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Transgenic Crops: The Good, the Bad, and the Laws

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Recent Developments

Transgenic Crops: The Good, the Bad, and the Laws

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INTRODUCTION

Advances in molecular biology and plant genetic engineering have made it possible to introduce genes from a variety of organisms into plants to create transgenic crops having agriculturally and commercially useful traits. In turn, the adoption of these crops by United States farmers has been rapid—between 1996 and 2002, the percent of transgenic corn or soybeans acres increased about ten-fold,[1] and more than $20 billion in crop value were attributed to transgenic crops in 2002.[2] In addition, more than forty transgenic traits have been approved for commercial release in the United States including herbicide-tolerant canola, corn, cotton, and soybean; insect resistant corn and cotton; and virus-resistant papaya and squash.[3]

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1. C. FORD RUNGE & BARRY RYAN, THE ECONOMIC STATUS AND PERFORMANCE OF PLANT BIOTECHNOLOGY IN 2003: ADOPTION, RESEARCH AND DEVELOPMENT IN THE UNITED STATES ii (2003), *at* http://www.agbios.com/docroot/articles/04-365-002.pdf (last visited Apr. 10, 2005); Press Release, International Service for the Acquisition of Agri-biotech Applications, Double-Digit Growth Continues for Biotech Crops Worldwide (Jan. 13, 2004), *at* http://www.cornandsoybeandigest.com/news/soybean_doubledigit_growth_continues/ (last visited Apr. 10, 2005).

2. RUNGE & RYAN, *supra* note 1, at ii.

3. Diana Pilson & Holly R. Prendeville, *Ecological Effects of Transgenic Crops and the Escape of Transgenes into Wild Populations*, 35 ANN. REV. ECOLOGY & EVOLUTION SYS. 149, 150 (2004).

The rapid adoption of transgenic plants has raised concerns about the impact of these plants on the environment and our food supply. Widespread cultivation of transgenic plants could lead to the development of weeds that are difficult to control, a decrease in biodiversity, or the contamination of food crops by products potentially harmful to humans. The risks associated with transgenic plants stem from pollen-mediated gene flow from transgenic plants to unintended recipients and seed dispersal during harvest, transportation, planting and re-harvest.[4] The current regulatory framework requires adoption of procedures such as physical and temporal separation to prevent gene flow from transgenic crops to unintended recipients. But as the range of genetic materials and traits being introduced into plants expands, there is increasing concern that the current regulatory framework may be inadequate to address the risks involved. Recently, numerous biological containment strategies such as male sterility and chloroplast engineering have been developed to circumvent gene flow. Although these techniques have been successfully demonstrated in several plant species, their effectiveness as mechanisms for preventing gene flow is limited. The move towards engineering plants to be host organisms for the production of pharmaceuticals and industrial chemicals has prompted some to call for a zero tolerance policy. But the evidence indicates that current practices and perhaps even biological strategies of gene containment cannot achieve absolute containment. This article will begin with a general summary of the benefits and risks of transgenic plants as well as the current laws and regulations governing agricultural practices and commercialization of transgenic plants. This will be followed by a discussion of the biological strategies that have been developed and their effectiveness in preventing gene flow.

I. THE BENEFITS AND RISKS OF TRANSGENIC PLANTS

Plant genetic engineering can be used to introduce into plants genes conferring a variety of traits that can improve crop production or the nutritional quality of foods. First generation crops, for example, are engineered with traits that confer a pure agronomic benefit.[5] These "input traits" include

4. Henry Daniell, *Molecular Strategies for Gene Containment in Transgenic Crops*, 20 NATURE BIOTECHNOLOGY 581, 581 (2002).

5. Stuart Smyth, George G. Khachatourians, & Peter W. B. Phillips, *Liabilities and Economics of Transgenic Crops*, 20 NATURE BIOTECHNOLOGY

pesticide or disease resistance,[6] herbicide resistance,[7] or environmental stress tolerance.[8] These traits attack the causes of crop loss such as pests, diseases, weather stress such as drought and frost, and competitors such as weeds. They facilitate production by allowing for increased yields and/or reduction in pesticide use.[9] By contrast, second generation crops are engineered so that the product that reaches the consumer has a health or nutritional benefit.[10] These "output traits" include higher vitamin content, healthier oils, improved protein content, higher starch content, and non-allergenicity.[11] Plant genetic engineering can also be used to create plants that produce industrial chemicals, nutraceuticals or pharmaceuticals.[12] These "pharm" and "industrial" crops promise to bring lower price drugs, drugs that would be unavailable otherwise, and inexpensive vaccines.[13] In addition, non-food crops such as turf grass could be engineered to be more resistant to pests, diseases, herbicides and environmental stress such as drought, salt and cold.[14] Similarly, flowers can be created in new colors.[15]

537, 537 (2002).

6. *See* THE PEW INITIATIVE ON FOOD AND BIOTECHNOLOGY, HARVEST ON THE HORIZON: FUTURE USES OF AGRICULTURAL BIOTECHNOLOGY 19-27 (2001) [hereinafter HARVEST ON THE HORIZON], *at* http://pewagbiotech.org/research/harvest/harvest.pdf (last visited Apr. 10, 2005). The most widely used method of engineering crops to be resistant to pests is by cloning and expressing a gene encoding the insecticidal protein from the soil bacterium *Bacillus thuringiensis* into the crop. *Id*. at 25.

7. *Id.* at 27-28. The best-known herbicide-resistant trait used in plant genetic engineering is resistance to glyphosate, also known as Roundup®. *Id*. at 28.

8. *See id.* at 29-32; AGRICULTURAL RESEARCH AND COMMERCIAL TECHNOLOGIES I: COMMERCIAL TRAITS [hereinafter ARCT], *at* http://www.iia.msu.edu/absp/biotech-ag1.html (last visited Feb. 25, 2005).

9. HARVEST ON THE HORIZON, *supra* note 6, at 10.

10. Smyth et al., *supra* note 5, at 537.

11. *See* HARVEST ON THE HORIZON, *supra* note 6, at 32-40; ARCT, *supra* note 8.

12. Smyth et al., *supra* note 5, at 537; UNION OF CONCERNED SCIENTISTS, PHARM AND INDUSTRIAL CROPS: THE NEXT WAVE OF AGRICULTURAL BIOTECHNOLOGY 3 (2003) [hereinafter PHARM AND INDUSTRIAL CROPS], *at* http://www.ucsusa.org/food_and_environment/biotechnology/page.cfm?pageID=1033 (last visited Apr. 10, 2005).

13. *See* Jim M. Dunwell, *Transgenic Crops: The Next Generation, or an Example of 2020 Vision*, 84 ANNALS OF BOTANY 269, 273-74, 273 tbl. 2 (1999); PHARM AND INDUSTRIAL CROPS, *supra* note 12, at 5.

14. HARVEST ON THE HORIZON, *supra* note 6, at 51.

15. *Id*.

The creation of transgenic crops with new traits has led to concerns about whether the product of the transgene would have a toxic effect on non-target organisms. A transgenic plant carrying a gene conferring pest resistance can adversely affect non-target organisms such as benign or beneficial organisms related to, or having similar physiology with, the target organism.[16] Whether a transgenic plant poses a threat to non-target organisms depends on the inherent toxicity of the gene product and the exposure level in the environment. For example, the *Bacillus thuringiensis* (*Bt*) toxin in pollen from *Bt* maize has been demonstrated to be toxic to monarch butterfly larvae at high levels under laboratory conditions.[17] The level of exposure in nature, however, was later demonstrated to be low, and the risk to the butterfly negligible.[18] A transgenic plant can also pose a threat to a predator or parasite of the target organism.[19] *Bt* expressed in corn leaves, for example, are toxic to lacewings reared on corn borers that had ingested *Bt*-corn leaves,[20] though actual environmental exposure levels are lower than that tested in the study.[21]

Toxicity of the *Bt* toxin to humans, however, is less certain. Transgenic plants could adversely affect humans if the product of the genetic modification, which can be allergenic, toxic, or otherwise not approved or intended for general consumption, enters and contaminates the human food supply. Contamination of taco shells by genetic material encoding the *Bt* toxin from StarLink corn™, for example, was reported in September 2000, and this was followed by reports of allergic reactions from consumers who had eaten food products

16. Philip J. Dale et al., *Potential for the Environmental Impact of Transgenic Crops*, 20 NATURE BIOTECHNOLOGY 567, 567-68 (2002).

17. John E. Losey, Linda S. Rayor, & Maureen E. Carter, *Transgenic Pollen Harms Monarch Larvae*, 399 NATURE 214, 214 (1999).

18. Arthur R. Zangerl et al., *Effects of Exposure to Event 176* Bacillus thuringiensis *Corn Pollen on Monarch and Black Swallowtail Caterpillars Under Field Conditions*, 98 PNAS 11,908, 11,911 (2001), *available at* http://www.pnas.org/cgi/reprint/98/21/11908 (last visited Apr. 10, 2005).

19. Dale et al. *supra* note 16, at 569; Angelika Hilbeck et al., *Toxicity of* Bacillus thuringiensis *Cry1Ab Toxin to the Predator* Chrysoperla carnea (Neuroptera: Chrysopidae), 27 ENVTL. ENTOMOLOGY 1255, 1260 (1998); Angelika Hilbeck et al., *Effects of Transgenic* Bacillus thuringiensis *Corn-fed Prey on Mortality and Development Time of Immature* Chrysoperla carnea (Neuroptera: Chrysopidae), 27 ENVTL. ENTOMOLOGY 480, 484-85 (1998) [hereinafter Hilbeck et al., *Corn-fed Prey*].

20. *See generally* Hilbeck et al., *Corn-fed Prey*, *supra* note 19.

21. Dale et al., *supra* note 16, at 569.

containing corn.[22] Although subsequent immunoassays conducted by the Center for Disease Control did not lead to evidence of hypersensitivity to the toxin, allergic reactions were not ruled out.[23] Another incident was reported in 2002 in which a transgenic corn plant engineered to produce a pharmaceutical was found growing in a field planted with soybean.[24] Although the soybeans did not reach the human food supply,[25] the incident illustrates the potential risks involved. Contamination of the human food supply stems from gene flow from a transgenic plant unintended for human consumption to food crops through pollen or seed dispersal.[26]

Pollen-mediated gene flow occurs through the process of hybridization or hybridization followed by introgression. Hybridization refers to the interbreeding of individuals from genetically distinct populations[27] via cross-pollination.[28] In order for cross-pollination to occur, the populations must flower at the same time, be sufficiently close in space so that the pollen can be carried between them, and be sexually compatible in order for the pollen to germinate and affect fertilization.[29] If the pollination process gives rise to embryos that develop into viable seeds and germinate, F1 hybrids are formed.[30] F1 hybrids, if fertile, can then backcross into one or both parental

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22. CTRS FOR DISEASE CONTROL AND PREVENTION, INVESTIGATION OF HUMAN HEALTH EFFECTS ASSOCIATED WITH POTENTIAL EXPOSURE TO GENETICALLY MODIFIED CORN – A REPORT TO THE U.S. FOOD AND DRUG ADMINISTRATION FROM THE CENTERS FOR DISEASE CONTROL AND PREVENTION 4, 6 (2001) [hereinafter CDC REPORT], *available at* http://www.cdc.gov/nceh/ehhe/Cry9cReport/cry9creport.pdf (last visited Apr. 10, 2005).

23. *Id.* at 10.

24. *See* C. Neal Stewart Jr. et al., *Transgene Introgression from Genetically Modified Crops to Their Wild Relatives*, 4 NATURE REVIEWS GENETICS 806, 815 box 3 (2003).

25. *Id.*

26. *See* PEW INITIATIVE ON FOOD AND BIOTECHNOLOGY, ISSUES IN THE REGULATION OF GENETICALLY ENGINEERED PLANTS AND ANIMALS 77-78 (2004) [hereinafter PEW INITIATIVE], *available at* http://pewagbiotech.org/research/regulation/Regulation.pdf (last visited Apr. 10, 2005); *see also* David S. Bullock & Marion Desquilbet, *The Economics of Non-GMO Segregation and Identity Preservation*, 27 FOOD POL'Y 81, 85 (2002).

27. Judith M. Rhymer & Daniel Simberloff, *Extinction by Hybridization and Introgression*, 27 ANN. REV. ECOLOGICAL SYS. 83, 84 (1996).

28. Norman C. Ellstrand et al., *Gene Flow and Introgression from Domesticated Plants into their Wild Relatives*, 30 ANN. REV. ECOLOGICAL SYS. 539, 541 (1999).

29. *Id*.

30. *Id*.

populations resulting in gene flow between populations.[31] Introgression refers to the backcrossing of hybrids into parental populations. Hybridization and introgression between sexually compatible plants are aided by seed dispersal, which can take place at various stages from the time of harvest to replanting. Seeds can be dispersed into the wild during harvest, transportation, planting and re-harvest.[32] Similarly, transgenic seeds can be mixed with other seeds during seed production, farm production, and in seed handling systems or processing systems.[33] When these volunteered seeds germinate and grow near sexually compatible plants, hybridization and introgression could occur.

Hybridization and cross pollination could also lead to development of weeds that are more difficult to control or decreases in biodiversity. Hybridization and introgression are frequent phenomena in plants.[34] Many cases of hybridization between crops and their wild relatives are known,[35] and in fact, it has been reported that of the world's thirteen most important food crops, twelve hybridize with wild relatives in some part of their agricultural distribution.[36] When a transgene conferring an improved-fitness trait such as herbicide resistance, or

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31. *Id*.

32. PEW INITIATIVE, *supra* note 26, at 77-78; *see also* Bullock & Desquilbet, *supra* note 26, at 86 tbl. 1, 87; Daniell, *supra* note 4, at 581.

33. Bullock & Desquilbet, *supra* note 26, at 86 tbl. 1, 87.

34. Ellstrand et al., *supra* note 28, at 541 ("More than 70% of plant species may be descended from hybrids . . . . Studies employing allozymes and DNA-based genetic markers have revealed dozens of instances of natural introgression in plants." (citation omitted)); Rhymer & Simberloff, *supra* note 27, at 84 ("Botanists have paid . . . attention . . . to the evolutionary consequences of hybridization and introgression, . . . because these are . . . common phenomena in plants.").

35. Ellstrand et al., *supra* note 28, at 541-42.

> The hundreds of well-studied cases of natural hybridization and introgression . . . suggest that most domesticated plants will hybridize naturally with their cross-compatible wild relatives when they come into contact. A growing number of . . . studies . . . have demonstrated that domesticated alleles can and do enter and persist in natural populations. The domesticated species involved are amazingly diverse, ranging from mushrooms and raspberries to ornamental shrubs and forage crops. The accumulating evidence suggests these examples are probably the rule rather than the exception.

Id. (citations omitted); *see also* Allison A. Snow, *Transgenic Crops – Why Gene Flow Matters*, 20 NATURE BIOTECHNOLOGY 542, 542 (2002) ("[G]ene flow can be surprisingly widespread. New cases of crop-to-wild gene flow are still being discovered, . . . and crop alleles can persist in weed populations for decades.").

36. Ellstrand et al., *supra* note 28, at 544 tbl. 1.

drought or frost tolerance, escapes into a wild population through hybridization/introgression, the transgene could increase in frequency in the wild population through natural selection.[37] This could give rise to weedy relatives that are resistant to herbicides or tolerant of environmental stresses and thus are more difficult to control.[38] Even if a transgene does not provide a survival advantage and thus may not increase in frequency through natural selection, it could adversely affect genetic diversity through demographic swamping.[39] Demographic swamping refers to continual gene flow from a large source population such as a crop to a smaller recipient population such as a wild relative with continuous planting of the source population.[40] In this case, if the rate of gene flow exceeds natural selection, the frequency of the gene in the recipient population will increase, and if expression of the transgene is costly to the plant or if the transgene reduces fitness in the plant, a reduced population size and possibly local extinction could result.[41]

Thus, gene flow and its consequences will take place when a plant is grown in proximity to its wild relatives. Although

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37. Pilson & Prendeville, *supra* note 3, at 158-61.

38. Snow, *supra* note 35, at 542 ("[W]hen novel genes spread to free-living plant populations, they have the potential to create or exacerbate weed problems by providing novel traits that allow these plants to compete better, produce more seeds, and become more abundant."); *Going with the Flow*, 20 NATURE BIOTECHNOLOGY 527, 527 (2002) (stating that a particular concern with respect to the impact of crop biotechnology on the environment was the "[t]he rapid spread of genes that confer to related weeds or crops novel fitness-related traits that were not previously available" and citing as support the fact that a canola resistant to three herbicides, Roundup, Liberty, and Pursuit, has emerged in Alberta "in just two years" as a result of cross-pollination); Smyth et al., *supra* note 5, at 538 ("There is already significant evidence that some weeds are developing resistance to one or more of the herbicides involved in the control of weeds in canola-growing areas."); *see also* Dale et al. *supra* note 16, at 568 tbl. 1, 569-70. *Cf*. John M. Burke & Loren H. Rieseberg, *Fitness Effects of Transgenic Disease Resistance in Sunflowers*, 300 SCIENCE 1250, 1250 (2003) (finding that a disease-resistance transgene would not increase the fitness of a wild plant).

39. Pilson & Prendeville, *supra* note 3, at 159.

40. *Id*.

41. *Id*.

> [A]lleles that reduce fitness can be fixed if the migration rate exceeds the selection coefficient, and when this occurs demographic swamping can lead to reduced population size and possibly local extinction. These effects could lead to extinction by hybridization and to wild populations that are endangered because of hybridization with crops.

Id. (citation omitted)).

certain plants such as corn and soybeans have no sexually compatible wild relatives in the United States, many, such as sorghum, alfalfa, canola, wheat, carrot, sunflower, radish and squash, do.[42] In fact, alfalfa, wheat, canola and sunflower are considered to be at moderate risk for crop-to-wild introgression, while sorghum is considered to be at high risk.[43] In addition, creeping bentgrass (*Agrostis stolonifera* L.), a wind-pollinated, highly out-crossing plant used on golf courses, is being developed for commercial use. Twenty-six species of *Agrostis* are considered native in North America, and can be found in riparian habits, agronomic and urban settings, mountain meadows and woodlands, coastal sand dunes, fresh and salt water marshes, ditches, pastures, grasslands, and roadsides.[44] Natural hybrids of *A. stolonifera* and six other native species have been reported, and although interspecific F1 hybrids are generally less fertile or even sterile, some have been found to out-compete both parents under favorable habitats.[45] Thus, gene flow though hybridization and introgression could lead to weediness or a decrease in genetic diversity among wild *Agrostis* species. Even if a plant has no compatible wild relatives nearby, pollen-mediated gene flow can take place between crops. Gene flow from a crop genetically engineered to produce an industrial chemical or a pharmaceutical, for example, to a food crop intended for human consumption could lead to contamination of the general food supply with the product of the genetic modification, which as discussed earlier, could be allergenic or toxic. The adventitious presence of genetically engineered products in human food crops is a significant issue as certain food crops such as corn, which undergoes cross-pollination,[46] also are used as animal feed[47] and as host plants for the production of pharmaceuticals.[48]

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42. *See* Stewart et al., *supra* note 24, at 810 tbl. 1; *see also* JANE RISSLER & MARGARET MELLON, PERILS AMIDST THE PROMISE: ECOLOGICAL RISKS OF TRANSGENIC CROPS IN A GLOBAL MARKET 29 fig. 2.4 (Union of Concerned Scientists 1993).

43. Stewart et al., *supra* note 24, at 811-12.

44. Lidia S. Watrud et al. *Evidence for Landscape-level, Pollen-mediated Gene Flow from Genetically Modified Creeping Bentgrass with CP4 EPSPS as a Marker*, 101 PNAS 14,533, 14,533 (2004), *available at* http://www.pnas.org/cgi/reprint/101/40/14533 (last visited Apr. 10, 2005).

45. *Id.* at 14,534.

46. Bullock & Desquilbet, *supra* note 26, at 85.

47. CDC REPORT, *supra* note 22, at 4 (noting that StarLink corn was approved for use as animal feed and other nonfood uses).

48. Corn, as well as alfalfa, canola, potato, rice, safflower, soybeans and

Thus, gene flow could ultimately lead to contamination of the human food supply.

II. THE LAWS AND REGULATIONS GOVERNING TRANSGENIC PLANTS

The approach to regulating the development and commercialization of transgenic plants in the United States was set out in the "Coordinated Framework for the Regulation of Biotechnology" in 1986.[49] Under the Coordinated Framework, transgenic plants are regulated by three agencies depending on their intended use: the Food and Drug Administration (FDA), the Environmental Protection Agency (EPA), and the United States Department of Agriculture (USDA).[50]

The FDA focuses on safety issues associated with foods derived from transgenic plants.[51] The FDA's authority to ensure that foods for human consumption meet safety standards stem from the Federal Food, Drug and Cosmetics Act[52] (FFDCA), which gives the FDA post-market authority to remove adulterated foods from the marketplace, that is, foods contaminated with a substance that may render the food unsafe,[53] and pre-market authority to approve foods containing a food additive, a deliberately-added substance, unless the substance is generally recognized as safe (GRAS).[54] Since 1992, the FDA has adopted the view that foods derived from

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tobacco, have been identified as potential hosts plants for the production of pharmaceuticals. BIOTECHNOLOGY INDUS. ORG., REFERENCE DOCUMENT FOR CONFINEMENT AND DEVELOPMENT OF PLANT-MADE PHARMACEUTICALS IN THE UNITED STATES 8-9 (2002), *at* http://www.bio.org/healthcare/pharmaceutical/pmp/PMPConfinementPaper.pdf (last visited Apr. 10, 2005). The well-established agricultural methods for these crops allow for cost-effective production and efficient handling. *See id.* at 9. Other advantages include safety and ease of establishing appropriate confinement procedures to meet regulatory requirements. *Id. See also* PEW INITIATIVE, *supra* note 26, at 71.

49. Rebecca M. Bratspies, *Myths of Voluntary Compliance: Lessons from the StarLink Corn Fiasco*, 27 WM. & MARY ENVTL. L. & POL'Y REV. 593, 599 (2003).

50. *See id.* at 600; *see also* U.S. DEP'T OF AGRIC., WELCOME TO USDA'S AGRICULTURAL BIOTECHNOLOGY WEBSITE, *at* http://www.usda.gov/agencies/biotech/ (last visited Feb. 26, 2005).

51. *See generally* PEW INITIATIVE, *supra* note 26.

52. 21 U.S.C. §§ 301-397 (2000).

53. *Id.* § 342.

54. *Id.* § 348.

transgenic plants are substantially equivalent to foods from conventional plants.[55] That is, the transgene, other genetic materials and their products that are engineered into a transgenic plant are presumed to be GRAS, unless (1) these novel components differ significantly in structure, function or composition from substances already in foods, in which case they would be treated as a food additive,[56] or (2) the genetic modification inadvertently altered the level of a naturally-occurring toxin to a potentially hazardous level, in which case the food would be treated as an adulterated food.[57] The FDA has not reviewed the food safety of transgenic crops, including transgenic crops that are not intended for use as foods, at the field trial stage, relying instead on its post-market power to remove adulterated foods and USDA regulations to prevent contamination of food crops by experimental transgenic crops.[58] This, in part, has prompted criticisms that the current regulatory system is inadequate to prevent contamination of the public food supply by the adventitious presence of genetically-engineered products.[59]

The EPA's regulatory authority is directed to pesticide use and its impact on human health and the environment. Thus, the EPA's oversight over transgenic plants is limited to plants that produce a pesticide. The EPA's authority stems from two federal statutes: the FFDCA[60] and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).[61] The EPA regulates the field testing as well as commercial use of pesticides under FIFRA. For field testing a new pesticide, an experimental use permit from the EPA is required if the cumulative acreage

55. *See* FDA Statement of Policy: Foods Derived from New Plant Varieties, 57 Fed. Reg. 22,984, 22,985 (May 29, 1992) [hereinafter FDA Statement of Policy], *available at* http://www.cfsan.fda.gov/~acrobat/fr920529.pdf (last visited Apr. 10, 2005); *see also* PEW INITIATIVE, *supra* note 26, at 74; Bratspies, *supra* note 49, at 607.

56. *See* FDA Statement of Policy, *supra* note 55, at 22,990.

57. *See id*. at 22,988-90; *see also* PEW INITIATIVE, *supra* note 26, at 74.

58. *See* PEW INITIATIVE, *supra* note 26, at 74, 78-79, 85.

59. *See id*., at 84-85 (summarizing the argument that even if containment measures could achieve zero gene flow in theory, food production is too complex to ensure 100% compliance and thus, the FDA's post-market authority alone is insufficient to protect the public from food safety risks associated with the adventitious presence of transgenic crops that produce substances such as industrial chemicals and pharmaceuticals).

60. 21 U.S.C. §§ 301-397 (2000).

61. 7 U.S.C. §§ 136-136y (2000).

exceeds a total of ten acres.[62] In order to be distributed commercially, a new pesticide must be approved by the EPA through registration.[63] To be registered, a pesticide must not cause unreasonable adverse effects on the environment[64] when used for the purposes, and in accordance with conditions, proposed by the registrant.[65] To prevent unreasonable adverse effects, the EPA can, with registration, impose additional conditions and use restrictions that are legally enforceable against the registrant.[66] Pesticides such as the *Bt* toxin produced within transgenic plants genetically engineered to be pest resistant are regulated as plant-incorporated-protectant (PIPs) under the same statutes governing conventional chemical pesticides.[67] Thus, the EPA could require registrants and seed companies to comply with extensive use and planting restrictions for a transgenic plant engineered to produce PIPs as part of the registration. Planting restrictions include, for example, maintaining refuges, the portion of a field consisting of a non-transgenic variety that surrounds a field of transgenic plants, to minimize development of resistant insects[68] as well as to minimize gene flow by cross pollination to unintended recipients. Planting restrictions are imposed on farmers who purchase transgenic seeds through private agreements between the farmers, who are not legally obligated to comply with EPA restrictions, and the seed companies, who are legally obligated to the EPA.[69] Such grower agreements are part of compliance assurance programs that the EPA requires of registrants and seed companies as part of registration.[70] Use and planting restrictions are economically costly, and there is evidence that

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62. EPA Pesticide Programs, 40 C.F.R. § 172.3 (2004).

63. 7 U.S.C. § 136a(a).

64. *Id*. § 136a(c)(5).

65. *Id*. § 136a(d), (c)(5).

66. *See* PEW INITIATIVE, *supra* note 26, at 39, 41; *see also* MICHAEL R. TAYLOR & JODY S. TICK, PEW INITIATIVE ON FOOD AND BIOTECHNOLOGY & RESOURCES FOR THE FUTURE, POST-MARKET OVERSIGHT OF BIOTECH FOODS: IS THE SYSTEM PREPARED? (2003) (examining the postmarket regulatory oversight of genetically modified crops and foods), *available at* http://pewagbiotech.org/research/postmarket/PostMarket.pdf. (last visited Apr. 10, 2005).

67. TAYLOR & TICK, *supra* note 66, at 20-21.

68. *Id.* at 21, 23.

69. *See* PEW INITIATIVE, *supra* note 26, at 41-43; *see also* TAYLOR & TICK, *supra* note 66, at 23.

70. *See* PEW INITIATIVE, *supra* note 26, at 41-43; *see also* TAYLOR & TICK, *supra* note 66, at 23.

relying on registrants and seed distributors to monitor and enforce compliance has limited effectiveness. Full compliance with refuge requirements among corn growers nationwide, for example, was reported at 80% and 71% for the 2001 and 2000 growing season, respectively.[71] Similarly, it has been reported that almost 20% of farmers who had grown StarLink™ corn had failed to comply with planting requirements.[72]

USDA regulations also address gene flow from transgenic plants to unintended recipients. USDA oversight over transgenic plants focuses on the environmental effects of these plants. The federal Plant Protection Act[73] (PPA) gives the USDA the authority to regulate the introduction of organisms deemed to be a plant pest or a noxious weed.[74] Within the USDA, the Animal and Plant Health Inspection Service (APHIS) specializes in the regulation of transgenic plants that could potentially be a "plant pest."[75] The term "plant pest" is defined broadly to include any living organism that can directly or indirectly cause harm to a plant.[76] A transgenic plant is assumed to be a plant pest until proven otherwise.[77] It is subject to regulation if (1) the plant itself, (2) the source of the transgene, or (3) the source of the vector used in constructing the transgenic plant falls into one of the taxa listed in 7 C.F.R. § 340.2.[78] A transgenic plant that satisfies this plant pest inquiry cannot be released into the environment without APHIS authorization, which can be obtained in a notification or permit process.[79] The notification process is applicable to plants that satisfy six eligibility criteria and the specific performance standards set out in 7 C.F.R. § 340.3.[80] Plants

71. TAYLOR & TICK, *supra* note 66, at 35.

72. Associated Press, *USDA Finds Farmers Don't Meet EPA Biotech Rules* (Sept. 10, 2003), *available at* http://www.siliconvalley.com/mld/siliconvalley/6742338.htm?template=contentModules/printstory.jsp (last visited Jan. 10, 2005).

73. 7 U.S.C. §§ 7701-7772 (2000).

74. *Id*. § 7712(a).

75. Animal and Plant Health Inspection Service, USDA, 7 C.F.R. § 340.0-.9 (2004).

76. *Id*. § 340.1.

77. *See* APHIS PLANT PROTECTION AND QUARANTINE, UNITED STATES DEPARTMENT OF AGRICULTURE, APHIS BIOTECHNOLOGY: PERMITTING PROGRESS INTO TOMORROW, APHIS FACTSHEET (2002) [hereinafter PERMITTING PROGRESS].

78. 7 C.F.R. § 340.1, .2.

79. *Id*. § 340.0(a).

80. *Id*. § 340.3(b), (c).

that do not meet the eligibility criteria for notification, such as plants engineered to produce pharmaceuticals, require a permit.[81] In either case, the applicant is required to take steps to prevent gene flow from transgenic plants to unintended recipients.[82] In the notification process, several of the performance standards are directed to preventing inadvertent mixing with non-regulated plants and persistence of the transgenic plant in the environment.[83] One aspect of satisfying the performance standards is to ensure that transgenic plants do not cross pollinate with compatible plants nearby, whether cultivated or wild.[84] Methods for minimizing the likelihood of cross pollination include detasseling, bagging of flowers/tassels to prevent open pollination, physical isolation such as that used in foundation seed production or temporal isolation to prevent overlap of the pollination period for transgenic and other plants.[85] Similarly, a permit for the field release of a regulated plant will include conditions requiring adoption of specific confinement measures such as isolation distances, temporal isolation, and planting restrictions appropriate to the transgenic plant to prevent pollen-mediated gene flow and inadvertent mixing.[86] With the exception of transgenic plants engineered to produce a pharmaceutical, once a transgenic plant is ready for commercialization, the developer can petition for "nonregulated status," that is, a determination based on results of field trails conducted under a permit or notification that a particular transgenic plant is not a significant plant pest risk with widespread planting.[87] A transgenic plant that is given non-regulated status can be planted under less restrictive conditions than those imposed by the permit or notification

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81. *Id*. § 340.3(a), (b)(4)(iii).

82. *Id*. § 340.4(b); *see also* PERMITTING PROGRESS, *supra* note 77.

83. *See* 7 C.F.R. § 340.3(c)(2), (5), (6); *see also* ANIMAL AND PLANT HEALTH INSPECTION SERV., USDA, USER'S GUIDE FOR INTRODUCING GENETICALLY ENGINEERED PLANTS AND MICROORGANISMS § VI.I,J, *available at* http://www.aphis.usda.gov/brs/usergd.html (last visited Mar. 3, 2005); USDA, BIOTECHNOLOGY INSPECTION MANUAL FOR NOTIFICATION FIELD RELEASE 3.3 (2002) [hereinafter USDA BIOTECHNOLOGY INSPECTION MANUAL], *at* http://www.aphis.usda.gov/ppq/manuals/pdf_files/Biotech_Manual.pdf (last visited Apr. 10, 2005).

84. USDA BIOTECHNOLOGY INSPECTION MANUAL, *supra* note 83, at 3.4.

85. *Id.* at 3.5.

86. *See* Memorandum from the Animal and Plant Health Inspection Service, United States Department of Agriculture (May 21, 2002); *see also* PEW INITIATIVE, *supra* note 26, at 32; PERMITTING PROGRESS, *supra* note 77.

87. PEW INITIATIVE, *supra* note 26, at 33.

process,[88] and neither the plant nor its descendants are subject to APHIS oversight.[89] Plants engineered to produce a pharmaceutical, however, continue to be subject to APHIS oversight under the permit process even during commercial production.[90]

Physical containment practices, however, have never been able to absolutely prevent pollen-mediated gene flow[91] as pollination depends largely on environmental conditions that affect pollen longevity and movement. Corn pollen, for example, could remain viable for twenty-four hours though viability diminishes rapidly with desiccation.[92] In addition, pollen movement depends on the dispersal mechanism such as wind speed,[93] and pollination has been detected at distances as far as 503 meters from the pollen source.[94] Thus, although current physical containment strategies can be designed to

88. *Id.*; *see also* BIOTECHNOLOGY INDUS. ORG., REFERENCE DOCUMENT FOR CONFINEMENT AND DEVELOPMENT OF PLANT-MADE PHARMACEUTICALS IN THE UNITED STATES 7 (2002) [hereinafter BIO REFERENCE DOCUMENT] (stating "crops cleared for commercial introduction no longer require the confinement measures that were required by APHIS at the field test stage"), *at* http://www.bio.org/healthcare/pharmaceutical/pmp/PMPConfinementPaper.pdf (last visited Apr. 10, 2005).

89. *See* PEW INITIATIVE, *supra* note 26, at 52.

90. BIO REFERENCE DOCUMENT, *supra* note 88, at 7 (stating "APHIS considers all pharmaceutical-producing plants to be "regulated article" regardless of the stage development . . . . [and] impose[s] carefully tailored, science-based confinement procedures by permit during commercial production.").

91. *See* Bullock & Desquilbet, *supra* note 26, at 85 (stating that pollen drift is a major potential source of seed impurity and although practices such as planting all-male border rows and increasing temporal and spatial isolation of seed-producing fields could increase seed purity, these methods are imperfect as pollen can travel wide distances); *see also* Mike Gray, *Pollen Drift and refuge-Management Considerations for Transgenic Hybrids*, THE PEST MGMT. & CROP DEV. BULL., Apr. 17, 2003 (quoting Martin Bohn, assistant professor in the Department of Crop Sciences at the University of Illinois, as saying "[a]n adjustment of technical farm procedures can be used to avoid mixing of GM and non-GM seed, e.g., planting and harvesting conventional crops before GM crops. However, a containment of pollen employing normal farming procedures is not possible."), *at* http://www.ag.uiuc.edu/cespubs/pest/articles/200304e.html (last visited Apr. 10, 2005).

92. *See generally* Gray, *supra* note 91 (discussing Martin Bohn's presentation on "Pollen Drift and Its Impact on Gene flow Between GM and Non-GM Cultivars").

93. *Id.*

94. *Id.* (citing findings of M.D. Jones & J.S. Brooks reported in the Oklahoma Agricultural Experimental Station, Bulletin T-38).

achieve at least 99.5% seed purity, in theory,[95] seed purity levels for corn are closer to 99%.[96] Furthermore, gene containment strategies that rely on physical isolation does little to circumvent pollen-mediated gene flow that could lead to increased weediness or a decrease in diversity in cases such as trangenic bentgrass which is widely used in golf courses, for which wild relatives could be found in a variety of habitats,[97] and where pollen drift can be detected as far as twenty-one kilometers away.[98]

III. BIOLOGICAL CONTAINMENT STRATEGIES

The need to prevent gene flow from transgenic plants has led to the development of numerous biological methods of containment. These include the creation of transgenic plants that are male or seed sterile and the use of chloroplast engineering.[99] Male sterility approaches involve the use of mutagenesis or genetic engineering to create mutations in male reproductive structures such as the anther, the reproductive organ that produces pollen grains containing sperm cells.[100] By interfering with the function of tapetum, a layer of specialized cells in the anther believed to be important in pollen development, researchers have prevented the formation of pollen in transgenic tobacco and oilseed rape plants.[101] A similar approach is used in glufosinate-tolerant rapeseed of Plant Genetic Systems currently commercially cultivated in Canada.[102] Seed sterility approaches target genes in the embryo and endosperm that are important for seed formation. These approaches involved the use of an exogenous stimulus such as temperature, osmotic shock, or application of an

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95. *Managing "Pollen Drift" in Ohio Corn Fields: Planting Considerations*, CROP OBSERVATION AND RECOMMENDATION NETWORK, Apr. 22-28, 2003, *at* http://corn.osu.edu/archive/2003/apr/03-10.html#linkb (last visited Apr. 10, 2005).

96. Bullock & Desquilbet, *supra* note 26, at 85 (citing D. Langer, Director of Parent Test Research at Pioneer Hi-Bred International, Inc.); *see also id.* (stating that the lower seed purity level for corn compared to soybeans stem from its tendency to cross-pollinate).

97. Watrud, *supra* note 44, at 14,533.

98. *Id*.

99. Daniell, *supra* note 4, at 582 tbl. 1.

100. *Id.* at 583.

101. *See* Celestina Mariani et al., *Induction of Male Sterility in Plants by a Chimaeric Ribonuclease Gene*, 347 NATURE 737 (1990).

102. Daniell, *supra* note 4, at 583.

antibiotic, to alter levels of an intracellular product whose function or lack of is essential for seed fertility. A well known example is the terminator technology in which application of tetracycline to transgenic seeds just prior to sale triggers expression of a gene encoding a product that destroys seed tissues.[103] Other variations of this approach include manipulating the level of an intracellular hormone that causes seed abortion[104] or engineering into a transgenic plant a function that blocks fertility and one that restores it in such a way that fertility can be controlled by controlling the expression of the appropriate function.[105]

A third biological method for gene containment, which has been met with much enthusiasm, is chloroplast engineering. Chloroplasts are chlorophyll-containing cytoplasmic organelles found in plants and algae within which photosynthesis[106] takes place.[107] Like the plant's nucleus, chloroplasts contain genetic materials, which can be expressed using the organelle's protein synthesis machinery.[108] Unlike genetic materials from the nucleus, chloroplasts genetic materials are typically inherited in a uniparental fashion through the female parent. This can result from unequal cell division during the formation of generative cells that eventually become sperm cells, or the degradation of chloroplast genetic material during generative cell formation, giving rise to sperm cells without chloroplasts.[109] In this way, transgenes cloned into chloroplasts would be confined to the egg and no pollen-mediated gene transfer occurs. Other advantages of chloroplast engineering include high-level gene expression stemming from the presence of multiple transgene copies thus allowing for efficient and low cost production of a desired product such as a pharmaceutical or an industrial chemical.[110]

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103. *Id.*

104. *Id.* (discussing a technology developed by D.T. Tomes).

105. *Id.* at 583-84 (discussing the recoverable block of function system developed by Koivu et al.).

106. Photosynthesis refers to the light-dependent synthesis of organic carbon from inorganic molecules.

107. *See* MICHAEL THAIN & MICHAEL HICKMAN, THE PENGUIN DICTIONARY OF BIOLOGY 116 (9th ed. 1995).

108. *See id.*

109. Daniell, *supra* note 4, at 581-82.

110. Henry Daniell et al., *Milestones in Chloroplast Genetic Engineering: an Environmentally Friendly Era in Biotechnology*, 7 TRENDS IN PLANT SCI. 84, 87, tbl. 2 (2002).

Furthermore, since the product of the trangene is compartmentalized to the chloroplast, there is minimal toxic effect to the transgenic host plant.[111] The promise of chloroplast engineering has led to the creation of transgenic plants expressing genes conferring resistance to the herbicides glyphosate and bialaphos, the *Bt* toxin, and bacterial and fungal pathogens.[112] More than thirty transgenes have been stably integrated into chloroplast genetic materials including genes conferring drought and salt tolerance, genes involved in amino acid biosynthesis or phytoremediation, and genes encoding biopharmaceuticals, monoclonal antibody, edible vaccines, and biomedical polymers.[113] Maternal inheritance of transgenes and prevention of gene flow through pollen have been successfully demonstrated in tobacco and tomato plants.[114]

Yet the initial assertion that chloroplast engineering could be a practical solution to gene flow[115] prompted quick responses from various members of the scientific community calling for caution in over-relying on maternal inheritance as a mechanism for preventing pollen-mediated gene flow.[116] The rule that chloroplast genetic material is maternally inherited is not without exceptions. Conifers, for example, exhibit paternal inheritance of chloroplast, while alfalfa, and occasionally rice, exhibit biparental inheritance of chloroplast genes.[117] Chloroplast genetic materials also have been detected in the pollen of some pea cultivars.[118] Even when maternal inheritance is the norm, chloroplast genes could be transmitted

111. *Id.* at 86, tbl. 1.

112. *Id.* at 87, tbl. 2.

113. Daniell, *supra* note 4, at 582; Daniell et al., *supra* note 110, at 87, tbl. 2.

114. Daniell, *supra* note 4, at 582.

115. Henry Daniell et al., *Containment of Herbicide Resistance Through Genetic Engineering of the Chloroplast Genome*, 16 NATURE BIOTECHNOLOGY 345, 345 (1998); *see also* Roland Bilang & Ingo Potrykus, *Containing Excitement over Transplastomic Plants*, 16 NATURE BIOTECHNOLOGY 333, 333 (1998).

116. *See* C. Neal Stewart Jr. & C.S. Prakash, Letter to the Editor, *Chloroplast-Trangenic Plants are not a Gene Flow Panacea*, 16 NATURE BIOTECHNOLOGY 401 (1998); *see also* Joseph E. Cummins, Letter to the Editor, 16 NATURE BIOTECHNOLOGY 401 (1998).

117. *See* Stewart & Prakash, *supra* note 116; *see also* Cummins, *supra* note 116.

118. *See* Stewart & Prakash, *supra* note 116; *see also* Cummins, *supra* note 116.

through pollen under stressful conditions.[119] These data suggest that the effectiveness of chloroplast engineering as a means of curtailing gene flow needs to be evaluated on a case-by-case basis.

Another potential problem with over-reliance on chloroplast engineering to abrogate pollen-mediated gene flow is the transfer of chloroplast genetic material into plant nucleus.[120] To date, two independent studies have reported significant chloroplast-to-nucleus gene transfer in tobacco plants. One study reported that about one in every five million tobacco leaf cells assayed contained a gene that had been engineered into the chloroplast.[121] A second independent study that looked at seeds derived from outcrosses using pollen from a chloroplast-engineered transgenic plant reported about sixteen transfer events among 250,000 seedlings.[122] These "massive" rates of chloroplast-to-nucleus gene transfers[123] obtained under laboratory conditions have been characterized as underestimates of the actual rates of transfer since in each case, only a particular trait that was highly expressed was evaluated.[124] The genomes of plants such as *Arabidopsis* and rice are also known to contain chloroplast genetic material.[125] These data suggest that even if chloroplast genetic material is solely maternally inherited, chloroplast-to-nuclear transfer occurs and could potentially limit the effectiveness of chloroplast engineering as a means of curtailing pollen-mediated gene flow. On the other hand, Pal Maliga has noted that even if a trangene engineered into chloroplast finds its way into the pollen of the transgenic plant as a result of a chloroplast-to-nuclear transfer, is it likely that the transgene would not be expressed in the nucleus, especially if it is linked to a chloroplast-specific promoter, a sequence that enables

119. *See* Cummins, *supra* note 116.

120. *See* Chun Y. Huang et al., *Direct Measurement of the transfer Rate of Chloroplast DNA into the Nucleus*, 422 NATURE 72 (2003); *see also* Sandra Stegemann et al., *High-frequency Gene Transfer from the Chloroplast Genome to the Nucleus*, 100 PNAS 8828 (2003); Pal Maliga, *Mobile Plastid Genes*, 422 NATURE 31 (2003); William Martin, *Gene Transfer from Organelles to the Nucleus: Frequent and in Big Chunks*, 100 PNAS 8612 (2003).

121. Stegemann, *supra* note 120, at 8832.

122. Huang et al., *supra* note 120, at 72.

123. Martin, *supra* note 120, at 8612.

124. *Id.* at 8614.

125. *Id.* at 8613.

expression of the gene in chloroplast, but not in the nucleus.[126] And if so, adverse effects associated with gene flow to unintended recipient would be unlikely.

Even in the absence of chloroplast-to-nucleus transfer, gene flow could occur between a chloroplast-engineered transgenic plant and weedy relatives when these relatives act as pollen donors.[127] In this case, repeated cycles of backcrossing in which weedy relatives act as pollen donors would result introgression of the transgene into a weed genetic background.[128] It has been reported that hybridization and introgression rates were higher in backcrosses between a weedy wild radish, acting as a pollen donor, and transgenic male-sterile canola, acting as the female parent, than the reciprocal, that is, when canola is used as a pollen donor.[129] A similar result was found in canola crosses with weedy *Brassicas*.[130] Thus, in both chloroplast engineering and male-sterility approaches, gene flow could take place if the transgenic plant is fertilized by pollen from a related plant.[131] Recently, a mathematical modeling study indicates that if the leakage parameter of a gene containment strategy is 10^{-3}, there will be a 60% chance of escape of the transgene within ten generations.[132]

CONCLUSION

Developments in plant genetic engineering have made it possible to engineer plants with a wide array of useful traits. Yet the benefits of transgenic plants come with risks to the environment, ecological diversity, and the safety of the human food supply. These risks stem in part from the difficulties in preventing gene flow from the transgenic plant into unintended recipients. Advances in genetic engineering have also provided biological methods for curtailing gene flow such as male sterility or chloroplast engineering. Although these biological containment strategies are promising, their effectiveness is limited, and given the possibility of chloroplast-to-nuclear

126. Maliga, *supra* note 120, at 32.
127. Stewart & Prakash, *supra* note 116.
128. *Id.*
129. *Id.*
130. *Id.*
131. Daniell, *supra* note 4, at 583.
132. Ralph Haygood et al., *Population Genetics of Transgene Containment*, 7 ECOLOGY LETTERS 213, 217 (2004).

transfers and hybridization/introgression with wild relatives as pollen donors it is unlikely that gene flow could be absolutely abrogated. Thus, if the range of traits being introduced into plants expands, particularly to include the production pharmaceuticals and industrial chemicals, then caution and vigilance become ever more important if we are to minimize disruption to our environment and ecological systems and the risks to the safety of our food supply.