growers or groups of growers to develop case-by-case plans for well-defined spatially

separated production areas within commodity production areas. These strategies would need to meet the needs described in conclusion #6.

Rationale

Most of the various confinement options are currently available except for seed sterility, additional means of biological pollen confinement, and appropriate management systems. We do not attempt to describe in detail how local confinement could be effective in ensuring virtually zero contamination of the food and feed supply. Indeed, some of the options have only been sketched conceptually.

The crucial management systems needed to provide disciplined, reproducible production and ensure virtually zero contamination are not yet available for corn and soybean. These systems have been developed for IP crops, however, so we are hopeful that similar systems can be developed in the future for corn and soybean pharma production systems.

Dedicated farm and off-farm machinery and infrastructure are essential for local confinement. Machinery used for the production, handling, processing, or storage of corn and soybean pharma crops must not be shared with normal commodity production, handling, processing, or storage. To prevent the inadvertent mixing of pharma corn or soybean into food or feed, the machinery and all associated products and infrastructure should be clearly marked.

Finally, harvested product should be transferred directly into containerized shipping units in the field. Sealing these units in the field and not opening them until they reach the processing company will reduce the probability of spillage or other mixing to a minimum.

Considerable effort must be expended in reducing vulnerabilities associated with pollen and seed gene flow. Spatial separation from conventional corn and soybean fields will help consider-

ably, but will probably not attain virtually zero contamination levels. Separation distances will need to be greater than the distances used to ensure sufficient seed purity.

Additional biological and operational safeguards against gene flow need to be implemented; many are not yet functional and require additional research. For example, it is currently possible to use both emasculation of corn tassels and male-sterile cytoplasm to reduce vulnerabilities associated with pollen flow, but a similar battery of biological and operational options to reduce vulnerabilities associated with seed gene flow is not available. In addition, it still needs to be determined how these multiple confinement options will work together to provide the fail-safe redundancy needed to ensure virtually zero contamination.

Because such a local confinement system has not been developed, the initial versions will likely have flaws, leading to the recognition of new vulnerabilities or actual contamination of the food/feed system with pharma crop products, triggering a crisis. Historical experience with the safety of airlines, nuclear power plants, and the electric generating system all demonstrate that system-wide failures can occur despite considerable efforts to avoid them. It is imperative that virtually zero contamination systems for local confinement have enough built-in flexibility so their failings can be rectified quickly in response to a crisis.

Mixing Isolation and Embedding

It may be possible to mix the geographic zoning and local confinement strategies while ensuring virtually zero contamination. For example, we have suggested that all seed production steps could be completed under geographic zoning, while the actual production process could be completed under local confinement.

Conclusion #7

A combination of confinement strategies for the various steps involved in seed development, seed production, and pharma crop production may provide practical, effective methods to achieve the goal of virtually zero contamination.

Recommendation #7

The infrastructure and information needed to develop, implement, and maintain pharma crop production in areas geographically isolated from commodity crops and/or embedded in commodity production areas must be developed as soon as possible if the use of corn or soybean as pharma crops is to succeed.

Rationale

It may be effective to use geographical zoning for all pharma crop breeding and seed production operations while concentrating the development of virtually zero contamination management systems on embedded production agriculture. This would serve to disconnect the breeding/seed production phase from the commercial production phase and lead to greater transparency for all interested parties, since the breeding/seed production phase is typically not readily visible to the public at large.

In addition, commercial production does not require the collection or use of transgenic pollen, whereas breeding and seed production does. Mixing isolation and embedded production also reduces the number of steps in pharma crop production that may contaminate the food or feed supply.

NON-FOOD/FEED CROPS

In 2003, the Grocery Manufacturers of America (GMA) called for a ban on transgenic pharma traits engineered into food crops until mandatory regulations that prevent contamination could be promulgated (GMA 2003). If food and feed crops were not used as pharma crops,

this would limit the possibility of contamination to the inadvertent mixing of non-food/feed crops into the food or feed supply. Because of the demand for agricultural production of therapeutic proteins, which could reduce production and transportation costs and improve storage and mode of delivery (oral versus intravenous), producing pharma products in non-food/feed crops is a logical solution.

Conclusion #8

Using non-food/feed crops as pharma crops does not by itself ensure virtually zero contamination of the food and feed supply. Additional safeguards are needed, including: confinement management systems and third-party oversight similar to that proposed for corn and soybean; barriers to pollen and seed gene flow (e.g., no wild relatives, low propagule viability, sterility); minimum production areas for pharma crops; and limited acreage for non-pharma crops.

Recommendation #8

Research on non-food/feed crops as potential pharma crops should be encouraged.

Rationale

To ensure commercially acceptable yields, a plant must produce large amounts of biomass and be able to store large concentrations of the pharma transgene product in tissue from which it can be extracted. Such tissues include tubers, leaves, and seeds. Storing high concentrations of product may also help reduce the potential for contamination by reducing the number of acres needed to produce sufficient product. In addition, an excellent commercial pharma crop will express the product in a tissue that can be easily stored, so it does not have to be processed immediately after harvest.

Several traits would be desirable for achieving virtually zero contamination. Contamination via pollen gene flow, for example, is related to the

possibility that contaminated wild relatives act as a bridge for the pharma transgene to contaminate a food or feed crop, or that contaminated wild relatives or non-pharma crop plants themselves can contaminate the food or feed supply (Figure 8-2, p. 112). Hence, a crop with no wild relatives eliminates potential contamination pathways via pollen and pollination of wild relatives. Male sterility, asexual reproduction, and biological confinement methods can also reduce the possibility of contamination via the non-pharma crop.

Contamination via seed gene flow is related to the possibility that pharma volunteers would occur in subsequent or nearby food/feed crops. Plants with low propagule viability or biological confinement mechanisms that reduce propagule viability would reduce this concern. Complete removal of volunteer plants can be facilitated by other traits that enable rapid recognition of volunteers, including early germination/sprouting, rapid early-season growth, and distinctive morphology. Transgene flow via pollen or seeds can also be confined by using non-food/feed pharma crops that are entirely propagated vegetatively, or by producing therapeutic proteins in vegetative organs (e.g., leaves) that could be harvested before the appearance of any reproductive structures.

The possibility that such a pharma crop will be mixed inadvertently into the food or feed supplies is greatly reduced by the fact that it is not a food or feed crop, but not eliminated. This possibility will be less likely if the non-pharma crop itself is not widely grown, because there will be fewer opportunities for inadvertent mixing and the pharma crop can be grown far from the conventional production areas.

In any event, it is essential that confinement management systems and third-party oversight similar to that proposed for corn and soybean be developed and implemented for these non-food/feed crops. Similar management standards should

apply to any pharma crop production and delivery system no matter what crop is used.

Conclusion #9

To ensure virtually zero contamination from future pharma crops, the use of non-food/feed crops should be considered seriously.

Recommendation #9

The information and technology necessary for pharma crop production in non-food/feed crops should be developed as soon as possible to ensure virtually zero contamination of the food/feed supply and enable pharma crop production to succeed. This may require some research incentives, as our genetic engineering expertise with other crops is not on the same level as corn and soybean.

Rationale

Crops other than corn and soybean should be considered for use as pharma crops if their use can ensure virtually zero contamination of the food and feed supply. As argued above, use of non-food/feed crops would present the lowest risk of contamination. However, food and feed crops that are planted on small acreages and are conventionally processed in ways that degrade the pharma product might also be considered as potential pharma crops. Such crops will require greater management and oversight than non-food/feed crops but will probably require less management and oversight than corn and soybean.

RESEARCH NEEDS

Because none of the proposed strategies—non-food/feed crops, geographic zoning, or local physical and biological confinement—is ready for immediate use in pharma crop production, we list the research areas below that must be addressed immediately to develop the scientific basis for ensuring virtually zero contamination of the U.S. food and feed supply. These recommendations echo

and expand on many of those presented in the 2004 National Research Council report on bioconfinement.

Conclusion #10

This study indicates a great need for both short- and long-term research.

Recommendation #10

Research should be conducted in each of the following areas:

1. **Development of non-food/feed crops**
 - a. Assessing the suitability of various non-food/feed crops to achieve virtually zero contamination (e.g., reproductive biology, genotype-specific differences)
 - b. Chloroplast transformation—chloroplast genome sequencing, transforming more species, improving tools to study chloroplast molecular biology (e.g., regulatory sequences)
 - c. Transformation systems—transforming target crops to express useful pharma traits
2. **Geographic zoning**
 - a. Needed isolation distances
 - b. Confinement management systems
3. **Local confinement**
 - a. Nuclear male sterility and seed sterility—transfer to corn and soybean
 - b. Maternal or other modes of inheritance of chloroplast traits
 - c. Failure rates for confinement options; how failures among various options interact; estimated leakage rate of biological confinement options
 - d. Genes associated with reproductive isolating mechanisms in plants

- e. Corn pollen movement in multiple environments; soybean pollinator research
- f. Assessing the efficacy of confinement management systems

TRANSPARENCY

Producers of pharma crops have chosen to limit the public's access to information about pharma crops by invoking laws governing confidential business information. The pharma product, the general location of its production, even the very existence of a pharma plant are generally not known to the public, and this information is exceedingly difficult to obtain. Indeed, most people in the United States will never know whether a pharma crop is grown near their home.

With such a dearth of information, the public will not be able to participate in any meaningful way in discussions about how these crops should be developed. While there may be good business reasons for concealing information, such actions suggest to the public that pharma crops need to be hidden. It may be helpful, therefore, for both pharma crop producers and the public if information about pharma crop production were transparently available.

Conclusion #11

Greater public transparency in the production of pharma crops is needed. For example, how are pharma crops produced, how are pharma plants bred, where is pharma seed produced, how is pharma seed handled, how and where are pharma crops produced? The public needs this information if it is going to participate in the development of policy to contain these crops.

Recommendation #11

Pharma crop producers should disclose information to the public about how, where, and when pharma crops are grown, from the initial seed

production stages to the processing of harvested products.

INTERNATIONAL ISSUES

There are many extremely sensitive international dimensions to the development and use of pharma crops. While all countries have the right to self-determination, the role and influence of the United States cannot be ignored in these issues, whether they are judged as good or bad. In this global economy, pharma crops are likely to move rapidly from the United States into many other countries.

Conclusion #12

At this time, it is not enough to rely only on the private sector to ensure adherence to standards meant to protect the food/feed supply from contamination.

Recommendation #12

Governments need to determine areas of responsibility with respect to the international movement

of pharma crops (e.g., harmonized regulations; capacity-building to manage and regulate pharma crops; improvement and dissemination of methods for detecting, reporting, and communicating about contamination by pharma crops).

Self-regulating systems require objective third parties to provide oversight and ensure compliance. These third-party systems could rely on government intervention or parties within the private sector that have the social legitimacy and authority to conduct the necessary oversight (e.g., an ISO-type system). The industry currently has no self-regulating system under development, let alone in place, and no legitimate, authoritative body has emerged to oversee such a system. At the present time, therefore, government authority is needed to ensure virtually zero contamination of the food and feed system.

REFERENCES

Grocery Manufacturers of America (GMA). 2003. Comments Submitted Re: Docket No. 03-031-1. GMA Comments on USDA Bio-Pharma Permit Regulations 03/10/2003: Field Testing of Plants Engineered to Produce Pharmaceutical and Industrial Compounds. On the GMA website at <http://www.gmabrands.com/publicpolicy/docs/comment.cfm?docid=1135>, accessed October 12, 2004.

National Research Council (NRC). 2004. *Biological Confinement of Genetically Engineered Organisms*. Washington, DC: National Academy Press.

GLOSSARY

For descriptions of seed- and grain-handling equipment, see Table 6-1 (p. 93).

Biological confinement

The use of biological methods such as chloroplast engineering, male sterility, and seed sterility to reduce **pollen** or seed dispersal.

Biotechnology

Term referring to practical uses of living organisms. “Old” biotechnologies typically include processes such as fermentation (to make foods such as yogurt, cheese, bread, and beer), animal and **plant breeding**, and food and fiber production from plants and animals. “New” biotechnologies include modern techniques such as genetic engineering and cloning. The term biotechnology is often used interchangeably with the terms **genetic engineering** and genetic modification.

Breeder seed

Seed held most closely by breeders of new plant **varieties**. Breeder seed is the class of **certified seed** with the highest standards for purity and is the source for production of **foundation seed**.

Bt crop

Insect-resistant crop variety engineered to produce an insect toxin originally found in the soil bacterium *Bacillus thuringiensis*.

Certified seed

Generically, seed that has been subject to certification by a seed-certifying agency. Classes of certified seed, listed from most to least pure, are **breeder**, **foundation**, registered, and certified.

Specifically, that particular class of certified seed typically produced from registered seed, but which also may be produced from foundation seed or other certified seed. Certified seed is usually the class of seeds sold to farmers, and is typically the least genetically pure of the four classes of certified seed.

Confinement

Restriction of a crop and its genetic material (in the form of seeds, **pollen**, and vegetative material) to a particular space.

Contamination

Seeds or **genes** that are unwanted in a particular place for any reason.

Crop gene pool

All the **genes** in all the **varieties** of a crop, plus the genes of all other plants that interbreed with the crop.

Cross-pollination

Transfer of **pollen** from the male part of a plant flower to the female part of a flower on a different plant. After **pollination**, male and female cells combine to form embryos (**fertilization**). Corn is a predominantly cross-pollinating crop, while soybean is predominantly **self-pollinating**.

Dedicated machinery/equipment/infrastructure

Confinement method that reserves farm machines and other infrastructure for use with **pharma crops** exclusively.

Disallowing food/feed crops

Confinement method that prohibits the production of pharmaceuticals or industrial compounds in crops used for food or feed.

Fertilization

The union of a male sex cell (carried within a **pollen** grain) with a female sex cell (egg), producing a single cell that develops into a plant embryo. Fertilization also triggers the formation of a seed, which contains the embryo.

Foundation seed

Class of **certified seed** produced from **breeder seed** or other foundation seed under conditions that maintain high standards of genetic identity and purity. Foundation seed is the source of certified seed, which is sold to farmers.

Gene

Functional unit of hereditary material usually carried on chromosomes and passed from parent to offspring. A gene codes for proteins (the molecules that are responsible for traits exhibited by plants such as height and seed color and shape).

Gene flow

The movement of **genes** from one population of plants to another, usually via **pollination**.

Genetic engineering

Molecular-level techniques capable of combining **genes** and transferring them into an organism. These techniques, which may be used to transfer genes between unrelated organisms or to remove and rearrange genes within a species, are also called **transgenic** or genetic modification techniques.

Genetically engineered organism

Organism (or progeny of an organism) whose genes have been modified using molecular-level techniques. Such organisms are also referred to as genetically modified or **transgenic**.

Genetically modified organism (GMO)

see **genetically engineered organism**

Genome

The full set of genes and associated DNA characteristic of an organism.

Hybrid variety

Offspring of two parental plants that differ from one another in one or more **genes**.

Identity-preserved (IP) system

Carefully controlled production and distribution system that segregates high-value crops from the time of planting to their delivery to the end user.

Inbred crop

Pure-breeding line of plants that has undergone controlled **pollination** for a number of generations.

Industrial crop

Crop engineered to produce substances (such as plastics or tanning and paper-pulping enzymes) used in manufacturing and other industries.

Novel gene

Gene transferred to a plant by **genetic engineering**. Also called a **transgene**.

Outcrossing

see **cross-pollination**

Parent seed

see **foundation seed**

Pharma crop

Crop engineered to produce pharmaceuticals.

Physical confinement

Method of growing crops within enclosed physical structures (such as greenhouses or mines) to reduce dispersal of **pollen** and seed.

Physical mixing

Introduction of the seeds or grains of one species or **variety** into the seeds or grains of another species or variety during production or processing. The major physical route by which the food/feed supply may be **contaminated** by **pharma crop** products.

Plant breeding

Scientific discipline for producing new crop **varieties** using sophisticated, field-based selection and mating techniques.

Pollen

Dust-like material, produced by the male parts of flowers, that contains male sex cells.

Pollen dispersal

Movement of **pollen** via wind, insects and other animals, or humans. The major biological route by which the food/feed supply may be **contaminated** by **pharma crop** products.

Pollination

Transfer of **pollen**, most frequently accomplished by wind or insects, from the male part of a plant flower to the female part. If the pollen is compatible with the female part of the flower to which it has been transferred, pollination is followed by **fertilization**.

Pollination is sometimes used as shorthand for both pollen transfer and fertilization.

Seed mixing

see **physical mixing**

Self-pollination

Transfer of **pollen** from the male part of a plant flower to the female part of a flower on the same plant. After **pollination**, male and female cells combine to form embryos (**fertilization**). Soybean is a predominantly self-pollinating crop, while corn is predominantly **cross-pollinating**.

Spatial separation

Confinement method in which **pharma crops** are grown in fields separated from conventional crops by distances far enough to make **cross-pollination** unlikely.

Temporal separation

Confinement method in which **pharma crops** are planted at different times from conventional crops to prevent overlapping flowering periods.

Transgene

Gene transferred to an organism through **genetic engineering**.

Transgenic

see **genetic engineering**

Variety

Subgroup of plants within a species whose genetic makeup and characteristics distinguish it from other varieties of the species. Crop varieties are often called cultivars, especially by agricultural scientists.

Zoning

Confinement method restricting the growth of a **pharma crop** to an area of the country where that crop is not usually grown for food or feed.