



April 2010

RISK ASSESSMENT

Modeling Pollen-Mediated Gene Flow in Rice: Implications for Assessing and Managing Transgene Escape	1
Barriers to Marketing GE Crops	4
Patent Rights and Patent Wrongs?	6
Is the Suspension of MON810 Maize Cultivation by Some European Countries Scientifically Justified?	8
Events	11

Modeling Pollen-Mediated Gene Flow in Rice: Implications for Assessing and Managing Transgene Escape

Bao-Rong Lu

Rice and rice gene pool

Asian cultivated rice (*Oryza sativa* L., referred to hereafter as rice) is an important world crop, providing staple foods for nearly one half of the global population. Achieving high productivity, including improved breeding methods, is always the challenge in meeting the demand for food security and nutritional sufficiency, particularly for the developing world. Apart from Asian rice, there is another cultivated rice species (*O. glaberrima*), domesticated in West Africa, that remains only locally important in some areas. In addition to the two cultivated species, there are more than 20 wild relative species in the genus *Oryza* and about 50 other wild species in the tribe *Oryzae* of the grass family (Poaceae).¹ All wild species in the tribe compose a valuable rice gene pool that is significant for providing germplasm for the genetic improvement of rice cultivars, in addition to other ecological functions. Species in the genus *Oryza* contain ten different genome types (i.e., AA, BB, CC, BBCC, CCDD, EE, FF, GG, JJHH, and JJKK genomes), reflecting their relatedness to each other in terms of evolution. Rice contains the AA genome, which is shared by a group of six wild (including weedy) *Oryza* species that have the closest evolutionary relationships to the crop. Consequently, pollen-mediated gene flow or hybridization occurs naturally between rice and its close wild relatives to various extents.¹

Genetically engineered rice and its biosafety concerns

Demand for high-yielding and efficient rice production and rapid progress in transgenic biotechnology have prompted genetically engineered (GE) rice research and development. To date, many GE rice lines conferring unique traits have been developed in different countries, and some lines have been released into the environment for biosafety assessments.^{1,2} As the world's largest rice producing and consuming country, China has actively engaged in GE rice research and development. Recently, two GE rice lines were approved by biosafety authorities in China for commercialization, and many more lines are in the pipeline. Like many other GE crops, the forthcoming extensive environmental releases and commercial production of GE rice have already aroused tremendous biosafety concerns worldwide. Among these concerns are transgene escape through pollen-mediated gene flow (PMGF) from GE rice varieties to non-GE rice and wild relatives and their potential (undesirable) environmental impacts. These concerns have become one of the most debated ecological biosafety issue, which has considerably constrained the commercialization and wide application of GE rice. Such biosafety concerns caused by transgene flow should be fully addressed with supporting and solid data, based on rigid scientific methodologies.

PUBLISHED BY

**Information Systems
for Biotechnology**Virginia Tech
1900 Kraft Drive, Suite 103
Blacksburg, VA 24061Tel. 540-231-3747
Fax 540-231-4434Subscribe to and access
archived issues of the ISB
News Report online:www.isb.vt.eduEditor:
Ruth Irwin
rirwin@vt.eduISB welcomes your comments
and encourages article sub-
missions. If you have a suitable
article relevant to our coverage
of agricultural and environ-
mental applications of genetic
engineering, please email it to
the Editor for consideration.The material in this News Report
is compiled by Information Sys-
tems for Biotechnology, Virginia
Tech. Any opinions, findings, con-
clusions, or recommendations
expressed in this publication are
those of the author(s) and do not
necessarily reflect the view of the
US Department of Agriculture or
of Virginia Tech. The News Report
may be freely photocopied or oth-
erwise distributed for non-com-
mercial purposes only, with attri-
bution.**Pollen-mediated transgene flow and its potential environmental impacts**

Previous studies have concluded that PMGF occurs frequently between rice varieties, as well as between rice and common wild rice (*O. rufipogon*) or weedy rice (*O. sativa* f. *spontanea*).³⁻⁵ The movement of transgenes from a GE rice variety to its non-GE counterpart can trigger disputes over trading and legal issues, due to the so-called “contamination” of non-GE rice varieties. Although common wild rice is the ancestor of rice and the most important germplasm for rice breeding, transgene escape from GE rice to wild relatives *via* PMGF can potentially increase the ecological fitness or invasiveness of wild populations, resulting in serious weed problems. Similar problems may also be caused by transgene flow to weedy rice that is already a noxious weed in rice fields. Conversely, such transgene flow may lead to the reduction or even extinction of local wild rice populations if the transgene reduces the fitness of wild populations.⁴ Rice is sexually compatible with all close wild rice species containing the AA genome, indicating that the likelihood of PMGF from GE rice to these wild relatives is relatively high.^{1,6} Given the importance of the frequency of crop-to-crop or crop-to-wild transgene flow that determines the magnitude of environmental impacts, accurate determination of PMGF will greatly facilitate the assessment and management of potential impacts caused by transgene escape in rice.

Modeling pollen-mediated transgene flow in rice

A considerable amount of data on PMGF in rice have been generated from field experiments worldwide, providing useful information for the basic understanding of transgene flow from GE rice to its non-GE counterparts and to wild/weedy relatives.^{1,3,4,5,6} However, these data, collected from different field experiments under specific environmental conditions, are often scattered and vary significantly; consequently much of it is not applicable to all situations. However, mathematical modeling can be used to capture the general pattern of PMGF within most biological and climatic parameters, and hence will facilitate the effective assessment and management of transgene flow in rice under diverse environmental conditions. A PMGF model can be used to accurately predict the frequency of transgene outflow under different circumstances and hence be valuable for designing appropriate control measures to minimize the frequency of transgene flow. Our study combined a mathematical tool and experimental data to achieve a PMGF model for rice.

We first determined the empirical dispersal pattern of wind-borne pollen in rice. An exponential function fitted nicely to pollen flow data generated from large-scale pollen-trap studies of both rice and common wild rice. The decay parameter β of the exponential function was negatively correlated with relative humidity, meaning that high relative humidity reduced pollen dispersal. The function indicated that rice pollen dispersal was essentially determined by the size of pollen sources, spatial distance, and relative humidity. Wind speed and temperature did not show a significant effect on pollen dispersal, possibly due to insufficient variation in wind speed and temperature to significantly change pollen dispersal. Therefore further validation studies are required for better understanding the detailed correlations between β and climate conditions in order to predict PMGF more precisely under different climate conditions.

Then, we established a quasi-mechanistic PMGF model using the empirical pollen dispersal pattern as a baseline, and adding the outcrossing rate of a recipient and cross-compatibility between rice and pollen recipients. In the model, a fixed fraction (s) of the ovules is self-pollinated prior to the arrival of alien pollen. The highest possible

outcrossing rate t equals $1-s$. The remaining ovules can be fertilized by alien or self pollen, depending on the ratio of the pollen that reaches the stigma. Actual outcrossing rates will be lower than the maximum t , and more so when self pollen is abundant.

The PMGF frequency *via* outcrossing also relies on cross-compatibility between the pollen donor and recipient. This model represents well previous PMGF data from rice and common wild rice; therefore, it provides a solid base for understanding the pattern of PMGF influenced by climatic and biological factors. If a model only uses empirical functions to describe relationships between frequencies of PMGF and spatial distances, it will have a relatively low predictive power, especially for crop-to-wild gene flow with evident reproductive barriers. Simulation results indicated that without consideration of such biological parameters, the model cannot avoid overestimation of PMGF from the crop to wild relatives. In addition, the PMGF model also addresses the concerns of the ‘size effect’ of using PMGF data obtained from controlled experiments and extrapolating to a large field production scale. Our model simulations showed that in a self-pollinating species, PMGF increased with the increase of pollen source size, but such a size effect leveled off quickly with increasing pollen source size. Such a “size effect” approached an upper limit when pollen source size became infinite. Thus, we can estimate PMGF on a large field scale using the PMGF model.

Implications of PMGF model for assessing and managing transgene flow

We explored the possibility of using the PMGF model as a practical tool for assessing and managing transgene escape in rice. The model can estimate the isolation distances required for minimizing the frequency of crop-to-crop and crop-to-wild PMGF. Under the worst case scenario of crop-to-crop gene flow, where the recipient plot is surrounded by pollen source plots with infinite sizes and pollen can easily disperse long distances, the size of a recipient plot has a meaningful impact: a greater isolation distance is required for small recipient plots than large recipient plots. In production, therefore, only a short isolation distance (a few meters) is required in rice to achieve a significant reduction of PMGF to frequencies of $< 0.9\%$ if large recipient plots are deployed, minimizing the potential ‘contamination’ from GE rice. Simulations are made under the assumption of extremely limited reproductive barriers between rice varieties. Given the observed reproductive barriers between some varieties, particularly between the two subspecies *indica* and *japonica* rice, the frequency

of PMGF may still be overestimated, compared with the actual situation in rice fields.

Under the worst case scenario, the attempt to reduce the frequency of PMGF from rice to common wild rice to a low level ($< 1\%$) requires a long isolation distance because the outcrossing rate of common wild rice could be as high as 40%. The exponential function fitted the pollen flow data excellently within the experimental scale (about 100 m). At distances of > 100 m from sources, pollen is still found and the amount is more or less consistent. If the amount of pollen is significant, a fat-tailed model should fit better the data for long distances. Additional data for long-distance dispersal could be collected to examine if this affects our calculations or that the effect is too small to be of quantitative importance. When the integral is used to calculate the conspecific pollen density in the wild rice population, the model simulation actually assumes that common wild rice occurs continuously with a high population density. Therefore, more effective isolation should be required to reduce crop-to-wild PMGF, because most common wild rice populations are relatively small and fragmented.

The established PMGF model can be used to predict transgene flow under diverse conditions, which provides a useful tool to determine isolation distances between GE rice and non-GE counterparts or wild relatives to minimize transgene flow. Given that pollen dispersal of other wind-pollinated crops (e.g., wheat and barley) is similar to rice, and the key biological parameters required by the model can be easily estimated from field experiments, the PMGF model has a good potential for use in these crops.



References

1. Lu B-R, Snow AA (2005) Gene flow from genetically modified rice and its environmental consequences. *Bioscience* 55, 669-678 Wang YQ, Johnston S (2007) The status of transgenic rice R&D in China. *Nat Biotechnol* 25, 717-718.
2. Rong J, Lu B-R, Song ZP et al. (2007) Dramatic reduction of crop-to-crop gene flow within a short distance from transgenic rice fields. *New Phytol* 173, 346-353
3. Song ZP, Lu B-R, Zhu YG et al. (2003) Gene flow from cultivated rice to the wild species *Oryza rufipogon* under experimental field conditions. *New Phytol* 157, 657-665
4. Chen LJ, Lee DS, Song ZP et al. (2004) Gene flow from cultivated rice (*Oryza sativa*) to its weedy and wild relatives. *Ann Bot* 93, 67-73
5. Lu B-R, Yang C (2009) Gene flow from genetically modified rice to its wild relatives: assessing potential ecological consequences. *Biotech Advances* 27, 1083-1091

Bao-Rong Lu
Ministry of Education Key Laboratory for Biodiversity and Ecological Engineering
Institute of Biodiversity Science, Fudan University
Shanghai 200433, China
brlu@fudan.edu.cn

Barriers to Marketing GE Crops

Janaki Krishna

The following is a summary of the review article “Barrier and paths to market for genetically engineered crops” authored by Caius M Rommens.¹

GE crops are widely regarded as an important part of the solution to the daunting problem of meeting food, feed, and energy requirements of future generations. The global area planted to biotech crops has increased 80-fold since they were first commercialized in 1996. According to a report by the International Service for the Acquisition of Agri-Biotech Applications (ISAAA), *The Global Status of Commercialized Biotech/GM Crops: 2009*, 14 million farmers in 25 countries currently benefit from biotech crops. On the other hand, progress is limited to a small number of crops and only a few traits, and globally GE crops face sizeable constraints before they may enter the market.

Caius M. Rommens, from J. R. Simplot Company USA, recently published a review in which he highlights seven likely barriers to the entry of GE crops into markets, and offers an explanation for the gap between research and development. The barriers he outlines are (1) trait efficacy, (2) critical product concepts, (3) freedom to operate, (4) industry support, (5) identity preservation and stewardship, (6) regulatory approval, and (7) retail and consumer acceptance.

Trait efficacy

Over the last two decennia, the scientific literature pertaining to the trait efficacy of gene function shows that a large number of abiotic and biotic stress control genes

have been identified in the laboratory. However, only a few of these genes have been tested in the field, and those that have often display poor performance. The list of such disappointing genes includes biotic stress tolerance genes, such as *Npr1*, *Rpm1* and *cpr6*, as well as various nitrogen assimilation genes.

Exceptional genes that were shown to provide stress tolerance without affecting plant agronomics include the insecticidal protein genes from *Bacillus thuringiensis* and certain *eIF4E* genes that prevent multiplication of RNA potyviruses. Ceres, in collaboration with Chinese Academy of Agricultural Sciences, evaluated the efficacy of about 600 transgenes in the field, but did so early in the development process in order to address some of the issues that limit trait discovery. The professional execution of field trials, designed with precise uniformity of parameters and minimized position effects, is critical to generating meaningful data. The USA and China are among a limited number of countries where field tests during the late stages of product development are conducted. Such activities are hampered by tight regulations in Europe, Australia, and elsewhere. Another essential factor for field trials is the availability of high throughput assay systems. The value of GE would be improved with the delivery of traits that have high value to the consumer, such as enhancing flavor, texture, taste, aroma, and color, and methods to increase food quality.

Going from trait to product concept

A number of GE crops displaying efficacious input traits failed to succeed on the market, as the introduced traits lacked enough relevance to local conditions and problems. One example relates to potato plants with resistance to the Colorado potato beetle. This pest did not represent a critical issue to US farmers, and the resulting lack of “pull” was one of the reasons that resistant potato varieties had to be withdrawn from the market within several years of launch. This failure reiterates the importance of first identifying the critical needs of end-users and then translating these needs back into product concepts for researchers, rather than the other way around.

A successful example of such a product concept is the transgenic papaya (*Carica papaya*) variety ‘Rainbow’, which expresses the viral coat protein of the papaya ringspot virus (PRSV-P). The Rainbow papaya exhibits resistance against a pathogen that threatened to eliminate Hawaiian papaya industry during the 1990s. In response to this threat, the the University of Hawaii in collaboration with the United States Department of Agriculture (USDA) and Upjohn Company developed a transgenic papaya, which is now extensively grown throughout Hawaii. Other crops with disease traits of significance from which product concepts are developing include the Cavendish banana, which is very sensitive to certain fungal pathogens, and potato, which is frequently infected by potato late blight. Potato and other starchy food products are also candidates for quality improvement traits to reduce the levels of the toxin acrylamide that is formed during processing. And the removal of food allergens from food crops such as peanut and wheat would also increase consumer demand.

From academic freedom to freedom-to-operate

Academic freedom, which is important for innovation, may be restricted because of intellectual property rights issues. The thousands of patents relating to transgenic plants act as powerful barriers to commercialization, as many patents are closely held by a relatively few companies, including Syngenta, Monsanto, and DuPont. And although a select group of companies have obtained licenses for Monsanto’s intellectual property for the development and commercialization of transgenic specialty crops, the high royalty fees and restrictions imposed are often prohibitive, leading many companies to develop their own novel methods instead. For example, the Simplot Company has developed marker free and all native DNA transformation methods, as well as highly efficient methods for gene silencing. The Public-Sector Intellectual Property Resource

for Agriculture (PIPRA) is also involved in the process of generating useful GE technologies, and developed a comprehensive *Handbook and Executive Guide* that provides new insights into agricultural biotechnology opportunities. Likewise Cambia, a non-profit research organization, Simplot, PIPRA, and others support public crop improvement programs for the practical application of technologies in the public domain.

From notebooks to identify preservation

Documentation plays a very important role in developing, patenting, and commercializing transgenic technologies. Corporate researchers must follow standard operating procedures to ensure data accuracy and patent compliance. The USDA issues movement and release permits before a product can be tested in the field. The permits stipulate rigid conditions for the trials in order to prevent any inadvertent release of the transgenic material.

In 2009, USDA’s Animal and Plant Health Inspection Service (APHIS) launched a pilot development project with five participants, including the Simplot Company, to develop, maintain, and implement a Biotechnology Quality Management System (BQMS). The program is intended to improve compliance with APHIS requirements for field trials and movement of regulated organisms, with the goal of preserving the identity of a product before its launch. Soon any producer in the USA will be able to quality for BQMS certification (http://www.aphis.usda.gov/biotechnology/news_bqms.shtml). The Biotechnology Industry Organization (BIO) intends to ensure segregation of products throughout their entire life cycle (production, marketing, distribution, and discontinuation), by implementing its new “Excellence Through Stewardship” system (<http://www.excellencethroughstewardship.org/>).

Other major factors hampering commercialization include obtaining support for a new (disruptive) technology from a conservative industry. The governments of importing countries, food retailers, and ultimately, the consumer, are often the targets of pressure from NGOs that oppose the commercialization of transgenic foods. Receiving regulatory approvals is another major constraint, as the approval process is much more stringent than for products developed by traditional breeding methods. Also the lack of public awareness about the benefits of transgenic crops, especially in some EU countries, is another major constraint, as consumers normally do not embrace new technology that is not perceived as providing any additional benefit.

In conclusion, Caius Rommens points out a few guidelines that might facilitate overcoming barriers to

REGULATORY

market GE crops: (1) assess carefully the efficacy of genes in the field by all means available; (2) focus on products that are need driven; (3) ensure licenses or work-arounds for all materials and methods employed; (4) ensure identity preservation following government regulations; (5)

garner early support of growers, processors, and retailers; (6) avoid genes with the potential for making toxins or allergens; and (7) create positive consumer perceptions and provide evidence of user benefit.

References

Rommens Caius M (2009) Barriers and paths to market for genetically engineered crops. *Plant Biotechnology Journal* 8 (2), 101-111

P. S. Janaki Krishna
Institute of Public Enterprise
Osmania University Campus, Hyderabad, India
jankrisp@yahoo.com

Patent Rights and Patent Wrongs?

Phill Jones

While collaborations between universities and businesses yield mutually beneficial results, they can also create a tangle of patent rights. Sometimes, a party's rights can vanish with a signature, leaving only a costly mirage. *Stanford v. Roche* is one such cautionary tale.

The case involved patents covering a polymerase chain reaction method for measuring Human Immunodeficiency Virus RNA in human blood samples. Stanford University and Cetus researchers had developed the technology during the late 1980s and early 1990s. One of the inventors, Mark Holodniy, had joined Thomas Merigan's Stanford lab as a research fellow in the Department of Infectious Disease in 1988. He signed the university's Copyright and Patent Agreement, which obligated him to assign his inventions to the university.

During 1989, Holodniy regularly visited Cetus to learn PCR and to develop a PCR assay for HIV. Acquiescing to the company's standard practice, Holodniy signed a Visitor's Confidentiality Agreement with Cetus.

Holodniy eventually devised a PCR assay to measure HIV RNA in human plasma. He published his findings with Cetus co-authors and collaborated with Stanford researchers to test the PCR assay on samples from patients undergoing antiretroviral drug therapy. Their results showed that levels of HIV RNA in human blood provided a marker of antiviral drug efficacy. With this important finding in hand, they filed a patent application: "Polymerase Chain Reaction Assays for Monitoring Antiviral Therapy and Making Therapeutic Decisions in the Treatment of Acquired Immunodeficiency Syndrome." The application matured into three patents. Cetus' agreement also matured: it developed into a time bomb that quietly ticked away.

Roche purchased Cetus' "PCR business" in December 1991; the bundle included Cetus' agreements with Stanford and its researchers. Roche began to manufacture HIV RNA detection kits that used PCR. In May 1992, Stanford filed the PCR-HIV RNA patent application. Holodniy and the other inventors assigned their patent rights to Stanford.

In April 2000, a Stanford senior licensing associate presented a slide presentation at Roche, in which Stanford asserted its ownership of the HIV RNA assay. The university offered the company an exclusive license to all related patents. Roche did not jump at the offer; the company declared that it owned the rights. Negotiations between Stanford and Roche continued for at least four years. On October 14, 2005, Stanford filed a lawsuit against Roche in the Northern District of California, alleging that Roche's HIV PCR detection kits infringe its patents. The university reportedly looked for more than \$200 million in damages. Roche answered and counterclaimed against Stanford, declaring, among other things, that Stanford lacked standing to maintain the cause of action against Roche, and that Roche owns the patents through the acquisition of Cetus's PCR assets.

The district court denied Roche's motions, viewing the company's ownership claim as a counterclaim barred by the statutes of limitation. Roche appealed to the Court of Appeals for the Federal Circuit.

The Federal Circuit agreed with the district court that the statutes of limitation prevented Roche from counterclaiming for a judgment of ownership of the PCR method. However, Roche also asserted Stanford's lack of ownership of Holodniy's interest in the technology as a challenge to Stanford's standing in the infringement

action. In other words, Roche had declared that Stanford could not sue the company for patent infringement, because the university had no right to the technology. A party can raise the question of standing at any time; it is not subject to statutes of limitation.

To determine whether Stanford owned the technology, the court looked at the various agreements that Holodniy had executed. In 1988, Holodniy had signed Stanford's Copyright and Patent Agreement, which states "I agree to assign or confirm in writing to Stanford and/or Sponsors that right, title and interest in . . . such inventions as required by Contracts or Grants." The Federal Circuit has held that the phrase "agree to assign" signals a simple promise to assign rights in the future.

In 1989, Holodniy signed Cetus' Visitor's Confidentiality Agreement, which states "I will assign and do hereby assign to CETUS, my right, title, and interest in each of the ideas, inventions and improvements" that Holodniy may devise "as a consequence of" his work at Cetus. Consider that last phrase first. Did Holodniy create his PCR invention as a consequence of his experience with Cetus researchers? Stanford argued that this point can be disputed. The Federal Circuit disagreed. Holodniy testified that his collaboration with Cetus had provided him with technical advice and the necessary reagents for the PCR reaction. The Stanford researcher had also received a PCR protocol, equipment for HIV RNA extraction, and access to equipment to perform reverse transcription of HIV RNA. "It is undisputed," the Federal Circuit wrote, "that Holodniy took this information and material from Cetus and used them to develop the PCR assay for HIV RNA, and thus developed the inventions 'as a consequence' of his access to Cetus."

The court then emphasized a critical difference between Stanford's Copyright and Patent Agreement and Cetus' Visitor's Confidentiality Agreement. Unlike the Stanford agreement, the Federal Circuit said, the Cetus document created a present assignment of Holodniy's future inventions. Cetus had immediately gained equitable title to Holodniy's inventions. Holodniy had completed his invention by the time that he filed his first HIV-PCR patent application that matured to a patent. No later than that filing date, the court said, Cetus's equitable title converted to legal title. It's true that Holodniy executed an assignment of his rights in the patent application to Stanford years later. By that time, however, Cetus's legal title had vested, and Holodniy no longer retained rights in the patent application that he could assign to Stanford.

The court's conclusion about ownership doomed Stanford's case: the university lacks standing to assert its

claims of infringement against Roche. While the other co-inventors named in the HIV-PCR patent applications had assigned their rights to Stanford, the university is not the owner of Holodniy's interest. Normally, all co-owners must join as plaintiffs in an infringement suit, an impossibility here, unless Roche as owner of Holodniy's interest agreed to sue itself.

Targeting "Gene Patents"

For decades, the US Patent and Trademark Office has granted patents on nucleic acid molecules that encode gene products. In doing so, has the USPTO performed unconstitutional acts and violated US patent law?

These are the allegations in a lawsuit filed in May 2009 by the American Civil Liberties Union and the Public Patent Foundation of the Benjamin N. Cardozo School of Law on behalf of various associations and individuals. The complaint names as defendants the USPTO, Myriad Genetics, and Directors of the University of Utah Research Foundation. While the plaintiffs target the practice of "gene patenting" in general, they focus on patents with claims to molecules with nucleotide sequences of the *BRCA1* and *BRCA2* genes, and diagnostic methods using the nucleotide sequences. The plaintiffs named Myriad Genetics as a co-owner of one *BRCA1* patent and as exclusive licensee of the University of Utah Research Foundation's related patents.

"The patenting of human genes," the plaintiffs asserted in their complaint, "the concept of looking at or comparing human genes, and correlations found in nature between certain genes and an increased risk of breast and/or ovarian cancer violates long established legal principles that prohibit the patenting of laws of nature, products of nature, and abstract ideas. These patents also violate the First Amendment and Article 1, section 8, clause 8 of the United States Constitution." The plaintiffs further alleged that the patents violate the Fourteenth Amendment.

The defendants filed a motion to dismiss the complaint in the New York district court. Plaintiffs' lack of standing to challenge the validity of the patents, and a lack of personal jurisdiction over the directors of the University of Utah Research Foundation number among a myriad of procedural problems raised by the defendants. A USPTO memorandum filed to support the motion to dismiss evidences frustration at the inability to tackle the ethereal rationale of the plaintiffs' case. "[E]very paragraph in plaintiffs' complaint concerning the Constitution recites nothing more than unsupported legal conclusions," the USPTO wrote. Where are the defendants' factual allegations? the USPTO asked. "Here, plaintiffs' allegations are unmoored to any plausible claim

of unconstitutionality. Put simply, plaintiffs fail to provide any basis for the conclusion that the USPTO's issuance of gene patents violates the clause of the Constitution that empowers Congress to 'promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries,' U.S. Const. art. 1, § 8, cl. 8. Plaintiffs likewise fail to provide any facts or rationale that might support the conclusion that the USPTO's issuance of gene patents prohibits plaintiffs' free exercise of religion, abridges plaintiffs' freedom of speech or that of the press, or interferes with plaintiffs' right to assemble or seek redress from the Government, see U.S. Const. amend. I."

Nevertheless, in November 2009, US District Judge Robert W. Sweet denied defendants' motion and allowed the case to proceed. "The Complaint," he wrote, "alleges that

the information encoded in the *BRCA1/2* genetic sequences, rather than being the result of an inventive process, exists in nature. The Complaint also alleges that the existence of certain mutations in *BRCA1/2* and their correlation with an increased risk of breast and/or ovarian cancer constitutes nothing more than a naturally occurring phenomenon. Based on these factual allegations, the Plaintiffs assert that the patents-in-suit grant Myriad ownership rights over products of nature, laws of nature, natural phenomena, abstract ideas, and basic human knowledge and thought in violation of the First Amendment's protections over freedom of thought."

If this reasoning survives to the end of the trial and through any appeals, the USPTO might as well close its shop.

References

1. Albainy-Jenei, S (2009) How To Lose A Patent? Have the Inventor Make a Secret Side Deal. Available at: www.patentbaristas.com.
2. *Association for Molecular Pathology et al. v. United States Patent and Trademark Office et al.*, Docket No. 09 Civ. 4515 (November 1, 2009).
3. *Stanford v. Roche*, Docket No. 2008-1509, -1510 (September 30, 2009; revised October 1, 2009). Available at: fedcir.gov.

Phill Jones
Biotech-Writer.com
PhillJones@nasw.org

Is the Suspension of MON810 Maize Cultivation by Some European Countries Scientifically Justified?

Agnès E. Ricroch, Jean Baptiste Bergé and Marcel Kuntz

MON810 is a transgenic trait introgressed into a number of maize varieties, consisting of a *Bacillus thuringiensis*-derived gene (Bt), or more precisely, a truncated cry1Ab gene encoding an insecticidal protein for control of some lepidopteran pest insects such as *Ostrinia nubilalis*, the European maize borer. We examined the justifications invoked by the German government in April 2009, and the previous year by the French government, to suspend the cultivation of these genetically modified maize varieties.

The German government has no valid scientific reason to ban MON810

The German Federal Office of Consumer Protection and Food Safety suspended, on 17 April 2009, the permit allowing the cultivation of these varieties on the presumption that they are a "hazard to the environment," specifically to non-target arthropods. The official

German suspension order (GSO) allegedly refers to "new information" resulting from force-feeding daphnia and ladybirds in laboratory experiments, as well as citing previous publications.

We have conducted a critical examination of these alleged "new data" as well as the previous data on *Lepidoptera*, and aquatic and soil organisms.¹ It appears that the results of the daphnia paper are inconclusive: Varietal effects, with no link to the transgenic toxin, that may affect feed composition cannot be excluded; and reported differences in the survival rate of daphnia are equivocal, due to the experimental design of the test. Furthermore, as the authors themselves admit "... this is an artificial situation. However, our study was not aimed at estimating the responses of *Daphnia magna* under natural field conditions, where they would have a diverse diet."

The paper on ladybirds consists of a laboratory study

measuring the mortality rate of preimaginal larval stages, the development time of these stages, and the body weights of *Adalia bipunctata* given feed spiked with different concentrations of trypsinized protoxin Cry1Ab or Cry3Bb. The data supporting claim of higher larvae mortality when fed Cry1Ab are quite weak: The laboratory test is insufficiently characterized, and the results on mortality are weakened by a high variability (see also ref. ²). Consequently, the article does not allow ecotoxicologically relevant conclusions to be drawn on the negative impact of maize MON810 on ladybirds in a field setting, where these insects actually feed mainly on aphids. It should also be mentioned that these are not “new data” since the same group had previously published them in 2004 (in German), a fact ignored in the GSO.

For *Lepidoptera*, the GSO mentions the well-known Monarch butterfly case and follow-up papers, but does not provide any evidence for deleterious effects of MON810 on *Lepidoptera* under field conditions. In addition, the GSO uses claims concerning Bt176 to argue for a suspension of MON810 varieties, which is inappropriate since scientific risk assessment follows a case-by-case procedure. The GSO mentions that toxins in transgenic crop by-products may affect headwater stream ecosystems but does not acknowledge that the group who performed these laboratory feeding studies on trichopteran species failed to observe effects during in situ experiments. Concerning soil organisms, the GSO refers solely to a poster presented in 2004 in which the authors reported inconsistent trends in field experiments over three years and suggested “closer observation in post-market monitoring.”

Thus, we have demonstrated¹ that the German suspension is based on an incomplete list of references, ignores the widely admitted case-by-case approach and confuses potential hazard and proven risk in the scientific procedure of risk assessment.

The available meta-knowledge (see below and ref. ³) on Cry1Ab-expressing maize is ignored by the German government, which instead uses selected individual studies. *It fails to take into account that many publications have shown that the differences are more significant between two non-Bt varieties than between isogenic Bt and non-Bt varieties at the farm scale.* Strangely enough, the justifications invoked by the German government are contradicted by its own publication: e.g., the BEETLE report co-authored by the Federal Office of Consumer Protection and Food Safety states that “The majority of laboratory studies and all the field studies reviewed did not reveal any unexpected adverse or long-lasting effect. One important

lesson is that even if negative effects were observed in the laboratory (e.g., under worst-case conditions) no similar quantitative or qualitative adverse effects were necessarily detected in the field.”

The German Central Committee on Biological Safety (ZKBS) concludes that the cultivation of MON810 has no adverse effect on the environment, which is fully in line with our conclusions (http://www.bvl.bund.de/cln_027/nn_1209020/EN/06_Genetic_Engineering/ZKBS/01_Allg_Stellungnahmen/05_plants/zkbs_mon810_engl.html).

The French ban on MON810

On 31 October 2007, the French government decided to temporarily suspend the cultivation of maize MON810. On 7 December 2007, while 1500 French scientists protested publicly against this suspension, the Ministry of Ecology created a provisional committee on genetically engineered organisms, composed of 34 experts (Comité de Préfiguration pour une Haute Autorité sur les OGM, CPHA) including 15 scientists (headed by a politician, Senator Jean-François Le Grand) to examine the impact of MON810 on the environment. In an interview on 8 January 2008, the French President Nicolas Sarkozy said he is willing to invoke a safeguard measure prohibiting the cultivation of the authorized maize MON810 if the committee raises “serious doubts” concerning its safety. The next day, the CPHA’s report was submitted to the French government. Sen. Le Grand announced to the press that CPHA found “a number of new negative scientific evidences for impact on flora and fauna,” raising “serious doubts.” On 11 January 2008, 12 of the 15 scientific experts of CPHA protested publicly against Sen. Le Grand’s statement: What is only a draft document “does not contain the words ‘serious doubts’, nor does it qualify the new scientific evidences as ‘negative’.”

On 7 February 2008, the French government suspended the authorization of MON810 cultivation.

Meta-knowledge on MON810 contradicts French government arguments

On 7 February 2008, we performed a meta-analysis⁴ on the CPHA document to examine their “new evidence” using our database, which (on 1 March 2010) contained 20,768 publications concerning the environmental and agricultural impact of GE plants. While we identified 1,438 publications on GE maize, the CPHA document cites scant scientific data (between 0.2% and 2% of the recorded references). Confirming the preliminary state of this document, we

noted numerous citation errors, the lack of a reference list, and, on several occasions, an interpretation of results differing from the cited authors'. Moreover, this document mentions references related to unrealistic conditions for drawing conclusions about environmental risks in the field.⁵

Regarding the pollen dissemination issue, we identified 560 publications, while the CPHA document is based on only five publications (some of which are erroneous). The long-distance pollen dispersal they cite is not "new evidence." Pollen dissemination relates to coexistence rules between different cropping systems and, in this context, the relevant question is not how many miles a pollen grain can travel but its impact, as pollen endures several constraints, e.g., a short lifespan and competition with autochthonous pollen. In a separate meta-analysis,⁶ we concluded that in the case of fully synchronous flowering, a separation distance of approximately 20 meters is sufficient to maintain the fortuitous presence of GE maize in a conventional field (as a result of pollen flow) below the 0.9% threshold level that determines the labelling obligation in the EU.

On 30 January 2008, the Monsanto Company published a scientific report to contest the arguments of the French government. The French Ministry of Ecology requested that Prof. Le Maho (a member of CPHA who did not protest against Sen. Legrand) overstep this report. In his memorandum, Le Maho mentions health and environmental risks. In our independent meta-analysis,⁴ we found numerous flaws in Le Maho's memorandum; for example, he does not distinguish between crops (maize and cotton) and traits (herbicide tolerance and insect resistance). Without a case-by-case procedure for both crops and traits, his approach for environment and health risk assessment cannot be scientifically validated.

On 5 September 2008, a French State administration for health issues commissioned the French Food Safety Agency (AFSSA) to examine Le Maho's memorandum. AFSSA published a critical statement on this document (<http://www.afssa.fr/Documents/BIOT2008sa0266.pdf>) and reaffirmed its previous food

safety assessment of MON810. After analyzing Le Maho's statements, the GMO Panel of EFSA (European Food Safety Authority) concluded on 29 October 2008 that "no specific scientific evidence, in terms of risk to human and animal health and the environment, was provided that would justify the invocation of a safeguard clause" (http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902156394.htm).

The French Ministry of Ecology justified keeping the safeguard clause, not based on health concerns (rejected by AFSSA and EFSA) but on environmental grounds. But this environmental argument was again rejected by EFSA (June 2009) in its statement concerning the normal renewal procedure for MON810 authorization (after 10 years) (http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902628240.htm).

Political interference undermines the credibility of European GEO risk assessment

European agbiotech research had been already strongly hurt before the events described here. Scientific risk assessment has often ranked second to political considerations. The novelty here lies in the apparent will of the French and German governments to deliberately manipulate the results of scientific studies on GEOs presumably to support their political interests.

Other European governments have followed the same road: In November 2008, Austria made public a non-peer-reviewed report with claimed effects of GE maize on the reproduction of mice. This report turned out to be grossly erroneous.

In the eyes of the European public, these political operations may strengthen the unfounded idea that GEOs had been authorized without serious evaluation of their biosafety, despite of the fact that Europe has a finicky authorization procedure, soaked in the precautionary principle (e.g., it took the EU 13 years to authorize Bayer's Amflora potato). These governmental manipulations undermine the credibility of the whole process of scientific risk assessment.



EVENTS

References

1. Ricroch A, Bergé JB, Kuntz M. (2010) Is the German suspension of MON810 maize cultivation scientifically justified? *Transgenic Res.* 19(1), 1-12
<http://www.springerlink.com/content/r6052757667ng364/fulltext.pdf>
2. Rauschen S. (2010) A case of "pseudo science"? A study claiming effects of the Cry1Ab protein on larvae of the two-spotted ladybird is reminiscent of the case of the green lacewing. *Transgenic Res.* 19(1) 13-6
3. Marvier M. (2007) There are enough data available to draw empirically sound conclusions. <http://www.gmo-safety.eu/en/news/572.docu.html>
4. Bergé JB, Ricroch /a, (2008). Meta-analyses of statements commissioned by the French government on the impact of MON810. Download at <http://www.marcel-kuntz-ogm.fr/article-germany-france-45973948.html>
5. Naranjo SE. (2009) Impacts of Bt crops on non-target invertebrates and insecticide use patterns. *CAB Rev. Perspect. Agric. Vet. Sci. Nutr. Nat. Resour.* 4:23
6. Ricroch A, Bergé JB, Messéan A. (2009) Literature review on the dispersal of transgenes from genetically modified maize. *Comptes rendus Biologies, Académie des Sciences* 332(10) 861-875. DOI :10.1016/j.crvi.2009.07.001

Agnès Ricroch
Université Paris-Sud 11, Laboratoire Ecologie, Systématique et Evolution, 91405 Orsay
& CNRS-AgroParisTech, UMR 8079, 91405 Orsay, France
agnes.ricroch@u-psud.fr

Jean Baptiste Bergé
Director of research (retired), INRA-Sophia Antipolis, 06600 Antibes, France
jean.berge@neuf.fr

Marcel Kuntz
Laboratory Physiologie Cellulaire Végétale, CNRS/CEA/INRA/UJF, 38054 Grenoble, France
kuntz@ujf-grenoble.fr

Sustainability Through Agricultural Biotechnology Food, Biomaterials, Energy and Environment

12th World Congress of the International Association for Plant Biotechnology (IAPB)
June 6 - 11, 2010
St. Louis, Missouri, USA

The Congress is being held in conjunction with the annual meeting of the Society for In Vitro Biology (SIVB). With an emphasis on the fundamental and applied aspects of sustainability through agriculture, topics will focus on food, biomaterials, energy and the environment. Approximately 1,500 research scientists in plant and agricultural biotechnology from around the world will attend.

Speaker presentations will focus on sustainability with reduced impact on the environment; political and social acceptance, especially in developing countries; translating fundamental knowledge into application; climate change; a mix of animal and plant biotechnology; and policy regulation.

For more information, see: <http://www.iapb2010.org/>

**ISB News Report
1900 Kraft Drive
Suite 103
Blacksburg, VA 24060**

**Non-Profit Org.
U.S. Postage
PAID
Blacksburg, VA
24060
Permit No. 28**