ISB NEWS REPORT

COVERING AGRICULTURAL AND ENVIRONMENTAL BIOTECHNOLOGY DEVELOPMENTS

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In This Issue:

NEWS AND NOTES

NAS AND SIX SISTER ACADEMIES RELEASE REPORT ON TRANSGENIC PLANTS AND WORLD AGRICULTURE

Seven academies of science, including five from developing nations, on July 11 released a report[1] describing the potential of agricultural biotechnology for alleviating hunger and poverty in the Third World, as well as obstacles impeding more widespread use of genetically modified (GM) plants. The Working Group on Transgenic Plants and World Agriculture included 22 scientists from the US National Academy of Sciences, Royal Society of London, Brazilian Academy of Sciences, Chinese Academy of Sciences, Indian National Science Academy, Mexican Academy of Sciences, and Third World Academy of Sciences. The Working Group called for developers and overseers of GM plants to ensure that their efforts reduce world hunger, while minimizing environmental impacts and providing productive employment in low-income areas.

Although GM plants can be developed to be more nutritious, stable in storage, and environmentally benign in production, most GM plants have not been developed with Third World needs in mind. GM plants that have been deployed so far in commercial agriculture are major cash crops resistant to pesticides, insects, or viruses. Millions of hectares of transgenic soybeans, cotton, tobacco, potato, and corn have been grown annually in the United States (28.7 million hectares in 1999), Canada (4 million), Argentina (6.7 million), and China (0.3 million). The report recommended the development of transgenic staple crops such as maize, rice, wheat, cassava, yams, sorghum, plantains, and sweet potatoes, which would benefit poor farmers in developing areas by improving their access to food and employment. The Working Group noted that cooperative efforts between the public and private sectors will be needed to develop such transgenic crops.

Citing the debate about potential benefits and risks from the use of GM plants, the report called for concerted, well-organized efforts to investigate potential environmental effects—both positive and negative—of GM technologies for specific applications. Such effects should be assessed against baseline data from conventional agricultural technologies. Public health regulatory systems need to be put in place in every country to identify and monitor any potential adverse human health effects of transgenic plants, as for any other new variety. The academies also recommended that national governments ensure that they have sufficient capabilities to facilitate implementation of biosafety guidelines.

The report recommended that private corporations and research institutions make arrangements to share GM technology, now most often held under restrictive

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patenting and licensing agreements, with responsible scientists who can use the technology to alleviate hunger and enhance food security in developing countries. Poor farmers in developing countries should be allowed to save seed from genetically modified varieties for their own use. An international advisory committee should be created to assess the interests of private companies and developing countries with respect to transgenic plants that can benefit the poor, not only to resolve intellectual property disputes, but also to identify areas of common interest and opportunities for public-private partnerships.

The general tone of the report embraced agricultural biotechnology and identified areas where public- and private-sector efforts might enhance the beneficial application of GM plants. Bruce Alberts, president of the US National Academy of Sciences, stated that “[biotech] companies are ready to share some technologies as long as it doesn’t backfire on them commercially.[2]” Val Giddings, Vice President of the Biotechnology Industry Association, agreed that “the technology is not being used as it could and should be, and that’s a very real problem.” However, Giddings went on to say that it is “not fair to look to the private sector to solve problems of international assistance,” and dismissed intellectual property issues as “way overblown.”

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PLANT RESEARCH

WHAT DO YOU GET WHEN A CHICKEN GENE IS PUT INTO MAIZE?

If the Gene is for the Egg White Protein, Avidin, You Get an Insect Resistant Transgenic Grain

What human food proteins might be candidate biopesticides in transgenic plants? Trying to answer that question was the motivation for a collaborative research project between biochemists, molecular biologists, and entomologists at the Agricultural Research Service, USDA’s Grain Marketing and Production Research Center (http://www.usgmrl.ksu.edu) in Manhattan, Kansas and two agricultural biotechnology companies, Pioneer Hi-Bred International Inc. (http://www.pioneer.com), Johnston, Iowa and ProdiGene Inc. (http://www.prodigene.com), College Station, Texas. Some of the results were published recently in the journal *Nature Biotechnology*[1]. With all of the controversy surrounding transgenes and the questionable safety of their encoded proteins, we thought that it would be beneficial to develop as biopesticides in transgenic plants some proteins that were already being consumed in the human diet. This type of advancement might result in fewer objections to the use of transgenes in foods or feeds for humans and animals. The end result of the project was the development of a transgenic maize that contains the hen's egg white protein avidin, which makes the grain resistant to stored-product insect pests.

The project began about ten years ago when Thomas Czapla, a graduate student at Kansas State University who subsequently worked as a molecular entomologist at Pioneer, expressed an interest in determining whether some of the proteins we were evaluating for biocidal activity against stored-product insect pests might also be tested against field crop pests such as corn borers and rootworms. At that time, as now, there were very few biopesticides other than the endotoxins from the bacterium, *Bacillus thuringiensis*, that have been commercially developed in transgenic plants for insect pest control. Pioneer was interested in prospecting for proteins that would have a broader spectrum of activity than Bt-type proteins.

Czapla, who unexpectedly passed away last January at the young age of 38, and members of my laboratory discovered that chicken avidin and a related protein, bacterial streptavidin, when administered in semi-artificial diets, caused a deficiency of the vitamin biotin in the corn borer and several species of stored-product insects. This, in turn, led to stunted growth and mortality of those species[2]. What makes avidin particularly unique as a biopesticide is that not only is it a common dietary protein, it also has an antidote, biotin, which may be used as a supplement to prevent toxicity or to rescue potential victims from adverse effects. Biopesticides such as the Bt toxins do not have any kind of antidote.

Those encouraging results led to the next phase of the project, which was the creation of transgenic avidin maize by scientists at Pioneer and ProdiGene. John Howard, who at that time was the manager of the Pioneer's Protein Products Group, which later was merged with Terramed Inc., a Texas pharmaceutical biotechnology firm, to form ProdiGene, and his group at Pioneer were developing maize for commercial production of industrial proteins. The first transgenic maize product commercialized by ProdiGene was avidin, which also is used as a research chemical and diagnostic reagent[3]. Avidin is produced in corn at a fraction of the cost that it can be produced in chicken eggs.

ProdiGene and Sigma Chemical Co., St. Louis, Missouri, began marketing avidin produced in maize in 1997. At about the same time, the Kansas research group began evaluating avidin maize for host plant resistance to stored-product insect pests. When present in maize at levels of ~100 ppm, avidin was toxic to and prevented development of many internally and externally feeding insect pests that damage grains during storage, including the rice weevil, lesser grain borer, Angoumois grain moth, warehouse beetle, sawtoothed grain beetle, flat grain beetle, red and confused flour beetles, Indianmeal moth, and Mediterranean flour moth. Other species reported to be susceptible to avidin toxicity include the house fly, hide beetle, fruit fly, olive fruit fly, flour mite, tobacco hornworm, tobacco budworm, black cutworm, sunflower moth, beet armyworm, and cotton bollworm. The only species tested to date that was not susceptible to avidin toxicity was the larger grain borer. This species is occasionally found in southern Texas but is not a significant pest in the US. It has been a pest, however, in Mexico, Central America, northern South America, and Africa. How the larger grain borer tolerates high levels of avidin is unknown but the question will be addressed in a future study. The existence of an avidin-tolerant species, however, may indicate the possibility of the development of insect resistance to avidin if resistance management is not conducted properly. Nevertheless, avidin acted as a biopesticide in transgenic maize with a specific toxicity comparable to Bt toxins, and the spectrum of activity of the former protein was much broader than the latter.

Because expression of avidin in maize was under the control of the ubiquitin promoter, expression of the protein in the anthers occurred, which caused male sterility and non-uniform protein expression. About half of the individual kernels had inadequate insect resistance because those kernels contained little or no avidin. That result led us to develop a nondestructive method, utilizing near infrared spectroscopy, to screen for avidin content and separate low- from high-avidin kernels prior to conducting bioassays of intact kernels. A future goal is to increase the proportion of avidin-containing, insect-resistant kernels by performing a new transformation event using promoters designed to avoid expression in the anthers and to yield kernels containing a more uniform and effective level of avidin.

Avidin maize was demonstrated to have excellent resistance to storage insect pests after the kernels were ground into a meal, because an average concentration of ~100 ppm avidin in the meal was sufficient for protection, a level substantially lower than that present in chicken egg white. Humans can suffer "egg white injury" but only after consuming exceedingly large quantities of avidin, such as eating a couple dozen raw eggs a day for several months. Avidin maize was not toxic to mice when administered as the sole component of their diet for three weeks.

Following a thorough and satisfactory safety risk assessment of avidin corn, its utilization as a food or feed grain would be an exciting development that could impact on post-harvest losses caused by stored-product insect pests. Avidin maize might be processed to include supplementation with biotin or by treatment with heat. The latter process would denature the avidin as well as the avidin-biotin complex and release most of the biotin for use by the consumer. Another use of avidin maize could be as an insect-resistant background host plant germplasm for farming of other valuable bio-pharmaceutical or industrial proteins. Whatever utilization does occur, avidin maize is at least a proof of concept for the efficacy of a common human food protein as a biopesticide in transgenic plants.

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Cyanogen Reduction in Transgenic Cassava:

Generation of a Safer Food Product for Subsistence Farmers

Many wild and domesticated crops produce secondary compounds that effectively reduce or deter herbivory by insects and animals. Some of these herbivore deterrents are relatively non-toxic; however, some herbivore deterrents are lethal if ingested. One of the more toxic classes of herbivore deterrent compounds is the cyanogenic glycosides. The cyanogenic glycosides are a group of nitrile-containing plant secondary compounds that yield cyanide following their enzymatic breakdown (cyanogenesis). It is estimated that between 3,000 and 12,000 plant species produce cyanogenic glycosides. Many important crops are cyanogenic, including sorghum, almond, lima beans (non-domesticated), and white clover. The most agronomically important of the cyanogenic crops is the tropical root crop cassava (*Manihot esculenta*, Crantz). Over 153 million tons of cassava root is harvested annually in the tropics, primarily for human consumption.

Cassava has many agronomic features that make it an ideal crop for cultivation on marginal lands in the tropics. It is drought tolerant, grows on nutritionally poor soils, and it produces large yields of starch. In addition, the presence of cyanogens in cassava has been shown to reduce herbivory. Recent studies also suggest that subsistence farmers in sub-Saharan Africa may rely on the toxicity of cyanogens to protect their crop from theft.

Various human health disorders have been linked to the consumption of poorly processed cassava containing residual cyanogens. Chronic cyanide exposure has been associated with the occurrence of several health disorders including hyperthyroidism and tropical ataxic neuropathy, particularly in sub-Saharan Africa. In addition, the consumption of unprocessed and highly cyanogenic varieties of cassava may cause permanent paralysis of the legs (konzo). The incidence of konzo is most frequent during crop failures or when less time is taken to process or remove cyanogens from cassava. Significantly, cyanide poisoning due to consumption of poorly processed cassava is exacerbated by insufficient consumption of the sulfur-containing amino acids, cysteine and methionine. The sulfur-containing amino acids are required for the detoxification of cyanide in humans by the enzymes rhodanese and/or ß-cyanoalanine synthase. Significantly, the conditions (e.g., drought) that may lead to the use of short-cut cassava processing practices often go hand-in-hand with reduced availability of protein (methionine or cysteine) in the diet.

Recently, the biochemistry and physiology of cyanogenesis in cassava has been elucidated. The generation of cyanide from linamarin (cyanogenesis) begins when the plant tissue is damaged. Rupture of the plant cell vacuole releases linamarin. Subsequently, linamarin is hydrolyzed by a cell wall ß-glycosidase known as linamarase. The products of linamarin hydrolysis are acetone cyanohydrin and glucose. Significantly, acetone cyanohydrin will spontaneously decompose to cyanide and acetone at pHs >5.0 or temperatures >35 ^{0}C. Acetone cyanohydrin also is broken down by the cassava enzyme hydroxynitrile lyase (HNL).

Until recently, it had been assumed that the only cyanogen present in processed cassava foods was linamarin. Several studies have shown that some portion of ingested linamarin is de-glycosylated in the body where cyanide is presumably produced from the spontaneous decomposition of acetone cyanohydrin. In 1992, however, Dr. Hans Rossling and colleagues demonstrated that the major cyanogen present in poorly processed cassava roots was not linamarin but acetone cyanohydrin. This result was quite unexpected since it was assumed that acetone cyanohydrin would be eliminated from foods by spontaneous (high pH and/or temperature) or enzymatic breakdown. Significantly, free cyanide has not been found in cassava foods, presumably due to its volatilization. To account for the presence of acetone cyanohydrin in cassava foods, it was hypothesized that the low pH conditions used during cassava processing (soaking and fermentation) reduced the rate of spontaneous acetone cyanohydrin decomposition. This hypothesis, however, did not address the issue of acetone cyanohydrin turnover catalyzed by HNL.

In 1996, we characterized the abundance, distribution, and kinetic properties of HNL in cassava roots, stems, and leaves. Our objective was to determine the biochemical basis for the unexpectedly high levels of acetone cyanohydrin in processed cassava food products. Significantly, we discovered that HNL was expressed and present only in leaves. Thus, it was apparent that the high acetone cyanohydrin levels present in processed cassava roots could be attributed to the absence of HNL in roots. This observation lead to the development of transgenic strategies to facilitate cyanogen elimination from processed cassava foods. A transgenic approach for expressing HNL in roots also was predicated on the fact that cassava produces few seeds and has a long life-cycle (one year seed-to-seed). Thus it would be difficult to use traditional breeding and selection strategies to identify plants expressing HNL in roots. Furthermore, cassava typically is propagated clonally as stem cuttings in the field.

Our strategy for reducing the cyanide toxicity of cassava food products was to express HNL in the roots of transgenic cassava. Using an *Agrobacterium* mediated transformation system we introduced a cassava cDNA encoding HNL into somatic embryos. Transgenic cassava plants were regenerated and verified by PCR screening for the integrated HNL cDNA. A total of eight transgenic plants have been obtained to date. The HNL activity of root extracts obtained from in vitro transgenic plants has been measured. HNL activities in transgenic plants range from 0 - 0.56 mmol CN/mg protein/hr. Significantly, the HNL activity of crude leaf extracts is 0.6 mmol CN/mg protein/hr. Thus, HNL activity rates comparable to those in leaves could be obtained in the roots of transgenic plants.

Currently, the transgenic plants are being grown under greenhouse conditions to produce full size roots. It is expected that the roots from transgenic plants expressing HNL will have reduced levels of acetone cyanide or cyanogenic potential relative to wild type plants following processing. Follow-up field trials will determine whether the expression of HNL in roots in fact reduces the cyanide toxicity of cassava food products. It is expected that the HNL-dependent acceleration and increased efficiency of cyanide removal from cassava roots will reduce the level of chronic cyanide exposure from cassava food products and facilitate the broader acceptance of cassava as a safe food product for the consumer.

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ANIMAL RESEARCH

GENE EXPRESSION ON TARGET IN SHEEP

The eagerly awaited paper reporting gene targeting in sheep has been published in the June 29, 2000 issue of *Nature* by scientists at PPL Therapeutics in Edinburgh, UK. Ever since the first report of sheep cloning in 1996, nuclear transfer technology has been heralded as a means of circumventing the block to gene targeting in species other than mice. Current gene targeting technology in mice requires embryonic stem cell cultures that remain undifferentiated after stable transfection and selection in culture. The lack of comparable embryonic stem cells in other species has limited gene targeting experiments to mice.

Gene targeting involves the precise manipulation of a specific gene or chromosomal location. The gene can be modified slightly by the insertion, deletion, or substitution of a few nucleotides or can be deleted entirely. Animals containing a functional deletion of a gene are referred to as "knock-out" animals. The potential advantages of gene targeting are numerous. Gene targeting can be used to correct or delete a deleterious gene or to ensure the precise chromosomal placement of a foreign gene during transgenesis.

In this report, the sheep alpha 1 procollagen (COL1A1) gene was selected as the target genetic locus because 1) it is one of the few well studied genes cloned from sheep, 2) it is highly expressed in fetal fibroblasts, facilitating selection for the gene targeted event, and 3) mutations in the gene can be used to generate animal models of human diseases (other than mice). In humans, mutations in the conserved COL1A1 gene cause connective tissue disorders, such as osteogenesis imperfecta.

Primary sheep fetal fibroblasts were transfected with two different gene targeting constructs. One targeting construct was designed to insert a selectable marker (neo) after the procollagen gene to produce a fused messenger RNA between procollagen and neo. The second targeting construct was designed to fuse not only neo but also a transgene, consisting of the ovine beta lactoglobulin promoter and human alpha 1 antitrypsin (AAT) gene, to procollagen. Following selection and screening for fetal fibroblasts containing the desired genetic modification of the procollagen locus, nuclear transfer was performed to generate lambs.

Out of the 417 reconstructed embryos, 14 liveborn lambs were generated. Seven lambs died within 30 hours of birth and four more died on days three and eight and weeks 7.5 and 12. Three lambs are still alive and are about one year of age. Post mortem examination of lambs that died in utero or after birth revealed that there was a high incidence of kidney defects, liver and brain pathology. These findings, however, are similar to previous nuclear transfer studies indicating that the developmental abnormalities are likely due to some aspect of the nuclear transfer protocol and not a consequence of gene targeting per se.

One of the surviving lambs, which had the human AAT transgene inserted at the procollagen locus, was hormonally induced to lactate. Milk samples from this lamb contained 650 micrograms of human AAT per milliliter of milk. This human AAT level is comparable to the highest level of AAT found in transgenic sheep containing the same human AAT transgene integrated at random chromosomal locations. This result indicates that the procollagen locus allows correct mammary-specific transgene expression even though the procollagen gene is not normally expressed in mammary cells. Thus the procollagen gene locus may serve as an ideal site for the insertion and expression of other therapeutically useful genes.

This report of successful gene targeting opens up a wide range of possibilities for genetic manipulation of livestock. Expression of human pharmaceutical proteins in the milk of transgenic livestock will not be such a hit-or-miss proposition caused by differences in the chromosomal location of the transgene. Also, key genes in the livestock genome can now be deleted. As mentioned in the paper, the authors have preliminary evidence showing that the alpha-1,3-galactosyl transferase gene in pig fibroblasts has been targeted. Functional disruption of this enzyme would make pig tissue less immunogenic to the human immune system and would be a major step forward in the development of pig organs and tissues for xenotransplantation.

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REGULATORY NEWS

REVERSAL OF FORTUNES

California court finds Monsanto's arguments appealing . . .

In March 1998, a San Diego Superior Court jury awarded $174.9 million in damages to Mycogen Plant Science, Inc. in a breach of contract suit against Monsanto, Inc. This case began in 1989 when Monsanto granted options to license technology, including *Bacillus thuringiensis* (Bt) insect-resistance technology, to Lubrizol Genetics, which was subsequently acquired by Mycogen. When Mycogen tried to exercise the options in 1993, Monsanto refused and Mycogen sued, seeking access to certain Bt gene technology.

A year later, a San Diego Superior Court judge granted Monsanto's motion for summary judgment, which effectively upheld Monsanto's refusal. But Mycogen obtained a reversal of the ruling on appeal, and then went on to file a damage suit for lost profits due to the lack of access to Monsanto's technology. The result: a $174.9 million award, which represented the largest compensatory award ever made by a California jury.

Monsanto appealed the verdict, arguing that Mycogen should not have been allowed to sue twice–once for a license to Monsanto technology, and once for presumed lost profits caused by the delay in granting the license. Monsanto also argued that Mycogen should not have received damages for future profits when there was no guarantee that the company would have created a profitable business from the technology.

On June 28th of this year, the California Court of Appeals in San Diego overturned the jury award. The three-judge panel voted unanimously that Mycogen should not have received any award from the second trial because the company had won its first lawsuit. The appellate court also rejected Mycogen's claim that Monsanto should license genetically engineered germplasm to Mycogen.

Dow Chemical Company, which acquired Mycogen in October 1998, has promised that it will seek review of the appellate court decision by the California Supreme Court.

. . . while plant-related patents wither by popular demand

Newly issued biotech patents are stimulating protests. During February, activists held a rally in front of the European Patent Office (EPO) in Munich to object to the issuance of a European patent for isolating and selecting stem cells. The EPO had accidentally allowed claims that were not restricted to nonhuman animals, and the protesters took the position that the claims could be read to cover the cloning of humans.

In the EPO, a third party can challenge the validity of a European patent within nine months of the publication of the notice to grant the patent. An "Opposition proceeding" may result in the patent being upheld in an unchanged or amended form, or the Opposition Division may decide to revoke the patent. In April, Greenpeace filed an Opposition request to allow the EPO the opportunity to reconsider the stem cell claims. Since both the EPO and the patent licensee have indicated an eagerness to resolve this issue, the proceedings should go smoothly. Protests against patents, however, do not always go well for the patentee, as shown by the fate of a patent naming the U.S. Department of Agriculture and W.R. Grace & Co. as applicants.

In 1990, the USDA and W.R. Grace & Co. filed a patent application with the EPO that covered a method for controlling fungi on plants using an extract of Neem tree oil. The patent was issued in 1994 (EP 0 436 257), and during the following year, an Opposition to the patent grant was filed on behalf of the Green Group in the European Parliament (Brussels), the Research Foundation for Science, Technology, and Natural Resource Policy (New Delhi), and the Germany-based International Federation of Organic Agriculture Movements.

Starting on the first day, the hearing attracted a great deal of fanfare, including demonstrations outside the EPO building, and the presentation of 500,000 signatures from those who demanded that all Neem tree-related patents be revoked. However, the validity of the patent hinged upon legal determinations, not rhetoric. During the Opposition proceeding, the Opponents provided evidence that the fungicidal effects of Neem seed extracts were known, and had been used for centuries in India. Moreover, Ajay Bio-Tech, an agrochemical company in Pune, India, demonstrated that it had been making a Neem-based fungicide since the early 1980's. The Opposition Division revoked the patent because prior public use destroyed the novelty of the claims.

There have been a number of similar patent-crushing cases during the last several years. For example, about three years ago, the US Patent and Trademark Office (USPTO) revoked a patent that claimed the use of powdered tumeric for wound and ulcer healing. Here, India's Council of Scientific and Industrial Research filed a reexamination request, and presented evidence that tumeric had been used in India for centuries to promote wound healing. This evidence was in the form of references, some of which were over 100 years old, and written in Sanskrit, Urdu, or Hindi. In light of these publications, and the USPTO decided that the claimed invention lacked novelty.

In a case that cropped up last year, the Coordinating Body of Indigenous Organizations of the Amazon Basin (COICA) and several other groups filed a request for reexamination with the intent to invalidate a US plant patent that was granted to Loren S. Miller in June 1986 for a novel variety of vine that he called "Da Vine." According to COICA, however, the vine grows naturally in the Amazon rain forest, where it is called ayahuasca, and Miller had not altered the naturally occurring form of the plant.

The USPTO agreed with the reexamination requestors, finding that publications describing the ayahuasca plant were available before the filing of the Miller patent application. An interesting aspect of this decision is that, for the first time, the USPTO considered plant specimen sheets stored in a herbarium collection as prior art publications, because they were publicly available and catalogued.

More recently, Pod-ners LLC, an entity that holds a patent claiming a particular *Phaseolus vulgaris* field bean, filed a patent infringement suit against Miguel Tachna's US importer of beans. Tachna is the president of a growers group in the northwest Mexican State of Sinaloa who asserts that his farmers have long cultivated the same bean claimed in the Pod-ners patent. With support from the Mexican government, Tachna's group and others filed a countersuit alleging that the bean patent is invalid, because the claimed bean is genetically identical to a bean that was registered in Sinaloa in 1978. No word yet on whether the Pod-ner patent is a has-bean.

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INDUSTRY NEWS

"NEW" CARGILL REMAINS COMMITTED TO BIOTECH

But Will Also Serve Emerging Niche Market for Non-Bioengineered Grain

It's been just over a year since Cargill's controversial acquisition of Continental's grain business was conditionally approved by the government. Since then, Cargill—with more than 85,000 employees in more than 1,000 locations in 60 countries—has quietly gone about its business of processing, marketing, and shipping grain to just about every latitude of the globe. Except now company officials say they have a greater ability to give customers what they want, including non-genetically engineered grain if customers so choose.

Under stipulations required by the US Justice Department, Cargill's acquisition, formally approved in July, 1999, did not include seven Continental facilities across the US, and Cargill divested itself of two grain-handling facilities in Illinois and another in Seattle. Cargill also agreed to make a third of its daily loading capacity at Havana, Illinois available to third parties to be used for delivery under Chicago Board of Trade contracts.

Continental's pork, poultry, cattle, aquaculture, animal nutrition, petroleum trading, financial services, and investment businesses were not included in the purchase—Cargill only assumed Continental's grain business. Based on past history, the combined grain businesses of the two companies were expected to handle about 35 percent of US grain exports, although Cargill officials say the actual amount is significantly less.

More IP Options

Terry Garvert, Cargill's wheat merchandiser, says the company now has better capacity to co-load several different classes of wheat on an export vessel. "We're able to do this more quickly and more cheaply than what we might have been able to do through our own facilities before."

Indeed, Ruth Kimmelshue, Cargill's river origination manager, says that Cargill's acquisition of Continental has given Cargill more options for handling and processing grain with specialized or "identity preserved" (IP) traits. "[Continental] brought additional storage capacity to Cargill, which certainly helps in the IP process," she says. "We have a greater capacity to supply a wider variety of products that are IP, or specific-attribute grain." Cargill has an active IP program for different types and varieties of grain, including food-grade soybeans and corn, organic corn, waxy corn, high-protein hard wheat, and white wheat. Another IP trait available through Cargill is grain that is not genetically enhanced, even though the company is supportive of biotechnology. (Cargill prefers to use the term "genetically enhanced" (GE) rather than "genetically modified," to refer to the improved or enhanced characteristics engineered in plants using modern biotechnology tools.)

Cargill has been voicing its market acceptance of GE crops since transgenic soybeans and corn were first commercialized in 1996. Amidst growing unrest about biotechnology in the US last year, Cargill issued a statement last December to the grain industry and producers planning their 2000 seed purchases that reaffirmed the company's commitment to finding markets for whatever producers choose to grow, whether it be bioengineered, conventional, or specialized grain. "For those customers who request we separate genetically enhanced grain from non-genetically enhanced grain, that's a consumer preference and we are happy to do that. We see it as just another part of the market basket of goods and services we can provide to customers," says Kimmelshue.

All Cargill grain elevators accept GE corn and soybean varieties approved for use in the US and Europe. Most Cargill grain elevators also accept GE varieties approved in the US, but not yet approved in Europe. "The only criteria we have in that case is that producers inform us if they will be delivering genetically enhanced grain not approved for use in Europe, so we can channel them into other appropriate markets," says Kimmelshue.

GE-Free Grain Still Niche Market

Despite the fervor surrounding biotechnology, Kimmelshue says world demand for non-genetically enhanced grain is limited. "The reality is that it's still a niche market. The only destination that's been willing to pay for non-GE grain in any kind of volume is Japan." There have also been some small shipments to a handful of European and Mediterranean countries. In the instances that Cargill does sell non-GE grain, it is grown by producers under contract, just like grain with other IP traits.

Greater interest in IP grain has been spurred in part by the increasing number of private grain buyers in the world today. Paul Dickerson is vice president of overseas operations for US Wheat Associates, the American wheat export development organization based in Washington, D.C. He says that 10 to 15 years ago, about 80 percent of wheat purchases were government-controlled and 20 percent were private. "Today that figure is reversed," Dickerson says. "And even where the public sector still functions, the private sector is often allowed to participate." A greater interest in quality is another result of privatization. Bill Wilson, a professor in the agricultural economics department at North Dakota State University, says that privatization has resulted in private buyers evolving to become "more specific in respect to their purchases," including quality.

Cargill's Garvert believes GE technology will help enable IP systems, and vice versa. For example, he points out that glyphosate-resistant wheat—still several years away from commercialization—will result in cleaner wheat fields with less dockage. An IP market for this wheat might be created and channeled to Pacific Rim countries that specify low dockage levels. "I think the same skills that we're going to use in trying to keep a white wheat from a red wheat or handling specialty wheats are going to be very similar to the skills that we're going to need to handle a genetically enhanced grain in the future," says Garvert.

Cargill pursues biotech R&D through Renessen, joint venture with Monsanto

Through Renessen, a company formed in a joint venture with Monsanto, Cargill is pursuing biotechnology and traditional breeding to develop quality traits and customized products that enhance the functionality of grains, oilseeds, and other crops. According to Renessen's Web site, http://www.renessen.com, the venture "will be the breakthrough leader in quality traits, connecting biotechnology innovations with processing know-how in the first global alliance that spans the agricultural value chain."

Besides the nearly 50 employees at Renessen, there are some 130 scientists, most at Monsanto, who are working with Renessen to add desired traits to crops, according to an article on Renessen in the June, 2000 issue of Cargill News International (http://www.cargill.com/today/cni.htm). So far the board of Renessen has approved about ten projects, according to the CNI article. Not all of those projects will be winners. In fact, Renessen expects only about a 30 percent success rate. But even at that, the impact could be huge. "If all the projects we're currently working on prove to be successful, they'd represent a market worth of around $5 billion," says Norman Hay, co-CEO of Renessen and former head of Cargill's grain business. "This is a business of big risks and big rewards."

In its first year, Renessen has concentrated on enhanced corn, canola, and soybeans for the swine and poultry industries, according to CNI. Besides improved feed products, Renessen's charter includes crops with benefits for the processing industry, such as oilseeds enhanced with tocopherols. Eventually, Renessen will move into quality traits for crops that will help the dairy and beef industries.

Renessen leaders say that just as important as the product will be the process. Thus, it is researching and developing processes and relationships that will apply to biotech crops coming down the road. "We're laying out the business systems so we can jump-start future projects," says Axel Hinsch, a Cargill employee who is supervising one Renessen program.

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Sunflower Industry Survival May Hinge on Biotechnology

The fact that there are no transgenic sunflower hybrids currently in the marketplace may present some commercial benefits to confectionery and oil sunflower producers in the short-term. Over the long-term, however, sunflower industry leaders say that biotechnology will be needed to help sunflower compete for acreage with other oilseed crops that already possess genetically enhanced traits.

Currently, NuSun sunflower, developed with standard hybrid breeding methods, not bioengineering, is gaining a predominant share of the US sunflower industry market. NuSun is the trademark name for a new category of cooking oil made from sunflower that is mid-oleic, predominantly monounsaturated, and low in saturated fat. NuSun does not need hydrogenation for commercial applications, making it appealing to processors and consumers. However, sunflower and snack food industry experts say that NuSun probably would not have gained as much popularity had it been a bioengineered product.

At the same time, sunflower is losing acreage to other row crops, including soybeans and canola, many of which are bioengineered with the glyphosate-resistant gene (Roundup Ready). “We would estimate that about 25 percent of our acreage has been converted to other crops in the last few years,” says Larry Kleingartner, executive director of the National Sunflower Association (NSA), Bismarck, North Dakota (ND). Hybrids resistant to glyphosate are easier to manage for many producers, with less chemical usage and better crop quality and yields in many cases. Meanwhile, conventionally-bred sunflower hybrids have fewer weed control options and are vulnerable to insect problems and disease, primarily sclerotinia.

Also referred to as white mold, sclerotinia has eliminated sunflower production in some areas such as Ohio. Losses from sclerotinia in 1999 are estimated at nearly $100 million in ND, the leading sunflower-producing state. Sclerotinia head rot affected more than 80 percent of sunflower fields in eastern ND last year, reaching epidemic proportions not seen since 1986, according to North Dakota State University. Viable sclerotinia bodies can remain in the ground for eight years.

Statistics lend credence to the estimated erosion of US sunflower acreage to other crops. In 1995, just prior to when bioengineered crops began to explode on US acreage, just over four million acres of US cropland was planted to sunflower, with about 600,000 acres grown for the confectionery market, and close to 3.4 million acres designated for oil sunflower production. This year, a total of 2.8 million acres of sunflower were planted in the US, with about 500,000 acres grown for the confectionery market, and 2.3 million acres for oil-type sunflower.

Sunflower Bioengineering Challenges

“As the industry determines whether GMO is [profitable] for sunflower [growers], we have to consider other crop options that farmers have. There may be trouble keeping sunflower as a viable option for producers without biotechnology,” says John Soper, director of sunflower research, Pioneer Hi-Bred International, Johnston, Iowa.

Soper says there are research, testing, and regulatory hurdles to overcome before any bioengineered crop can be commercialized. Among many factors that must be analyzed and reported, the research developer must indicate the source of the gene, submit data proving whether it could be toxic or cause allergies, and whether it will affect yield or other plant characteristics and attributes. “If we put a transgene into sunflower, we would also need to prove whether it would change the composition of oil or meal or other factors,” says Soper. Environmental safety would also need to be proven. “Since sunflower is open-pollinated and can cross pollinate with wild sunflower and related species, that puts an extra regulatory burden on sunflower,” adds Soper. “We feel responsible for generating data that show if and when [commercial sunflower is bioengineered], there will be no negative impact on the ecology of wild sunflower.” Studies on the effect of bioengineered sunflower on wild species are currently being conducted.

Soper says the regulatory approval process can take a minimum of four years to complete and cost more than $2 million to introduce a single trait. Pioneer is collaborating with Advanta (Interstate Seed is its US-based entity) on the development of a sclerotinia-resistance gene. Soper estimates that a commercial sunflower hybrid bioengi-neered with sclerotinia-resistance wouldn’t be available on the market until 2005. “Sclerotinia resistance will most likely be achieved by combining transgenic resistance enhancement with natural tolerance,” he says. The gene that is being used to induce sclerotinia resistance is an oxalate oxidase gene, isolated from the Pioneer wheat variety 2548. Pioneer is also working collaboratively with Dow AgroSciences to develop genetic resistance to Argentina Looper, a leaf-feeding sunflower pest in Argentina.

Publicly available information from CONABIA (The National Advisory Committee on Agricultural Biosafety: http://siiap.sagyp.mecon.ar/http-hsi/english/conabia/frameing.htm) indicates that research also has been conducted in Argentina on glyphosate tolerant sunflower. Industry experts say that, from a regulatory standpoint, a hybrid with bioengineered sclerotinia resistance may be easier to introduce than glyphosate resistance because of fewer concerns related to outcrossing with wild species.

Preparing Processing, Marketing Channels

Robert Whyte, with Cargill Processing, West Fargo, ND, believes eventual development of a genetically engineered sunflower is likely. “The consumer will make the decision, but ultimately, we will go in that direction.” With bioengi-neered sunflower several years away from commercialization, Whyte believes the timing is right for the sunflower industry to build processing and marketing channels for genetically enhanced sunflower and non-transgenic sunflower, and answer key systematic questions. “Can grain handlers identity-preserve seed and oil? At first blush you might say no problem, but there would be increased costs. Will the market pay for GMO-free sunflower? Right now, the sunflower market is all GMO-free in the US. So the market may say, 'Why pay a premium if I can get it free now?'"

US confectionery sunflower distribution is split almost evenly, with about half used in the domestic market and half exported. "If we had GMO sunflower for the domestic market, I don't think we'd have a problem. It would be different with exports," says Bob Majkrzak, president and CEO of Red River Commodities, Fargo, ND. Majkrzak says the attitude is negative toward crop bioengineering at European industry trade shows his company has participated in. "We keep assuring them we don't have transgenic sunflower," he says.

However, Majkrzak agrees that over the long run, biotechnology may stabilize the decline in sunflower production. He says that genetically engineered sunflower could help solve problems that the industry now faces. "It would help assure consistency of the product we could market. It would help the sclerotinia problem. It would help weed control in confectionery sunflower, including cocklebur. It would help with insects. No one would appreciate that problem in a salad bar." John Riley, a Cresbard, South Dakota producer and a board member on the National Sunflower Association, says that glyphosate-resistance would be a big plus for sunflower production. "It would make the window of opportunity for timely treatments a lot wider."

The NSA's Kleingartner believes there is enough sophistication in the marketplace to manage bioengineered sunflower. Kleingartner says the NSA, which supports biotech sunflower research and development, will likely establish policy recommendations on biotech sunflower this fall. At the same time, if a bioengineered sunflower hybrid was ready to be commercialized now, he would urge the industry to differentiate it in the marketplace.

<u>Source</u>
National Sunflower Association (http://www.sunflowernsa.com), summer meeting, July 12, 2000, Detroit Lakes, MN.

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Correction
In March of 1998, an article published in this News Report used the term "Molecular Pharming." "Molecular Pharming" is a registered trademark of Meristem Therapeutics. This error was inadvertent.

UPCOMING MEETINGS

More meetings can be found at: http://www.isb.vt.edu

ENVIRONMENTAL CONTAMINATION, BIOTECHNOLOGY, AND THE LAW: THE IMPACT OF EMERGING GENOMIC INFORMATION

August 16, 2000
Washington, DC

This US National Research Council workshop will explore current and emerging biotechnology-based approaches and associated legal issues relevant to: (1) evaluating potential human health effects caused by exposure to environmental contaminants, and (2) cleaning up contaminated areas. It will focus on how the emerging genomic information will impact each of those areas. Advanced registration is recommended.

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ENGAGED INSTITUTIONS' ROLE IN BIOTECHNOLOGY EDUCATION

October 8-10, 2000
Iowa State University

This national symposium for educators and administrators will explore how biotechnology education can be improved and is designed for anyone involved in educating students in K-12 schools, community colleges, or four-year universities. It also will be a valuable learning experience for extension personnel who are expected to provide unbiased information to audiences. Agricultural producer organizations, industry, and other partners in education are encouraged to attend.

Conference is receiving major support from USDA-CRSEES and local sponsorship from ISU Extension and the ISU Office of Biotechnology.

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