LMOS and the Environment

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LMOs and the Environment

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The Proceedings

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Craig R. Roseland, Editor
LMOS and the Environment. Proceedings of an International Conference

The Conference

I thank APHIS management, and among them, Kevin Shea especially, for their encouragement to hold the Conference and to publish the Proceedings from it. I also acknowledge the major contributions of the EPA, especially those of Elizabeth Milewski, Ina You and Denise Roush, who helped to bring about this Conference. I would also like to thank the USDA-APHIS and EPA for funding the Conference and providing for many speakers. A large number of people assisted with the arrangements before and during the meetings at the conference site, including Pat McQuillan, Tony Paris, Kathy Balderson, Betsy Randall-Schadel, Lauren Jones and Kay Peterson of the USDA, the technical specialists Dennis Trainum and Michael Hargett of USDA and Eric Haugh of the Sheraton Imperial, Peter Kearns, Rebecca Weiner, and Sally DeMarcellus of the OECD. I especially appreciate Ved Malik, who made the initial arrangements for the facility, the refreshments and meals. I thank Sam Taylor for arranging and securing funding for the welcoming reception event. Finally, I would like to thank Crop Life International, Syngenta Biotechnology, Vector Tobacco, Inc and Hutchison & Mason PLLC for their financial contributions.

Sally L. McCammon, Chair
OECD Steering Committee
USDA APHIS Biotechnology Regulatory Services

Preface

The Conference in Raleigh-Durham, North Carolina, *LMOs and the Environment*, was convened to discuss the science needed to assess the effects of transgenic organisms in the environment. The OECD and its Steering Committee have organized this meeting as one of an ongoing series. The conveners appreciate their efforts as well as the financial backing of the U.S. Department of Agriculture and the U.S. Environmental Protection Agency. A diverse group of speakers considered a range of topics, aiming to present policy issues, research findings, and the needs and international considerations that are relevant to risk assessment.

These Proceedings reflect the breadth of topics presented in the Conference and include a few additional contributed papers that subsequently were developed by participants. A broad range of experience was represented in the Conference, including that of academics, researchers, government regulators or policy makers and staff from independent nonprofit agencies. The participants represent countries that currently engage in risk assessment, some for more than a decade, but also others that were invited whose representatives come from countries that have only recently begun this work. More than 200 people attended the Conference and were part of the discussions and deliberations. In the Rapporteur's Report, the three authors have attempted to come to a consensus on the outcomes and conclusions to be drawn from the meeting, and I will not add my opinions to their worthy summary. Their work identified areas of agreement and disagreement about the practice and science of risk assessment. They presented opinions for how practices of assessment of risk could be improved, especially by promotion of increased research into gene flow issues and nontarget effects of transgenic plants.

The conveners were pleased that these Proceedings received manuscripts deriving from some of the larger-scale, and multi-crop monitoring research efforts that were initiated to study the possible impacts of LMOs on sexually compatible plants and other organisms in the environment. These investigations are taking place in the United Kingdom and France. Such efforts may serve as a foundation for future research on additional crops for which evidence of environmental impact or benefits will be sought. Reports were also contributed on risk assessment for single crops, such as sugar beets and rice. Another report described how impacts of transgenic microorganisms on the soil environment have been monitored.

These Proceedings contain descriptions of the risk assessment process made for specific crops, as well as presentations for how the process should be undertaken for any engineered crop. These papers, in some cases, supply useful direction for ongoing risk assessment, and in others, provide more theoretical considerations. Some of the papers offer suggestions on how to deal with controversial issues surrounding risk assessment, such as the role of uncertainty. Other papers provide a rationale for considering impacts on social and economic factors when risk assessments are conducted.

One of the highlights of the meeting was the Session on Maize at the Center of Origin and Diversity. This session focused on the challenges confronting Mexico following the discovery of unauthorized maize (corn) varieties in areas of the country cultivating large

numbers of maize land races. Stakeholders raised numerous concerns following the discovery. I am pleased to present some important contributions by those closest to the issues, including representatives from agencies of the Government of Mexico, CIMMYT (International Maize and Wheat Improvement Center) and a perspective from an environmentalist. Another paper outside this section showed how biological databases are used in Mexico to assess potential for gene flow. The diversity of opinions about farm impacts, necessary considerations for a crop at the center of origin, and the role and importance of social issues are worthy contributions to the discussions centering on release of transgenic maize in the center of maize's origin.

It was clear from many presentations that our knowledge of the consequences of engineered plants may be imperfect, and improving the risk assessment process needs further support through funding of research programs. This research could result in proposals for new data requirements prefatory to regulatory approval, or could help define and describe appropriate means to monitor environmental consequences of transgenic crops after approval. One paper distinguished research that focused on higher order and landscape ecological effects from research at the population level and onsite effects. Among the higher order effects are impacts on land management, which subsequently affect biodiversity. These higher order effects are not studied as frequently as the more local effects. Priorities need to be determined for which level of biological organization new research efforts should focus.

Finally, the need for capacity building to enhance the research and decision-making expertise by individual states is discussed. The issues that surfaced at this conference will need to be addressed by each country that is developing its own capacity to produce, purchase, manage, and monitor LMOs. While most of the issues discussed in these papers are those of LMO crop production, some are related to trees, fish, insects and microorganisms. Clearly, there is need for additional research and for policy decisions about how to predict the impacts resulting from some of these other engineered organisms as well as the impacts of the more familiar engineered plants.

The papers included in these Proceedings will condense and clarify the important issues, and I hope, will provide material for further discussion about risk assessment and for setting new research directions. Additionally, these papers may help shape the structure of programs as well as the policies of agencies that will make decisions on products of biotechnology. I expect that you will find these papers as useful I have.

I am most appreciative of all those who made an effort to describe the needs, challenges and future directions for risk assessment and research to support it. There is no doubt that these papers will be most helpful for countries that are currently setting up risk assessment and evaluation processes, some of whom were represented here. Other papers will resonate with those whose national agendas continue to raise questions surrounding the acceptance and use of transgenic crop commodities and products. The shared experience of different countries and regions of the world that are recorded in these Proceedings should provide some substance for such future discussions. The papers that have been included also offer an introduction to some of the leading scientists and policy makers who have contributed to the analysis of risk of genetically modified organisms.

Craig R. Roseland, Editor
LMOs and the Environment, Proceedings of an International Conference

Proceedings of the LMOs and the Environment: An International Conference

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Session 1. Genetic Modification: Current and Future Applications

Session 2B—Risk Management Issues

The relationship between the assessment and identification of mitigation measures

The regulatory environment and process

How a scientific assessment addresses uncertainty

How to factor environmental benefits into an assessment

Session 4: Future Need: Unique Challenges and Opportunities for Environmental Assessment

Steering Committee for the International Conference

The Steering Committee chose the topics for the Conference and made selections of the speakers who made presentations. The Committee was responsible for oversight of the Conference, as well as the work of the Site Coordinator and Local Arrangements Director, Sally McCammon. The Committee also provided directions for the OECD Staff who were instrumental in arranging this International Conference.

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Living Modified Organisms and the Environment— An International Conference

Welcoming Address

Rita R. Colwell,
Director
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Delegates, distinguished speakers, panelists, and guests—it is an honor and a pleasure for me to be here today to chair this important OECD-sponsored conference on living modified organisms (LMOs) and the environment. In the opening comments this morning we will have remarks by Mr. Donald Johnston, Secretary-General of the OECD, and Mrs. Joke Waller-Hunter, the Director for Environment of the OECD.

It is also my pleasure to make some overarching comments on science and science policy to set the tone for our deliberations and conversations today. Let me begin with the wisdom of the late Congressman George Brown of California. Some of you may remember him as science's best friend and most constructive critic in the U.S. Congress. We in the science community sorely miss his foresight and vision. I bring his words to you because you are an international community of scholars and scientific experts. As always, he left us with important ideas. In a 1993 speech titled *"A New Paradigm for Development: Building Dignity Instead of Dependence"*, he said that

> This work must begin first by viewing developing nations as partners instead of as step-children. Of all the many ways in which we can cooperate for the global good, the case for science and technology cooperation with science-poorer nations is perhaps the most compelling.
>
> To do so, we must abandon the instinct to judge others by their past accomplishments or to judge our own accomplishments as the proper path for others. We know that science and technology are an important force to help balance the world's inequities. The job of the science community, and our nation's leaders is to find a host of mechanisms to make use of the knowledge and benefits working as partners."

I come to you today in that spirit and in the hope that our deliberations will be guided by George Brown's thoughts.

In the long sweep of civilization, science and engineering have had an ever-increasing influence on the life of society. We've used most of that knowledge to remediate an existing problem or to address a current need. Currently, biotechnologies have been designed to address nutritional deficiencies and to combat disease. We all know the example of golden rice, engineered to reduce vitamin A deficiency. Rice is the staple food for most of the world's population—in fact, 80 percent of the global population. Golden rice could prevent nearly half a million cases of childhood blindness and a startling one to two million deaths each year. UNICEF estimates that some 124 million children around the world are dangerously deficient in vitamin A. Bioengineered fruits and vegetables are being developed into edible vaccines for a host of debilitating and deadly diseases. Vaccines for hepatitis B and rabies are notable examples.

The same techniques are being applied in veterinary medicine to protect valuable livestock and fish crops. Plants that resist pests and herbicides promise to reduce contamination from harmful pesticides and boost crop production. This is just a small smattering of the potential that biotechnology holds.

However, we now recognize that we also need to draw on one of science's most potent capacities—prediction. If we can predict, we frequently can prevent. The centuries of our accrued knowledge can and should increasingly be directed toward prevention.

In an old Icelandic saga there is a description of the character Snorri. It was said of him, "He was the wisest man in Iceland without the gift of foresight." To me, this has always meant that Snorri had a great deal of knowledge but he didn't quite take his knowledge to the next step. He didn't use it to see implications, to anticipate the future. Without foresight, he could easily be caught by surprise, and obviously without a plan.

As a community of nations, we need to develop a broader, more anticipatory perspective in our research. We need to increase our emphasis on envisioning future possibilities, good or ill, as a mechanism to predict. Undoubtedly, this will open new vistas in our exploration and discovery. This must take place at the same time that the research community maintains a freedom and passion for new frontiers and the rigor of merit review. As all of you know so well, knowledge is our strongest insurance for preparedness.

Without new knowledge we cannot develop foresight. As we evolve increasingly into a knowledge-based society, our economic growth, our national security, and our social well-being will depend on the most advanced discoveries in every field. Knowledge is the bedrock. Our ability to use foresight gives us a kind of early warning system – a guard against unintended consequences. For example, we know that devastating floods are frequently caused by intense over logging of an area. Our science knowledge can accurately predict such consequent flooding and devastation.

Science can be an effective predictor. To *prevent* requires more. The research community needs to find more effective methods to use its capacity to predict in order to meet real-world needs through prevention. Everyone in this room knows that by solving a present problem we can easily sow the seeds of genuine dilemmas for the next generation.

History is replete with examples. When foresight directs our actions and the use of knowledge, we are a lot less likely to fix the present at the cost of the future. There's good reason, then, to be thoughtful about the use of all new knowledge, techniques, and technologies, including biotechnologies.

Thoroughly evaluating potential risks and reducing uncertainty about unintended effects is just plain good science. Assessment is an important component of the process. And we know that we can never think of our current knowledge as a security blanket for the future. It will help us in the present, but as the renowned mathematician Alfred North Whitehead said, "Knowledge doesn't keep any better than fish." New, more complete knowledge replaces it—a process of constant renewal and at an ever-accelerating pace. This makes an unshakeable case for consistent research in all eras, at all times. We are just discovering the vast implications of what I call "biocomplexity in the environment." This term refers to the dynamic web of often surprising interrelationships that arise when living things at all levels—from molecular structures to genes to organisms to ecosystems—interact with their environment. Links within and between different systems at different levels of organization often exhibit features of complexity characterized by abrupt changes, thresholds, and nonlinear dynamics. My own research on cholera has convinced me that a better understanding of these complex phenomena can help us to understand and eventually predict the web of relationships that connect an engineered molecule, the plant that contains it, the human who eats it, together with its effect on the ecosystem in which the plant grows. This frontier science that looks at the whole system of interrelationships is absolutely essential for the future of biotechnology.

Despite our vast knowledge base, we likely still know very little of what there is to know. This should prevent us from being arrogant about what we do know. That doesn't always happen. In fact, we do ourselves a global disservice when we educate and train our scientists and engineers only in science and technology. The world in which our work bears fruit is a world of integration and overlapping consequences. Narrow knowledge can become incorrect knowledge.

In the 21st century, success will be determined increasingly by science and technology. Therefore, economic survival for all of us means being on the cutting edge of discovery and knowledge creation. Choosing otherwise is not frugal; it's just shortsighted. The alternative to not utilizing the power of science and technology is the alternative of being left behind. It does not matter if the field is biotechnology, advanced computing, nanotechnology, or any number of other new or emerging fields. That is why George Brown's concept of partnering between and among nations is so critical in this new era. No one culture or country has a monopoly of capable workers. Globalization has proven this repeatedly in the last decade. There is a reservoir of talent in other cultures whose languages we may not be able to speak but whose ideas and objectives are important to include.

As we seek the greatest advantage from our research enterprise we should never mistake science and technology for a linear process. Although science often leads to the development of new technology, new technology just as frequently enables science to explore new realms previously unreachable. Science does not enter a tunnel and come out the other end as technology. These two distinct forces historically have functioned in complement. Their

relationship is symbiotic. The word that is the very linchpin of this conference—biotechnology—is the deft fusion of the science of biology and the exquisite technology of genetic manipulation. Together they form a new whole.

And the advances continue like a braid of skeins winding back and forth across each other. This intertwining of knowledge—ideas, if you will—and tools has moved us to new understanding. We recognize that many disciplines converge to unlock the complex operation of systems—everything from climate patterns to terrorist movements. In my own research on cholera, technology played a crucial role. I could not have identified the cholera bacterium as water-borne and tied cholera outbreaks to the rise in sea surface temperatures without satellite remote-sensing technology to scan expanses of ocean. I have done most of that research over the last 25 years in the developing world, primarily in Bangladesh. There, deadly pandemics of cholera devastate villages and traumatize urban areas. For Americans, news of these dreaded scourges was sad statistics from far away. Since September 11, deadly disease scenarios are no longer implausible in our own backyard. No nation is immune from danger. In a world driven by science and reduced to a village by instant communication and lightening-swift transportation, safety is either for all of us or for none of us.

Less than 3 months ago, we saw a glaring example of why it is also important to have a public educated to the issues of science and technology. The surprise emergence of anthrax in the mail set in motion a race for information. It is vital that the global citizenry and all our leaders have a better working knowledge of the science and technology that defines our very existence. Although anthrax is not an everyday occurrence, there were many, including public officials, who thought it was contagious. Without correct information, we breed chaos and hysteria—neither of which fosters appropriate responses. In the United States, we have a new battle to fight and that is to prevent man's deliberate turning back the clock of progress in public health.

A citizenry literate about science and technology serves several goals. It gives the nation a workforce educated and trained to compete in the increasingly competitive global marketplace. It promotes good judgment as voters on both issues and candidates. It serves as strong defense against delusions of safety as well as threats. I cannot stress enough the primary importance of a scientifically literate citizenry. I cannot stress enough the responsibility of the science community to help meet that goal.

In multiple aspects, September 11 was a knife-sharp awakening for our nation and its leaders. Not the least of those surprises was how little people outside of the science community and those on the periphery understand science and technology issues. At this time of uncertainty, the need for all of *you* is greater than ever before. Your experience, wisdom, research, and measured debate can bring both historical context and analytical order to precipitate public discussion and debate.

Alfred North Whitehead said of science that "the aims of scientific thought are to see the general in the particular and the eternal in the transitory." And so we must ask how science can elucidate these times. We know that science brings fresh knowledge of our planet and ourselves and thus what is newly possible. That, however, is not enough. Science and technology are neutral. They are neither inherently good nor bad. What we choose to do with the potential that scientific knowledge offers is another matter. We have seen that so clearly in the last several weeks.

Modern biotechnology allows us to feed the world with improved nutrition but also allows terrorists to make more lethal bioweapons with greater ease. The same fertilizers that make our agriculture more productive were the mechanisms for destroying the Federal building in Oklahoma City just a few years ago. Scientists and nonscientists alike are all guardians over such choices. The world has always been a delicate balance of many complex forces, not the least of which is humanity—in all of its diversity of cultures, goals, and behaviors. Today, sophisticated knowledge, powerful tools, and high-speed transportation and communication amplify that complexity.

Two things will not change: humanity depends upon the complex and diverse systems of the planet to survive and prosper; the survival of the planet depends on the knowledge and know-how that humanity brings to the delicate environmental complexity that sustains us. I look forward to lively discussions that shed new light and knowledge on both.

Living Modified Organisms and the Environment— An International Conference Welcoming Address

James G. Butler,
Deputy Under Secretary
Marketing and Regulatory Programs
United States Department of Agriculture
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Conference Objective

Good morning and welcome. The stated objective of this conference is to bring together a diverse group of people to talk about the underlying science for assessing transgenic organisms in the environment. Looking at the list of attendees, I believe we have already met part of this goal. We have here today more than 230 registered participants from more than 40 countries representing a wide range of disciplines. Thank you all for coming.

Organization for Economic and Cooperative Development

Thank you also to the Organization for Economic and Cooperative Development (OECD) for once again bringing such a diverse group together. For almost 20 years, OECD has been addressing the issue of biosafety at the international level. Through its Working Group in the Harmonization of Regulatory Oversight and the Task Force for Novel Food and Feed, it has developed technical information useful for environmental safety assessments. By promoting international forums such as the one we are taking part in this week, OECD encourages us to learn from the experiences of other countries and, it is hoped, take home the best approaches to safety assessment available.

Thank you also to Dr. Rita Colwell, the Director of the National Science Foundation, who has graciously agreed to be the conference chair; Mr. Donald Johnston, the Secretary-General of the OECD: and Ms. Meg Scott Phipps, Commissioner of the North Carolina Department of Agriculture.

U.S. Government's Role in Regulating Biotechnology

I think all of us here would agree that, as new agriculture technologies are developed, safety is a major concern. To ensure the safety of our people and our resources, there are questions we must ask ourselves before introducing transgenic plants and other living modified organisms (LMOs) into the environment). Achieving production goals and creating successful applications for biotechnology are important, but just as important is our ability to assess the impact LMOs may have on the environment. The foundation for all such assessments must be science.

For more than 15 years, The U.S. Department of Agriculture (USDA) has been aware of the driving need to ensure the safety of LMOs through sound science. As the Deputy Under Secretary of Marketing and Regulatory Programs for USDA, one of my responsibilities includes the oversight of a regulatory agency known as the Animal and Plant Health Inspection Service. We are tasked with reviewing LMOs before they are field-tested or commercialized. The United States has been proactive in establishing a regulatory system for the safe development and commercialization of plant biotechnology. Since 1987, when USDA established its regulations for the field testing of transgenic plants, we have authorized more than 6,000 field trials at 27,000 sites in the United States. All have been conducted safely. Our regulatory system is not static, however. As new products are developed and new scientific information becomes available, our system and assessments evolve.

This conference presents us with a unique opportunity to participate in a constructive dialogue on issues of biotechnology and the environment. It is an opportunity to look at the most up-to-date information and root our discussions firmly in a scientific framework. In the coming days, the meeting will highlight the products being developed, the practice of environmental assessment, the scientific framework for assessing transgenic organisms in the environment, and the unique challenges and opportunities for the future.

Conclusion

This conference is meant to foster a dialog among developed and developing countries, industry, and environmental groups about transgenic organisms and the environment. Working together in a forum such as this one – with participants from all over the world – allows us the chance to understand the environmental assessment processes we have in place. I look forward to learning from you and hearing your views on this important topic.

Living Modified Organisms and the Environment— An International Conference

Opening Remarks

Donald J. Johnston,
Secretary-General
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I am very pleased to be with you today at the opening of this important Organization for Economic Cooperation and Developoment (OECD) conference on living modified organisms (LMOs) and the environment. I thank the U.S. Government for its generous support in sponsoring this event.

We have here in Raleigh today a wide range of globally acclaimed scientists in relevant areas of biotechnology and the environment. We have responsible government officials from many countries. We are joined by representatives of important public interest groups concerned with preserving the environment. I am pleased to note that our participants come not only from OECD countries but also from around the world. This is right because developments in biotechnology and LMOs will have important implications for all people and all environments.

In opening this conference I would like to comment on the following:

- The potential importance of these technologies;
- What governments and international organizations must do to make it possible to realize this potential; and finally
- How this conference is an important part of that process.

Importance of Biotechnology or Living Modified Organisms

Perhaps the most important thing to say about the potential for LMOs is that we really do not have a very good idea of what that potential is.

In the early 1980s I was the minister responsible for Science and Technology in the Canadian Federal Government. In that capacity, I convened an international conference in Ottawa entitled, "Canada Tomorrow." The purpose of the conference was to look to the scientific advances that we would welcome over the course of the 20 years till just beyond the end of the century. That period is almost behind us,

and I can report that the "Canada tomorrow" we envisaged is far different from the world we now see. That is because advances in science and technology are almost never linear and hence are unpredictable. So it will be with biotechnology and LMOs.

In 1983 we focused on the arrival of the information society and thought it had arrived! Some of us had begun to use computers or word processors in our offices, which are all antiques for today's generation. But no one contemplated nor mentioned the possibility of the virtual explosion of the information and communication technology that we have seen and continue to witness. The Internet, the World Wide Web, did not exist, and no one as I recall had heard of Moore of Moore's law!

At that time biotechnology was already showing promise. In 1983 we saw the potential in pharmaceuticals, the use of bacteria in waste control, and the cleanup of oil spills. Even in mining biotechnology, applications could leach valuable minerals from their environment. In fact, at the time, many governments expected that biotechnology would be the major area of economic growth in most of our countries by the 1990s. That has not been the case. Our timing may have been too ambitious. But compared with its likely ultimate role, biotechnology is probably in its infancy.

I think we will be able to compare its impact with the tremendous changes and economic, social, and scientific progress that have flowed from information and communications technologies. International Communications Technology (ICT) has permitted the dissemination of knowledge across the planet at an unprecedented rate. This has allowed us to take and apply successes in medicine rapidly and agriculture—in fact in all areas of human endeavor—Through ICT we have created a powerful global knowledge network that allows researchers and innovators to build upon the accomplishments of others at an unprecedented rate. What took decades, sometimes centuries to disseminate and apply now takes a day, a week, a month—seldom a year. And this process creates a highway for advances in biotechnology.

Government and Stakeholders

Will the scientific community be able to realize these advances on its own? Or does it need government—national and international—as well as other stakeholders?

This brings me to one of my concerns and the principal reason I see this conference as very important. Change is taking place so quickly, with effects on so many aspects of daily life, that many people are frightened and insecure. The average person cannot stay abreast of, and understand, these developments. I worry that the rapidity of change is the major obstacle to change itself in democratic societies. As always, ignorance is the enemy of progress.

Furthermore, the ICT revolution has inundated each citizen with information, including misinformation and exaggerated claims and alarms. It becomes difficult even to hear the scientific community. And we have the problem of making the truth sound convincing. Public fear can stampede governments into policies that will fetter new technologies and make them fall short of realizing human progress. How can the scientific community answer the

legitimate questions raised by many with respect to the environmental dimensions of biotechnology as used, for example, in agriculture? The public deserves answers. That is in large measure what this conference is all about.

In June 1999, the Heads of State of the G8 at the Cologne Summit asked the OECD to provide input for their discussions on biotechnology and food safety. At that time, I wrote to OECD Governments to make clear: in order to offer effective assistance to governments in developing approaches to biotechnology—in particular related to issues of food safety, GMOs and trade—the OECD and other international forums must address the interaction of three elements:

> Science: findings on the implications of the technologies for human health and the health of the environment need to be presented clearly and underpin policy considerations.
>
> Regulation: regulations need to be consistent with scientifically defined risks to health and the environment, and the similarities and differences in regulation across countries need to be analyzed in relation to rigorously defined standards.
>
> Public information: governments and the scientific community must be transparent in presenting findings on risks and in putting in place measures to address them.

The first action we took in responding to the G8 request was to organize a meeting in November 1999 with representatives from all the stakeholders in the biotechnology issue. I was present throughout, and I must say that I was very impressed by how thoughtful the contributions were.

In March 2000 the United Kingdom hosted an OECD Conferencein Edinburgh titled, *GM Food Safety: Facts, Uncertainties and Assessment* that again involved all the stakeholders and many non-OECD countries to discuss specifically the health aspects of genetically modified (GM) foods. The Chairman's Report of this conference concluded that worldwide many people are eating GM food with no adverse effects on human health reported in the peer-reviewed scientific literature. The report goes on, however, to state, that in theory there could be long-term effects of GM foods on human health that have not been detected because these foods have been available for less than 10 years. Environmental impacts were also identified as an area of uncertainty. The report of this meeting was an input to the July 2000 Okinawa Heads of State G8 Summit.

In early July this year, again the United Kingdom generously hosted in Bangkok an OECD conference titled, on the *New Biotechnology Foods and Crops: Science, Safety and Society*. This conference specifically sought to involve scientists, officials, and stakeholders from non-OECD countries. The Chairman's report of this conference recommended that all stakeholders commit to greater transparency on GMOs and that governments increase their support for independent and publicly funded scientific research into the risks and benefits of GM foods and crops. The output of this meeting was provided as input to the July 2001 G8 Heads of State summit in Genoa.

From the preceding it is evident that the OECD has been deeply involved in furthering the science-based debate on this new technology. This is not surprising because biotechnology is a crosscutting issue, and in the international arena, OECD, by its multidisciplinary nature, is well placed to organize such a debate. In fact, the OECD has taken up the scientific, agricultural, environmental, health, trade, and development aspects the various aspects of biotechnology.

An important task of OECD, as an intergovernmental organization, is to assist countries to ensure that their systems of regulatory oversight are not duplicative internationally and make sense together. The OECD has been working on this since 1982, and good science has always been the basis of our efforts. By bringing together experts from many countries to discuss how to bring the latest science into regulatory efforts, we also assist countries to improve the quality as well as the efficiency of their regulatory instruments. In doing this work we can count on close cooperation with the other intergovernmental organizations that are working in this field. For example, we were pleased to contribute to setting up the Inter-Agency Network on Biotechnology, which includes nine organizations.

After the three major conferences described above, it is now time to discuss what might be one of the most difficult issues in relation to biotechnology, namely, the question of the environmental impacts this technology may have. I thank the United States for providing the possibility here to discuss this issue in the same participatory way as at the earlier OECD conferences.

Finding answers to the environmental questions related to biotechnology is a key challenge and will indeed weigh heavily in the balance between opportunities and possible risks of biotechnology. We have a wealth of scientific expertise assembled here that can look at the issue from different perspectives. I hope that by Friday afternoon we will have a better idea whether there are gaps in our knowledge with respect to the environmental impacts of LMOs and, if so, what these knowledge gaps are and what needs to be done to address them. And in keeping with my earlier comments, it is important that the public be informed about what science knows, where there may be gaps, and how risk in this area is to be assessed and by whom.

The conference results will form a basis for discussing followup work in various fora. The OECD Working Group on Harmonisation of Regulatory Oversight in Biotechnology, in which relevant stakeholders and a number of non-OECD countries participate, is certainly one of the bodies that will carefully look at the outcomes of this conference. It will then decide on how it can contribute to addressing the unanswered questions that might come out of this conference.

We have an exceptional collection of experts here, an excellent chair, and great hospitality from our U.S. host. We have all the conditions united here that are necessary to have a good dialog. Therefore, we have good reason to look forward with great expectations to the contributions from all of you.

I will conclude with three quotes from the late American philosopher Lewis Mumford. He has said that

> Western society has accepted as unquestionable a technological imperative that is quite as arbitrary as the most primitive taboo: not merely the duty to foster invention and constantly to create technological novelties, but equally the duty to surrender to these novelties unconditionally, just because they are offered, without respect to their human consequences.

I believe that Mumford's view would not hold today where we all recognize the importance of examining the opportunities and challenges of new technologies and assessing their benefits and risks. And while doing this I think we can all be inspired by a second quote from the same philosopher. He also wrote that "however far modern science and technology have fallen short of their inherent possibilities, they have taught mankind at least one lesson: nothing is impossible."

And I conclude with a final quote from Mumford, which I am often disposed to use, namely, "I am optimistic about the possibilities, pessimistic about the probabilities." I hope that at the outset of this conference we can declare that we are optimistic about both insofar as the potential of biotechnology for improving the human condition on a global basis.

Keeping this in mind, I wish you all a very good conference.

Living Modified Organisms and the Environment— An International Conference

Final Rapporteurs' Report

Introduction

1. Status Review
2. Areas of Broad Convergence
3. Outstanding Issues
4. The Way Forward

Introduction

This report has been produced by the co-rapporteurs — Calestous Juma, Audia Barnett, and Iain Gillespie. It represents their personal interpretation of the key issues brought out in the conference. This final version has benefited from comments made by participants to the Conference over the following six weeks. The decision to incorporate specific comments in the text has been the sole responsibility of the three rapporteurs.

The objective of the Conference was to bring together a diverse group of participants for a constructive dialogue on the underlying science for assessing living modified organisms (LMOs) in the environment. The emphasis was on transgenic crops because these are the most common applications at the current time. However, other applications were also considered, such as the use of transgenic trees in forestry and fish in aquaculture. The conference promoted a dialogue between developed and developing countries in order to identify unique assessment needs and experiences of different countries and regions. The Conference was attended by around 250 participants from some 20 OECD countries and around 25 non-OECD countries drawn from government, industry, academia and civil society.

The conference was chaired initially by Rita Colwell and in the later stages by Calestous Juma and sought answers to four general questions:

- What are the current trends and future prospects for applications of LMOs and what are the potential benefits and risks?
- What are the current scientific data, information and hypotheses underlying the assessment of LMOs in the environment?
- What are the particular issues with respect to the environmental assessment of transgenic crops and what are the similarities or differences between environmental assessments conducted on transgenic crops and other types of LMOs?
- What future work on scientific environmental assessment is necessary?

In opening the conference, Dr. Colwell emphasized the value of a broad inclusive dialogue between countries. Science needs to refocus from enabling remediation and amelioration and do more to support prediction and prevention.

Accurate, accessible and high quality data and information could help create knowledge and development. Notwithstanding recent concerns about misuse of biological data, the clock must not be turned back on exchanging knowledge and information. On the contrary, science can elucidate our times and contribute to the further development of our world, but the scientific community clearly needs to do more to bring this message of promise to a wider public audience.

In his opening remarks, the OECD Secretary General, Donald Johnston, also emphasized the need for public dialogue, not least to help engender more confidence and less insecurity about biotechnology especially in view of its rapid pace of development. There is a need to communicate knowledge convincingly to the public and to continue the debate on issues raised by biotechnology with all stakeholders. The environmental impacts of the technology continue to need to be considered. The key challenges are to achieve balance between scientific opportunity and safety and to identify gaps in knowledge and what more needs to be done to address these gaps.

Structure of this Report

This report is divided into four parts. The first section provides a status review of trends in the development of LMOs, the practice of risk assessment, the scientific framework for assessment and challenges and opportunities for environmental assessment. It is, in effect, a précis of the proceedings of the conference. The second section summarizes the key areas of general agreement among participants while the third section covers areas where there is as yet no general agreement. The final section charts the way forward focusing on measures which might help to improve ways of assessing the impact of LMOs on the environment, areas requiring further investigation and opportunities for international harmonization as well as cooperation.

1. Status Review
Trends in the commercialization of transgenic crops

Agriculture has always been based on selecting and modifying plants to develop useful crops. Agricultural science is utilizing biotechnology.

Advances in genomics and informatics are helping push back the limits to agricultural production. A new generation of potential traits is being addressed – including factors affecting yield, quality, tolerance to environmental stress. While there has been a great deal of research work on transgenic varieties in many important plant species, large scale and commercial experience to date has been predominantly based on a relatively few crops modified in the main for herbicide tolerance or pest resistance. Changes in technology, including plastid transformation and better gene targeting may contribute to improved safety of LMOs.

Adequate food availability and food security continue to be considerable challenges for many developing countries. Biotechnology potentially offers "packaged technology in a seed" that could improve quality and quantity without compromising local traditional or established cultural practices.

In China, one LMO crop has been commercialized (Bt cotton) and work continues on development of several others. Data that were presented at the conference suggests that there are benefits to the health of agricultural workers (from reduced pesticide poisoning) and that economic benefits appear to accrue mainly to small farmers.

The agricultural priorities in developing countries – including food security and supply, nutritional and post-harvest quality, and appropriate pest resistance - are not always the same as those of developed countries. Most commercialization of LMOs has focused on the needs of the latter. Local farmers are important actors in uptake of technology and better ways need to be found to improve communication between scientists and society. While biotechnology is not likely to be the whole answer to human and environmental needs, international dialogue is required to ensure developing countries' priorities are not ignored.

Future trends and applications

The exponential growth in genetic data has enormous potential to deliver improvements for crops. The key challenges are, in an era of agribusiness consolidation, to move to a more precise discovery model for new agrochemicals, develop better ways to process the flood of available genetic data, and deliver useful new traits and genes to meet the expectations of those investing in research.

A number of current trends were identified. Functional genomics and the ability to sequence whole plant genomes provide a powerful model system for discovery. "Industrialization" of phenotype analysis is increasing the rate of trait assessment. There is greater integration of information scientists with biologists in discovery teams, and combining genomics, proteomics, "transcriptionomics" and "metabolomics" heralds the age of "system biology". The key drivers for these developments are the increasing trends towards narrower, more targeted markets and increasing "democratization" of discovery and information sharing.

The practice of environmental assessment

Many countries have systems of risk/safety assessment in place to evaluate release of LMOs into the environment. The Cartagena Protocol on Biosafety, as well as many national systems, lays down a methodology for risk and safety analysis including a number of systematic steps and a list of points to consider. Different regulatory systems base their assessments on very similar sets of data requirements concerning the organism, insert, trait and environment. Although there is variability between the detail of risk assessments, the issues that they address are common across OECD countries and beyond. Several initiatives are in place to offer capacity building on the practical application of risk assessment to LMOs. Even in relatively developed non-OECD economies human capacity remains a challenge.

There is over ten years of field release data on LMOs. The available information includes data on agronomic and environmental effects. The current regulatory systems have dealt with these releases. Some participants were of the view that the systems need to be looked at to ensure that they are able to cope with future introductions of increasingly complex genetic constructs in LMOs. For example, crops containing stacked genes for herbicide tolerance could be assessed for unexpected secondary functions of introduced sequences. A number of participants were of the view that the regulatory frameworks in their countries allow for these broader and more complex issues to be taken into account.

Much debate continues to focus on gene flow between LMOs and other plant species in the environment and on the extent to which increased weediness might occur. To assess gene flow, when plants with which genes might be exchanged in the environment are present, more knowledge is often required on the biology and spatial location both of the LMOs and such plants. . To assess the potential impacts of gene flow, the characteristics of the introduced genes and related altered traits have to be taken into account. Uncertainty about the implications of gene flow is more of a concern when there are wild relatives in the environment and most particularly when such wild relatives are within centers of diversity.

The availability of robust data on the potential for gene flow – and particularly on the location of wild relatives – is sometimes patchy. However, it is feasible to construct databases of the biology and location of wild relatives, landraces and LMOs. Such databases can be used to identify areas where there is a high or a low probability of introgression following the release of LMOs, although the predictive ability of such systems for environments that have not been rigorously mapped needs to be further tested.

Many countries have regulatory systems in place addressing the issue of gene flow. Different countries place different relative emphasis on various factors affecting gene flow.

Many experts emphasized that a distinction needs to be drawn between information necessary to reach a conclusion on safety or risk assessment and information that would simply be scientifically interesting. Lessons can be learned from chemical risk assessment experience, but there are important differences.

Many if not most experts consider that gene flow *per se* is not harmful. However, relatively few empirical data are available on the long-term consequences of gene flow. Uncertainty about possible consequences of gene flow may be higher for these potential long term effects than for short term effects. Assessment of whether flow of particular genes affect fitness, for example, could be done stepwise, including prospective assessment of wild populations to determine likely selection pressures and head-to-head fitness comparisons of transgenic with non-transgenic populations. Assessment might also address whether mitigation measures could be appropriate and available.

Some evidence suggests that there are environmental benefits associated with the introduction of some LMOs. For example, in South Africa there are indications that insect, bird and frog biodiversity may benefit from the use of Bt cotton rather than traditional varieties subject to normal insecticide regimes. Speakers also referred to work in Columbia and China that suggests some environmental benefit. However, more research is needed to validate this.

Risk assessments of genetically modified crops have in the main focused on agronomic characteristics in temperate regions. Comparative risks and benefits of the introduction of LMOs with alternative cultivation methods need to be assessed on a case by case basis, taking into account regional agricultural practices and, where appropriate, socio-economic considerations. Baseline data required for environmental impact assessment, including information on endogenous species and existence of sexually compatible wild relatives of agricultural crop plants are scant.

While the likelihood of harm is a function of both hazard and exposure, the public debate is dominated by hazard identification, often neglecting issues such as exposure and the likelihood of harm, an evaluation of the final consequence and a comparison with the existing situation. The press coverage of potential harm to the Monarch butterfly is a prime example of this focus on hazard identification.

In ecological impact assessments, it is problematic to extrapolate from small scale field trials to the commercial scale cultivation. Countries have taken a number of approaches to dealing with this problem. In the UK, the approach has been to hold farm scale field trials that address scale, and integrate regional cultivation practices and farmer behavioral issues. The research process takes into account factors affecting credibility. It is entirely government funded, foresees peer review and public review of results. The driving issue of this study is the assessment of the impact of herbicide tolerant crops on farmland biodiversity. An ecological model is being developed using specific species as indicators for this purpose.

The cost of these issue-targeted farm scale field trials may be prohibitive for routine assessments of impacts of individual LMOs in every case. More generally, regulatory requirements may impose a cost barrier for development of minor crops (e.g. many vegetables and fruits).

Risk assessments are based on the best available sound science. However, there remains debate about the extent to which subsequent regulatory approvals currently or in the future ought to draw on other factors such as public attitudes and socio-economic factors. One view is that the assessment of risk from LMOs is currently performed on too narrow a basis and that a more interdisciplinary approach is required that draws on more ecological data, considers long term effects, and considers risks alongside benefits in a more transparent and participatory manner.

There is a clear need for better communication on scientific and risk issues between scientists and the public. Public participation is essential in risk assessment and management. However, the debate continues as to how this can best be achieved.

There also remains a difference of view in how to cope with uncertainty in risk assessments. Some participants thought that lessons might be drawn from the introduction of chemical entities where harmful effects took some time to manifest themselves. According to this view, risk management might be applied in advance of assessment, so that risks that, based on current scientific knowledge, could not be assessed rationally were simply avoided. A number of countries apply such a “precautionary” approach. However, others thought that it is not possible to manage risks that cannot be assessed rationally and that governments should focus on assessing and managing identifiable risk.

Further issues that remain under debate are whether assessment of risk and uncertainty should be applied primarily to new technologies or might also be applied to conventional practices and the extent to which the use of concepts like life cycle assessment might contribute to sustainable agricultural development.

Scientific framework for assessment

There was a discussion about the science underpinning effective risk assessment.

Assessing ecological impacts of LMOs is not without problems, particularly long term or "secondary" impacts. One approach could be to compare LMOs with organisms produced using more traditional breeding techniques. However problems remain such as lack of reliable base line data, the relevance of extrapolation from small to large scale, ability to detect rare events within a relatively short experimental time scale, lags between introduction and manifestation of impacts and general ignorance about the complexity of ecosystems. Furthermore, there remain problems, concerns and/or disagreements around how to place any observed change in the context of changes occurring through traditional agricultural practices. There is a need for international consensus on how these difficulties might best be addressed.

Measuring ecological impact within soil systems is perhaps most challenging of all. Relevant indicators need to be selected that reflect changes in the rhizosphere and that affect crop performance or food quality. Accurate measurement of rhizosphere populations is difficult. Changes in soils have to be measured by changes in gene products and marker genes or both rather than as change in microbe populations.

Assessment of non-target impacts of LMOs needs to reflect the complexity of real environments. For example, exposure experiments need to consider how an organism accesses its food chain within a given environment as well as considering potential impacts on non-target species that play a significant role in ecosystem functioning when such impacts might plausibly introduce risks.

A more systematic approach is possible and necessary to assess non-target effects.

Constancy of yield is important for developing countries. An inclusive approach to use of technology may be required that integrates pest control, farming and social practices. LMOs that could impact on pest or weed control are best introduced within this integrated framework, cognizant of regional conditions and practices, so that there are adequate levels of control of the target.

Introducing into an LMO several genes that assist the LMO to resist a pest ("stacking" or "pyramiding" of these genes) rather than a single gene is one strategy for reducing the probability that the target pest population will develop a means of countering these genes. Adequate information exchange between public and private sector researchers is necessary to develop a battery of resistance genes for stacking. Risk assessment systems need to evolve to deal with such stacking or pyramiding strategies and international discussion may facilitate this.

For the most part, transgenic plants expressing pharmaceuticals are being developed to reduce production costs and may improve product safety. The gene products expressed by such LMOs may pose different challenges for the assessment methodology. Close monitoring will be required of such LMOs which are likely to be grown in sites dedicated to maintaining product quality through a variety of enhanced isolation procedures.

LMO trees may increase quality and yields and promote sustainability by concentrating planting areas. The technology for the production of transgenic trees is developing faster than the technology for conducting sound environmental risk assessment. OECD first considered genetically modified trees in 1999. The case by case and step by step approach was considered important. Monitoring is difficult because of tree longevity.

Though transgenic insect technology is promising as a possible method of controlling parasite vectors, we know very little about hazards and risks. There is a need for scientific peer review as well as government funds to support research on risk analysis.

Some argue that transgenic fish may pose negligible ecological risks as they are unlikely to be selected for in the presence of wild populations. However, large numbers of LMO fish interbreeding with natural populations may present an issue. Recovery after release is unlikely. Studies based on one individual environment, for example in contained facilities, are inadequate to predict behavior and performance in natural environments.

Advances in genomics raise questions about how we approach risk assessment, as novel genes identified by genomics and available for biotechnological applications will be characterized by novel standards. The general principles underlying risk or safety assessment, however, remain similar.

Maize at the centre of origin and diversity

There was a presentation about maize production in Mexico. Local farmers routinely incorporate genetic material in land races to maintain vigor. Preliminary data presented suggest that Mexican land races might contain introgressed transgenic sequences. These data, however, need to be confirmed through other methods of detailed molecular analysis.

The question was posed whether there are any unique risks posed by the introgression of transgenic traits into land races. Discussions centered around whether an adverse effect would be associated with introgression of the Bt trait into land races. Questions raised in this context included:

- will such introgression affect future levels of diversity in maize?
- will such introgression affect other organisms?
- will such introgression require adaptation of crop management practices to control the pests?

This discussion included questions about whether there had been any adverse effect demonstrated with the use of the Bt gene in any instance. In Mexico socio-economic considerations were said to be important since cultural practices of farmers greatly influence their farm management.

A number of questions were posed about the implications of these events for regulation. Stakeholder and public consultation on the appropriate course of action was considered paramount, as fundamental national values are attached to maize in Mexico. The appropriateness of a moratorium was debated, and the ability to enforce quarantine measures was discussed.

Mention was made of the need to continue to promote cooperation regarding implementation of the objectives of the Cartagena Protocol on Biosafety.

Challenges and opportunities for environmental assessment

Public wariness of new and novel food products is not a new phenomenon, but rather has occurred many times over the centuries. The story of the adoption of coffee is an eloquent illustration of earlier debate on the consequences for society of introduction of new types of products.

Monitoring can be a key element of risk management. Insect resistance management in Bt crops has been the topic of much debate during the meeting. Program designs, and the reasons for them, need to be well communicated to and understood by farmers as well as scientists. Farmers are likely to be one of the best early warning mechanisms for any adverse events and cooperation between neighboring farmers is invaluable. Different approaches will be appropriate for different crops and environments, and for different countries and regions. In the US, no field resistance to Bt in LMOs has been reported to date and farmer compliance with insect resistance management strategies has been very high.

Common elements of all pre-commercial and commercial monitoring programs include:

- stakeholder consultation on parameters and implementation
- scientific consultation
- peer review of monitoring plan
- close collaboration of public sector, private sector and farmers in implementing programs to take account of the regional diversity in ecological and agronomic environments and cultivation practices
- public workshops
- communication of results

The processes described were all iterative, to provide for continuous review of what is monitored and how monitoring proceeds according to the latest scientific developments and feedback from scientific and public consultation.

Challenges include sampling methodologies and cost effectiveness of methods in particular if they are to be carried out on a case by case basis. Common international methodologies could be developed for monitoring and sharing of data. Particularly in the tropics there is a real need for more baseline data. Integration of information derived by molecular techniques, global information system technology and ecological studies may help to map areas where gene flow could occur.

An interdisciplinary approach to use of the technology might take into account costs of labor, time, management skills, as well as income to farmers and public acceptability.

There is a need for a common understanding of what constitutes an adverse effect, as well as a common understanding of indicators, risk assessment criteria, and end points.

A key set of questions remain around the extent to which biotechnology will successfully deliver benefits to developing countries and represent a true public good. Delivering research and products that address local needs, but with an eye on international markets, creates great challenges to the leadership and available capacity in developing countries. Public research in Africa, South America and Asia is addressing a number of crops and traits. Progress is being made but few are yet commercialized. In countries carrying out such LMO research, biosafety systems are in place though capacity, management and administration and the wider legal system needs development.

2. Areas of Broad Convergence

Provided that the health and environmental impacts of the technology are responsibly addressed, LMOs can offer the opportunity to address global food security and supply challenges.

Recent advances in molecular and evolutionary biology have opened a wide range of opportunities related to biotechnology. Advances in genomics, informatics and proteonomics are being integrated into systems biology. These advances open possibilities for the development of products more suited to specific human and environmental needs. At the same time, advances in science offer possibilities to improve safety assessment.

Future trends in the economic application of LMOs will depend largely on the extent to which concerns about their environmental implications are addressed. The promise of biotechnology in addressing economic and environmental problems (as reflected in Agenda 21) has been superseded by public skepticism and caution in many countries.

There is common agreement that regulatory practices should be built on scientific knowledge.

Environmental concerns regarding the commercialization of LMOs are renewing interest in ecological research. As the range of products expands so will the need to better understand the functioning of ecosystems. This should be matched by adequate funding.

There is general agreement that case-by-case, step-by-step approaches are the best available tools for managing risks associated with LMOs. A great deal of experience in field trials has generated much information, but risk assessment needs to continue to make use of best available science as new, less familiar trait and organism combinations are developed. There is agreement that gene flow to wild relatives or other LMOs needs to be considered carefully as part of risk assessment. The view of many participants is that gene flow *per se* is not a particular concern. However, the impact of individual traits in individual circumstances does need to be considered. Centers of origin or diversity offer more potential targets for gene flow that require study and evaluation and so may be particularly vulnerable to gene

flow from LMOs.

Risk assessment practices need to evolve continually to take account of new developments. There is agreement that better communication with the public is needed to improve the understanding of scientific developments. The European Commission, for example, has launched a public consultation on life sciences and biotechnology that aims to include social and policy considerations in research and make such research activities as inclusive as possible.

Continued international co-operation amongst OECD countries and between OECD and non-OECD countries remains essential to harness the potential benefits of this technology in a safe and sustainable way. While assessments need to take into account country or region-specific environments, common approaches and methodologies can nevertheless be developed.

As the scientific basis for decision-making becomes increasingly evident, so does the global nature of the policy aspects of the economic use of LMOs. This is partly because of increasing globalization of the world economy and the associated interdependence among countries through international trade. Resolving many of the considerations associated with LMOs will require international action and cooperation. But the global nature of these concerns are also accompanied by the need to take into account diversity among nations, ecological systems as well as local or regional needs and priorities.

The role of LMOs in solving specific problems of the developing world is emerging as a major policy challenge for the international community. While most of the major crops in commercial use were developed for temperate climates, future technological developments must involve identifying traits of relevance to the needs of developing countries. Indeed, several developing countries are already engaged in research that reflects their own priorities. Nevertheless there is a need to strengthen scientific and technological capabilities in developing countries and foster appropriate partnerships between these countries and industrialized nations.

3. Outstanding Issues

While there is general agreement that scientific knowledge is essential for risk assessment and management, discussions continue on how to identify appropriate baselines and what constitute appropriate data sets for identifying risks and estimating the likelihood of the identified risk occurring. There was discussion of the distinction between "what it is necessary to know" versus "what it is nice to know" in order to make a determination of risk, and what differentiates the two. Discussion also continues about whether a generic approach to risk assessment might be explored for certain applications.

One of the unresolved issues is whether concerns about uncertainty should be applied primarily to crops developed using new technologies and LMOs or should also be applied to crops developed using conventional methods such as wide crosses in breeding.

Some conference participants thought that uncertainty over issues such as labeling and traceability might be resolved by using international standards. They considered that such standards could help to avoid disrupting international trade or undercutting the capacity of developing countries to use emerging technologies, while allowing all countries and regions to meet their needs. Many believed strengthened efforts in international co-operation are essential to improve harmonization of regulatory oversight. Many participants urged that any such international cooperation keep in mind the international framework that will be set up as a

result of the Cartagena Protocol on Biosafety.

Many of the general safety principles that guide debate over LMOs have been developed in fields such as chemical and nuclear safety. While these areas have provided an initial approach to risk or safety assessment and are a major source of information and experience, it is not clear the extent to which the lessons are really applicable to living organisms like LMOs.

4. The Way Forward

Improving Assessments

After a decade or more of work, much progress has been made in understanding the underpinning science and a great deal of experience has been gained with the application and safety assessment of LMOs, including on the environmental aspects of commercial use, though most is drawn from a relatively small number of crop-trait combinations. The time has come to look back on this work and evaluate the data that have been generated.

There is a significant body of knowledge on the environmental impacts of the commercial use of LMOs. Much of this information remains unpublished though some has been quoted widely in public discussions over the environmental safety of LMOs. Synthesis and communication of this existing information might be helpful to inform more authoritative biosafety assessment in the future. Research showing no impacts tends to be regarded as unattractive for publication in the scientific literature. To the extent possible, companies and other institutions should publish or synthesize unpublished information on the safety of LMOs and make it readily available.

In addition to synthesizing the available information, there is a need to improve on existing environmental assessment methodologies in the light of experience gained from commercial and research use of LMOs.

Most existing risk assessment and management methodologies do not consider in detail the benefits that LMOs might deliver. As a result, much of the policy debate about the risks of LMOs creates the impression amongst the public that such products only carry risks and offer no benefits.

Undertaking Further Scientific Investigation

There are a number of areas that require further scientific investigation. These include issues such as gene flow, development of resistance and impact on non-target species. The success of such investigations will depend on the development of agreed baseline data, appropriate databases, assessment methodologies that capture the diversity of ecological systems while at the same time allowing for comparability. Also important is the role of modeling (which is used widely in climate impact studies) as a way of dealing with lack of information and other limiting factors in ecological knowledge.

Specific issues might include:

(i) more scientific knowledge to establish the way in which ecosystems will respond to

introduction of more complex LMOs.

(ii) better understanding of the mechanics and potential impacts of gene flow from living organisms, including LMOs, (the individual trait being a key determinant in considering potential impact) where there are potential hybridization targets available.

(iii) refinement of research on non-target organisms to ensure that it is relevant to real ecosystems.

International harmonization and co-operation

The flow of ideas for new LMOs is not limiting new advances, but transfer from the laboratory to the glasshouse and then to the field is slowly drying up. An important factor remains the unresolved societal debate.

Early phases of technological development are often characterized by regulatory uncertainty and rapid social learning. This requires flexibility and adaptability in existing regulatory frameworks and institutional arrangements based on harmonization and cooperation in research and assessment methods.

A number of opportunities for such international cooperation have emerged from discussion. These include:

- giving further thought to whether comparative risk assessments might usefully be applied to LMOs
- developing consensus on more specific definition of the environment into which LMOs are released in the context of risk or safety assessment (in particular how non-target effects might best be assessed).
- discussing the extent to which current risk assessment techniques are sufficient and appropriate to deal with non agricultural LMOs, LMOs with stacked genes and products of "systems" biology.
- addressing appropriate baselines for assessment and determination of long term effects.
- working together towards a more harmonized understanding of what constitutes an adverse effect, as well as towards developing risk assessment criteria, assessment endpoints and biotic and abiotic indicators in the context of risk assessment and monitoring of LMOs.
- developing more predictive tools for environmental impact of LMOs
- considering how and when future monitoring schemes for research or commercialization of LMOs might best be designed
- developing cooperation on research methodology including, for example, detection methods, monitoring and sharing of data
- seeking agreement on how best to determine risk associated with release of "second-generation" LMOs into environments where other LMOs are already present
- encouraging a discussion of whether, in light of knowledge derived through genome analysis, unexpected secondary functions of inserted genes should further be pursued.

International co-operation is also essential in area of *capacity building* for science-based and evidence-based biosafety management. Such capacity building should involve cost-effective methods of institutional development. This could be done through the expansion of the mandate and capabilities of existing institutions to address biosafety concerns. Where such institutions do not exist, there may be a case to establish new institutions. Regulatory capabilities for biosafety need to co-evolve with developments in biotechnology competence.

The rapporteurs are grateful for the assistance of OECD staff and consultants in assembling this report: Sally de Marcellus, Ariane König, Michael Ryan and Rebecca Weiner.

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Session 1: Genetic Modification:
Current and Future Applications

Overview of Current Commercial Applications[1]

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United States of America

I want to start by quoting a statement from a gentleman who has never been known to mince words when he talks about starvation and suffering. He is the agronomist whose discoveries sparked the Green Revolution that has saved literally millions of lives. This individual, Nobel Peace Prize and Medal of Freedom winner Dr. Norman Borlaug, states that we cannot turn back the clock on agriculture and only use methods that were developed to feed a much smaller population. We cannot feed our global population unless farmers across the world have access to current high yielding crop production methods as well as new biotechnology breakthroughs that can increase yields, dependability, and nutritional quality of our basic food crops.

We need to bring common sense into the debate on agriculture and science and technology, and the sooner the better. I believe that this conference today—and thank you for inviting me—is going to focus on the application of common sense to improving food productivity and food security worldwide.

I think the African scientist Florence Wambugu of Kenya best describes the real potential for application of biotechnology insofar as developing countries are concerned, and indeed for any country. She states that the great potential of biotechnology to increase agriculture lies in its "packaged technology in a seed." This is scale neutral and it ensures that farmers can adopt the benefits of these technologies without changing local social and cultural practices. Dr. Wambugu has stated that, in the past, all attempts to improve productivity, specifically in her region in Kenya, have, in large part, failed because they demanded massive cultural change that farmers were not willing or able to undertake.

To illustrate the amount of land that would be needed to produce the same amount of crops today if we were to use the technology that was available to us in 1929, look at the map of the United States of America. Over two-thirds of the country would be under plow. We would lose our national parks, wetlands, and our marginal lands if we were to try and achieve equal productivity using "natural methods of production."

If you look worldwide, a more devastating picture develops. Every single second, we lose 3,000 square meters of forest and 1,000 tons of topsoil. The arable land shrinks by 20,000 hectares every single year, and erosion has made 1 billion hectares

This paper is an edited version of a video transcription.

of soil unusable for agriculture. These are devastating numbers. We lose land to irrigation-induced salinity every year. We have lost about 25 million acres of land this way. This is approximately one-fifth the size of California. At the University of California, Davis, scientists have developed tomatoes using a transport protein that will allow these plants to grow in up to one-third the salt concentration of seawater. This will have enormous potential for developing countries. Over 25 percent of the grain needed in Africa is imported, whereas up to 40 percent of the harvest is lost owing to postharvest damage. One cannot imagine how we can achieve adequate productivity while minimizing the impact on our environment without using the tools of biotechnology.

Here are some examples of the technology available today that can be used to address these issues. In 1906, Luther Burbank wrote, "We have recently advanced our knowledge of genetics to the point where we can manipulate life in a way never intended by nature. We must proceed with the utmost caution in the application of this newfound knowledge." Burbank (1849–1926), contributed significantly to modern agricultural technology by introducing some of the first scientific approaches to crossbreeding and selection. In fact, we have been modifying the world around us, primarily agricultural crops, for thousands of years. The notion of referring to modern genetically modified crops as living modified organisms is a slight distortion of the truth. Everything you are looking at around you today, from a crop point of view, is a living modified organism. Burbank was one of the first to apply scientific principles to modified organisms, but we have been modifying organisms for about 10,000 years. It has taken 10,000 years to reach the current levels of production of about 5 billion tons per year. And we are going to have to double that level of production by the year 2025.

If many consumers in the street, and even many of you, were to look at this century's applications of technology, it would boggle the mind. The current technologies we use to increase productivity lend themselves to the map of the United States of America referred to earlier. One example of technology that we have been using is embryo rescue and wide crosses. We are using technological methods in which genes are integrated from very wide crosses that would not cross in nature because of reproductive isolation. These genes are sexually incompatible in nature, and although sex is wonderful, it is limited as far as the farmer is concerned. Modern technologies provide means to bypass this sexual incompatibility barrier. A green-looking cauliflower, called brocciflower, is an example of a wide cross of two species that would not cross in nature.

An example from work conducted at UC Davis helps to illustrate this point. High soluble solids are the Holy Grail for processing tomatoes—the higher the solids, the more paste there will be for the cannery. The common processing variety of tomato, *Lycospersicum esculentum*, has about 5 percent soluble solids because it is a hexose accumulator. There is a wild variety of tomato, *Lycospersicum chimielewski*i, that has 10 percent soluble solids, for it is a sucrose accumulator. But that is the only good characteristic that it has. The other characteristics are rather undesirable: small size, bitter taste, lower yield, toxicity, because, like potato, the tomato is a member of the deadly nightshade family that produces glycoalkaloid toxins. Toxic pizzas would probably not pass muster with the Food and Drug Administration (FDA). The researchers in a laboratory at UC Davis (Alan Bennett, personal communication) decided to try to transfer the higher soluble-solids-accumulation characteristic from the wild tomato to the domesticated tomato and yet retain all of the other desirable characteristics of the domesticated variety. Using a classical breeding approach to achieve this, first the researchers crossed the wild tomato with the domesticated tomato and over many years of

backcrossing to the domestic parent came up with a tomato with higher soluble solids content. One of the other sequences contained in the introgressed genes caused reduced fertility in the resulting tomato. Also, it is difficult to determine how much of the toxic gene information is still in those introgressed sequences. This illustrates that with classical breeding, breeders do not always get just the characteristics desired; sometimes they also get somewhat undesirable characteristics. And the breeder has little control over this outcome.

In the second approach the goal again was the same: to increase the soluble solid content of the tomato. This time the researchers looked at the metabolic pathway for simple carbohydrate synthesis and determined that if one gene is switched off (one responsible for coding for an enzyme that converts the sucrose accumulator [high solids] into a hexose accumulator [low solids], they could engineer a more valuable high-solids tomato. Through modern molecular breeding technologies they were able to turn off that gene by adding a complement of it using antisense technology that acts like a complementary piece of Velcro to turn off the machinery that makes the sugar-converting enzyme.

The application of technology to improve in-crop agriculture experienced a paradigm shift with the advent of recombinant DNA technology. Technology is shifting yet again with the application of the knowledge developed through the Human Genome Project and the discipline of bioinformatics. We are using the power of computational knowledge to understand the genes that are important in agricultural crops. For example, we can look at centuries of gene maps of cereals and take genes from distant relatives to see how they could be applied to improving productivity in cultivated species. The Native Americans did this for years. The ancestor of modern-day corn, teosinte, has a very thin ear, yet it has nearly all the genetic information necessary to produce modern-day corn. It has taken many years of mutation and selection to achieve today's large, bountiful ear of corn.

Most people do not realize how much we actually use mutation—chemical or irradiation mutagenesis—to modify our crops. Japan is one of the countries that is quite skeptical of genetically modified organisms. But in fact Japan has been using radiation mutagenesis to produce mutations in crops for some time. The Institute of Radiation Breeding in Ibaraki-ken, Japan, uses cobalt-60 at the center of a field that produces 89 TBq of gamma radiation for radiation breeding. This field has a shield dike 8 meters high, and the source is so powerful, that workers must retract it into the earth before going in to the field to select the plants. Breeders look for the plants produced by the grown seeds that have the specific advantageous morphological changes desired.

This particular last-century technology has an interesting bearing on the complex issue of labeling. The Minister for Agriculture in Italy was horrified when he read in a German magazine in the summer of 2001 that his spaghetti had been modified using mutagenesis. He said, "Absolutely not, our spaghetti is pristine." Well, actually, the durum wheat used to produce the spaghetti was produced using artificial mutagensis. In addition, the Asian pear was improved by irradiation breeding. All Asian pears are susceptible to black spot disease. Through irradiation mutagenesis, we now have a pear perfectly resistant to black spot disease. If it were to be labeled, it would read, "Pear bred through radiation technology produced in California." This statement is scientifically accurate but is not informative to the consumer. In fact, this statement would probably be construed as a major warning by the consumer.

The estimated global area of transgenic or modified crops for 2001 is 130 million acres grown by 5.5 million farmers in 13 countries. Globally, the principal modified crops were soybean, occupying 33.3 million hectares (ha) in 2001 (63 percent of global area) followed by modified corn at 9.8 million ha (19 percent), transgenic cotton at 6.8 million ha (13 percent), and modified canola at 2.7 million ha (5 percent). In 2001, herbicide tolerance, deployed in soybean, corn, and cotton, occupied 77 percent or 40.6 million ha of the global modified 52.6 million ha with 7.8 million ha (15 percent) planted to Bt crops, and stacked genes for herbicide tolerance and insect resistance deployed in both cotton and corn occupying 8 percent or 4.2 million ha of the global transgenic area in 2001. Developing countries account for 24 percent. Although 24 percent is a large percentage, almost all of that production is from one developing country, Argentina.

The timeline of biotech crop traits can be divided into three categories:

- agronomic traits, (both biotic and abiotic stress), and yield,
- qualitative traits,
- novel crop products and the environment.

I want to focus on the top few crops that have been commercialized primarily in the area of biotic stress and speak specifically on insect resistance, herbicide tolerance, and virus resistance. The primary crops are soybean, corn, and cotton.

The area of abiotic stress is equally important—especially for developing countries. Work has been done at UC Davis to develop transgenic tomatoes with a transport protein that takes the sodium ions in the vacuole and allows the plants to grow in 200 mmol salt, which is about one-third the salt concentration of seawater. Because 40 percent of soil is lost each year owing to irrigation, this could be of great benefit in developing countries. Likewise, aluminum is a major problem with respect to poor soil. Research is being done in Mexico on the production of citric acid in the roots that would allow plants to grow in soils contaminated with aluminum.

Crop yield is a critical issue for developing countries. Currently, we have maximized our capability of increasing crop yield through normal physiological processes. However, metabolic engineering holds incredible potential for increasing yield. The majority of genetically engineered plants now under development are the result of single-gene transfers. Such efforts, although important to raising actual yields, are unlikely to raise potential yields. To break yield barriers, the plants will have to be thoroughly reengineered. Nordine Chiek, director of Calgene research, defines several parameters for yield increase, including water use efficiency, thermostability, source capacity, starch synthesis, seed weight, and nitrogen metabolism. He has taken two main approaches to increasing yield in maize. One is through increased starch biosynthesis, and the second is through improved nitrogen assimilation. For the former he has modified starch metabolism to increase sink strength, and for this again he has taken two approaches, both of which depend on a thorough understanding of carbon metabolism and starch biosynthesis.

One approach is to improve the activity of an existing enzymatic step, and the second is to alter the metabolic pathway. There are many intermediary enzymatic steps in the metabolic pathway from sucrose to starch, and Chiek has targeted the two ends of the pathway to enhance the efficiency of going from source to product by increasing sucrose hydrolysis through altering the pathway and increasing sucrose biosynthesis by improving an existing

enzymatic step. He achieved the former through the introduction of a new gene coding for sucrose phosphorylase, which takes the pathway straight to glucose-1-phosphate, thereby bypassing UDP-glucose. The second boost also was achieved by introducing a new gene, but this time it has an endogenous counterpart. The idea of the new gene is that, because it is from another source and under the control of a different promoter, its activity is not subject to the same degree of inhibition by the plant's native regulatory machinery. This new gene from *Escherichia coli* codes for the enzyme ADP glucose pyrophosphorylase and is under the control of a seed-specific promoter. Taking this approach, Chiek found on average a 23 percent increase in grain weight. Taking the same gene and this time placing it under the tuber-specific patatin promoter in potatoes, Chiek increased starch content by over 30 percent. This has an added bonus, as the higher starch content results in a lower moisture content that in essence gives not only more potato for one's money but also far less fat absorption during frying because moisture lost during the process is replaced by oil uptake.

Increased yields by improved nitrogen assimilation may be the next breakthrough. Benefits of improved nitrogen assimilation in crops include optimization of crop response to fertilizer, increased yield potential at low and high levels of nitrogen, positive environmental impact, reduction of nitrate in ground water, improved crop quality and seed composition, and higher protein in leaf and seed.

Nitrogen is fixed, or combined, in nature as nitric oxide by lightning and ultraviolet rays, but more significant amounts of nitrogen are fixed as ammonia, nitrites, and nitrates by soil micro-organisms. More than 90 percent of all nitrogen fixation is effected by them. The major sources of nitrogen fixation for plants are soil and symbiotic bacteria such as *Rhizobium* associated with leguminous plants. Nitrates and ammonia resulting from nitrogen fixation are assimilated into the specific tissue compounds of algae and higher plants. Asparagine and glutamine are the main forms of transported nitrogen in cereals. Higher plants are more versatile than animals; they can make all of the amino acids required for protein synthesis with either ammonia (NH_3) or nitrate (NO_3^-) as the nitrogen source. Chiek has improved the assimilation process by taking advantage of the importation of ammonia into the intermediates of metabolic pathways mainly via the glutamate dehydrogenase (GDH) reaction. He has introduced GDH from an algal origin, bypassing two intermediate steps in the metabolic pathway for the production of glutamine and has thereby increased kernel protein by 6–12 percent.

Research is even being conducted on oxygen assimilation by modifying stomata or introducing hemoglobin genes that would carry oxygen more effectively through the plants. That task is daunting enough, but other researchers would like to go even further and tinker with the mechanisms of photosynthesis itself. Controlling such basic multigene traits is a complex, unpredictable task. Photosynthesis is a process that evolution has not changed fundamentally in a couple billion years. To improve crops' ability to turn atmospheric carbon dioxide into food, genetic engineers have focused on RuBisCo, the principal catalyst for photosynthesis and a notoriously inefficient enzyme. Laboratories across the world are trying to improve the RuBisCo in food crops either by replacing the existing enzyme with a more efficient form identified in red algae or "bolting on" what could be thought of as molecular superchargers.

Some critics, however, question whether this approach will benefit agriculture. Since at least 1970, research has shown little correlation between crops' photosynthesis rates and their yields, suggesting that improvements in RuBisCo will not automatically translate into better harvests. Thus, even if the work is a technical success, the payoff may be minor because traditional plant breeding has already pushed up crops' harvest index and ability to capture sunlight about as high as they can go. Still, altering photosynthesis remains a hope for the future of agriculture. Once all the relatively obvious steps have been taken, photosynthesis is what is left.

Let us now look at some environmental benefits of engineered crops. The biggest environmental impact of quality traits research is in the area of phytase. One might ask, What importance has this from an environmental point of view? Seeds store the phosphorous needed for germination in the form of phytate, a sugar alcohol molecule having six phosphate groups attached. In terms of food and feed, though, phytate is an antinutrient because it strongly chelates iron, calcium, zinc, and other divalent mineral ions, making them unavailable for uptake. Also, in this form phosphorous is not bioavailable to animals, and one must supplement it in feed in most instances—especially for monogastric animals—with phosphate. But the problem with that, from an environmental point of view, is the animals end up excreting most of that phosphate into the environment. This excreted phosphate can lead to environmental pollution and eutrophication. Introducing a phytase enzyme into the plant breaks down the phytate and renders it bio-available and also makes divalent ions available. The food does not have to be supplemented with phosphate, thus eliminating the excretion of phosphate and reducing eutrophication. This is an environmental benefit.

From a broader environmental perspective, I think the greater potential for biotechnology is to use the incredible amount of biomass in the environment as a source not just for biofuels but also as feedstocks for the production of raw materials such as synthetics and chemicals. But this is far into the future, for it is not economically feasible right now.

Currently, as far as the United States is concerned, the three main biotech crops are soybean, corn, and cotton. Despite predictions of doom and gloom from the European Union perspective, the only crop that decreased this year, in fact, was corn. It went down not because farmers had a fear about the technology (farmers are very wise) but because the farmers did not consider it necessary in 2001 to buy insurance in the form of the technology premium. The prime reason to purchase *Bt* corn is to protect against loss due to the European corn borer. Farmers felt the pressure from the European corn borer was going to decrease this year, and therefore they did not need to pay the premium cost to get this guarantee.

But if you look at the actual adoption for soybean and cotton, it has skyrocketed this year. It has increased to 64 percent for cotton and 63 percent for soybeans. In fact, as the numbers come in, it is now probably closer to 70 percent in real terms. Rapid adoption and planting of transgenic crops by millions of small and large farmers around the world; growing global, political, institutional, and country support for biotech crops; and data from independent sources confirm and support the benefits associated with biotech crops, which according to estimates exceeded $700 million for growers in the 1999 growing season. These results demonstrate that even with issues to acceptability —especially in Europe—the benefits are so great for farmers that they are still increasing their use of this technology. As to the actual overall numbers with respect to environmental impact, growers have found a reduction of

greater than 20 million applied-acre treatments of pesticides. This representat an enormous cost reduction, to the farmer and particularly in cost to the environment. Adopting this technology, as opposed to relying on traditional insecticides, has proven beneficial.

Another advantage of *Bt* corn, which was not unexpected by scientists and was, to an extent, not expected by farmers, is the collateral reduction in fumonisin. People often think of something natural as good, but believe me, some of the worst toxins in the world are produced by fungi. This particular toxin, fumonisin, has been known to cause liquefaction of horse's brains and liver cancer. It is rather unpleasant stuff. But by protecting the plant and the ear of corn from being nibbled by insects, the spores of the fungus do not have access to the corn. Thus, you can gain a reduction of up to 90–95 percent of contamination of fumonisin. This is a significant improvement, and thus your corn flakes will be free of fumonisin. Right now, growers must use fungicides to control it.

Much attention was devoted to the recall of taco shells and other food products possibly containing StarLink corn. The *Bt* protein in StarLink, Cry9C, does not resemble any known allergens and was not derived from an allergenic source, nevertheless the protein is more stable in some digestion tests (one attribute of allergenic proteins) and thus needs more research before receiving approval for human consumption. Allergenicity experts say that a high level of exposure to a protein is needed over a considerable period of time for an individual to be sensitized. The amount of Cry9C in corn kernels was less than 0.03 percent with considerably less than that in the shells themselves because the protein was only a small component of all the corn and other ingredients used. In addition, as this corn is processed at high temperatures, the protein is denatured and therefore no longer in a form that could cause an allergic response. Those who claimed to have suffered an allergic response having consumed products containing corn from the Cry9C cultivars had their blood tested by the Centers for Disease Control to determine if it contained Cry9C-specific antibodies. None were found in any example. Although this does not completely eliminate the possibility of a potential for allergenicity in a subpopulation, a 100 percent negative finding is relatively strong evidence of a nonevent. In effect there was little cause for concern, and the various companies' quick action in recalling the product and Aventis' decision to stop all sales of the seeds eliminated any possibility of harm.

Likewise, the other area of concern with respect to Bt corn was the potential impact on Monarch butterfly larvae. Six papers were published in October 2001 Proceedings of the National Academy of Sciences to indicate that Monarch butterflies are not in danger from this technology. In fact, the numbers of Monarchs have increased in the fields of farmers who have adopted *Bt* technology because, of course, now growers are no longer using broad-based pesticides that kill Monarch butterflies.

Another significant area that has proven advantageous, and in fact the one that has probably the greatest impact on field acreage, is the glyphosate-tolerant soybean. The advantage of this is that not only does it improve weed control but also actually helps farmers adopt no-till technology. Using no-till growers is improving the probability of diminishing soil erosion, for farmers do not need to plow into the surface anymore. Additionally, this means that the debris remains in the field from year to year, which allows beneficial insects to come back to these fields. Scientists have found small mammals and birds returning. Farmers are not using fossil fuels, and growers are not compacting the soil with heavy machinery.

But as far as the farmers are concerned, the real saving is to their pocketbook. In 1998 farmers saved $280 million by adopting this technology because they were no longer dependent on having to make multiple applications of complex herbicide cocktails. They only have to apply herbicides if weeds are present. In addition, this technology saves farmers' time and does not affect crop rotation. There is less damage to the crops using this herbicide because it does not persist in the environment and is not carried on to the following year.

Herbicide concentrations have also decreased markedly since 1998 in groundwater, of farmers who adopted this technology as evidenced by a reduction in the number of groundwater label advisories for herbicide residues. Contamination in groundwater is decreasing substantially. In fact, in Illinois water monitoring samples, these herbicides are no longer measurable which is another success story.

Outside the three principal modified crops the most significant impact of a lesser crop has been demonstrated in Hawaii. In that State, a virus called papaya ring spot virus was devasting the Hawaiian papaya crop. There is no natural resistance to this virus. One could look in all the plants in all the countries of the entire world without finding a resistance gene. Dennis Gonsalves isolated the coat protein of the papaya ring spot virus, which he used to protect the plants. This is similar to a person being vaccinated against a virus. Plants, of course, do not have an immune system. But interestingly enough, this coat protein confers immunity against the virus. By inserting the gene coding for this coat protein, Gonsalves succeeded in protecting the crop, and the papaya economy is thriving in Hawaii.

Of course, the problem with using a coat-protein-mediated resistance is that it depends on a single gene. Increased selection pressure will be imposed on the virus to overcome protection; just one gene is involved. Scientists are now focusing on developing multiple strategies and taking a pyramid approach to reduce the probability of developing a resistance against this coat protein. They are looking at ways of using alternate techniques such as antisense technology and ribozymes. Ribozymes are catalytic ribonucleic acids (RNAs) that can be used to break down the virus. Scientists are looking at ways of modifying movement proteins to stop the virus from going from cell to cell. They are also looking at protease inhibitors. This is similar to the technology used in AIDS research to stop replication of the virus. These approaches all have different modes of action, thereby increasing the probability of reducing selection for resistance to the system.

You already heard about Pam Ronald's work from Dr. Chen. Dr. Chen talked about the advantage of this particular gene, which confers resistance against bacterial blight caused by the bacteria *Xanthomonas oryzae*, which is responsible for a highly destructive disease of rice that often causes 50 percent yield losses in some areas. In fact, by taking the gene XA21 from the wild resistant variety and introducing it into the japonica variety (which is susceptible as manifested by about an 85 percent harvest loss each year), scientists have found the japonica variety developed 10 times the resistance of the donor plant. Pam has insisted that companies licensing this technology set up a scholarship fund for the country where the germplasm originated, India. (Some scientists believe in payback too.)

Another plant we are working on at UC Davis is called *Striga gesneioides*, which is a major biotic constraint on cowpea production. *Striga* is a parasitic weed that results in losses of $7 billion worth of crops in the savannah regions of Africa each year. Herbicide tolerance will not work in this plant because the seeds of the weed itself form a very close association

with the plant. It is a very intimate association. When the farmers harvest the seed each year and put it back into the ground, they compound the problem by putting the parasite back as well. These parasitic weeds depend on signaling systems from the host plant. The parasites are actually very cleverly using the signaling systems plants normally use called "xenonosins," which is a term deriving from the Greek word meaning to recognize the stranger. *Striga* has turned the signalling system on its head, and instead of allowing the host to recognize the stranger, *Striga* use's it to hone in on the host plants. John Yoder has developed a mechanism that actually interferes with the signaling system. By inhibiting the signaling system, researchers are hoping to generate parasite resistant crops.

I would like to address some of the concerns about biotechnology. From a scientific perspective, antibiotic resistance, in reality, is not an issue. In 20 years of trying, no scientist has succeeded in transferring the antibiotic resistance genes from any crop plants into our commensal bacteria, potentially turning them into the multiple resistance strains encountered in hospitals. There is a far greater chance of acquiring resistance from an antibiotic-resistant bug by walking through a hospital than from eating a transgenic plant. However, researchers are looking at other mechanisms such as transposon tagging or positive selection in which there is exclusive energy source—for example, phosphomannose isomerase. Plant cells without this enzyme will not grow on media that have mono-6 phosphate as the sole carbon source. This is a much better selection method.

Likewise, with respect to gene flow, the real focus is on the whole area of chloroplast transformation because chloroplasts have their own DNA. They stay in the maternal line; the genes cannot get out. Numerous tests have been conducted in this area. Chloropast transformation is also more efficient because there are far more copies of chloroplast DNA than of genomic DNA. This could address the issue of resistance in, for example, *Bt*, because a very high dose results owing to the number of copies inserted into the chloroplasts. Thus, researchers are also going to be using site-specific recombination to get chloroplast transformation. One concern that arises invovles not knowing where the gene has been inserted, which, of course, is an issue in traditional agriculture as well. It is not necessary to know how the genes are going to come together. Using site-specific recombination, or what is called the Cre–lox site-specific recombination system, one can be very specific about where these genes are being targeted. Likewise, with respect to effects on nontarget species, one can have tissue-specific expression, and again, chloroplast transformation. I talked about the issue of loss of effectiveness by using gene-pyramiding or gene shuffling, which entails actually using gene rotation to modify the environment to which the pests are being exposed at all times.

I will leave you once again with the a thought from Norman Borlaug, who stated that the affluent nations can afford to adopt elitist positions and pay more for food produced by the so-called natural methods. The billion chronically poor and hungry people of this world cannot. New technology will be their salvation, freeing them from obsolete, low-yielding, and more costly production technology. As Jimmy Carter has observed, "responsible biotechnology is not the enemy. Starvation is."

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Overview of Crops Important to the Developing World[1]

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We know that some of the challenges to agriculture in developed countries are also very familiar to people in developing countries as well. One of the foremost challenges is a rapid increase in the population along with a decrease in our farmland. Population issues are of concern especially in developing countries such as in China but also for other countries. A dependent problem is a severe shortage of water. We also see dramatic increases in the cost of farming, which is especially expressed in a need for increased pasture size and in increased fertilizer costs to farmers. The last challenge to those developing countries, especially to China, is entry into the World Trade Organization (WTO) and its associated requirements for agriculture.

Premier Zhu just last month stated that, after entry into the WTO, agriculture is the issue of most concern to him. He recognized that we are using 7 percent of available land to feed about 22 percent of the world's population. And you know that the population increased dramatically in China as well as in India and other countries between the 1950s and 2002. Meanwhile, the average amount of farmland per person decreased since the 1950s up through the present. Grain productivity increased owing to production of hybrid rice and other technologies. However, beginning in 1996 and 1997, the production in grains has become quite stable. It has not increased while the population was increasing so dramatically.

Thus, the governments of developing countries, for example China, decided to establish agriculture as a top priority. In China, biotechnology was placed among the top technologies, which included lasers, space, information, and automation. However, biotechnology was put in the very top priority in the Government's agenda in the past 10 years and for the next 5 years. The budget for biotechnology from our government increased dramatically from 2 billion to over 13 billion yuan, just for biotechnology research.

In the next 5 years, Government strategic planning identifies biotechnology as a national priority. The first area of emphasis for biotechnology is that of so-called molecular breeding, which basically refers to production of transgenic or genetically modified organisms. The next area is genomic research. We also have research funding in the National Program for Biosafety Research.

[1] *from an edited transcript of the presentation*

Since 1986, the two principal areas to which we pay attention, crop improvement and genomics, have been quite similar to those of importance in other developing countries. The first priority for the biotechnology program is developing hybrid rice, which is very important for China, and the second is for the development of transgenic cotton with resistance against insect pests. Additional crops include transgenic plants like rice, wheat, corn, and others. I was in charge of the transgenic plants program in China from 1986 to 2000.

I would like to present a brief background on transgenic plants in China. We started to release transgenic plants, both tobacco and tomato, in 1989. In 1993 the first regulation on biosafety was issued by the Chinese Government. In 1997, the Ministry of Agriculture started to enforce the law on commercialization—the approval, release, and commercialization of transgenic plants—1997 is the year that transgenic plants were first officially commercialized in China. And then in 1999, 2000, and 2001, zero approval was given to any new crops in China, owing to very severe problems that originated within the European Economic Union (EEU) and some other countries, and the pressure they exerted. I will go on to describe some of the issues.

On 9 May 2001 Premier Zhu Rongji issued a new national regulation applying to management of agriculture and genetically modified organisms (GMOs) (see the website http://www.chinafeedonline.com/dbnews/ news_show.show_news_detail_en ?newsid=5833&tmptt=forprint). I understand that Canadian officials and scientists are very familiar with this because they recently sent a letter to our Government about their concerns with this new regulation.

The area planted to commercialized transgenic plants in China was the fourth largest in the world. From 1997 to 2000 applications rose from 55 to 443 applications per year, which is a dramatic increase. Before commercialization is approved, environmental release, field trials and also pending productive release must be approved for field trials of the major crops in China. These large numbers are only field releases and are not allowances for commercialization.

For field release, the largest crop approvals are for rice. Two major problems have been addressed. One is insect pests, and another is bacterial disease. Line XA–21, for example, expresses both insect and bacterial resistance. Several other genes are also being tested and released in the fields.

And then we have corn, soybean, and wheat trials. At present, only four crops are approved for commercialization, and only six major licenses have been approved by the Chinese Government. The four approved crops are transgenic cotton plants with Bt against insects; tomatoes with Bt virus and a third expressing control over ripening sweet peppers; and another with resistant to the petunia with altered color expression.

Transgenic cotton has very dramatically influenced Chinese cotton production. The Bt cotton lines commercialized in Hebei Province are produced on over 99.7 percent of personal land. Hebei Province is a very significant location for transgenic cotton. I will go over some transgenic cotton data evaluating effects on the environment and also on the farmers.

Now, the second major (transgenic) crop is rice, and those lines being released are in Fujian Province in the southern part of China. Compared with nontransgenic rice, control of insect pests in transgenic rice is significantly improved. This crop has been allowed to be planted in field releases and tests. We have also transferred a second gene together with the Bt gene into hybrid rice. Again, we have seen significant control of insect pests and also bacterial diseases.

At present, we have some transgenic rice and wheat tests in the fields. We have a Bt corn and soybean, a tomato, a sweet pepper, and petunia flowers as well as continuing research with international cooperation on transfer of genes into rice for producing vitamins A and E. Now, vitamin D expression has attained importance as a goal so that it will be made available in Chinese rural areas. We are in the process of transferring the genes to synthesize vitamin D in rice.

Transgenic plants have been released in most parts of China from the southern part to the northern part. As I just mentioned, China is ranked the fourth largest country in the world right now for transgenic crop production next to other developing countries such as, for example, South Africa and Argentina.

In Asia, there are only two countries in which transgenic crops are officially approved for commercialization: China and Indonesia. Among the challenges to transgenic crops in China and other developing countries are four issues that people mention again and again: environmental safety, food safety, public acceptance, and finally—and this is a very key issue—the trade issue.

A very complicated situation has developed in the past 3 years. It involves the scientific community, the public, politicians, farmers, companies, and consumers. I took a photo at the last OECD meeting in Edinburgh (Scientific and Health Aspects of Genetically Modified Foods) with its contentious asides, and the photo has been published in Chinese newspapers. I took the photo to show the very complicated situation in Europe. We in China should be careful because of A, because of B, and because of C and D. However, the applications to China—perhaps with the most acute consequences—are those arising because of impacts on global relations. We thought that we might do much in response to these issues, but that has actually not been the case. The situation is difficult.

The consequence of the sanctions placed against transgenic tobacco produced by China was that no more transgenic tobacco would be produced. The sanctions were also placed on soy sauce because Europeans understood that we use American imported transgenic soybeans to produce soy sauce, and therefore EEU countries quickly placed sanctions on our soy sauce. That made people very concerned. So the Government introduced a new law, a new regulation, to enhance accountability and management of food content, and that got more ministries involved.

Originally, just the Ministry of Agriculture was involved in regulating biotechnology. Now, we have Public Health and Environment, Import–Export, Inspections, and also the Ministry of Science and Technology involved too, and thus the regulatory climate has become more complicated. It is even becoming difficult to approve any new crops for commercialization.

The new regulations have resulted in concern by officials from different countries about the details we are proposing. We will issue new regulations announced in advance by the premier on 9 May 2001, this year. These will include four additional requirements in addition to those established by the law in 1996. The first requirement is that several more ministries must together approve the new license for commercialization and field release. The second requirement is that we have one more trial in addition to a field trial, field release, and medium trials. The additional one is called a production trial, and requires a lengthy effort for its accomplishment.

The third requirement is a labeling system. We presently have a labeling system in the country similar to that of the United States and Canada. However, because, Japan and Europe have requirements, and especially now because we are a member of WTO, that must change. Obviously, after entering WTO, we needed to have labeling, and this is a very complicated situation now. The last requirement is for import and export certificates in this new regulatory system.

Thus many puzzling arguments arise in China, a developing country, as they also do in other countries. I am sure that many arguments arise. The first is that this technology only benefits the multinational companies, not consumers or farmers. The controversy over who receives the benefits from this technology comes up again and again along with many other similar arguments. Recently conclusions were reached that organic agriculture will be the production system of the future and that GMOs have no future. Those ideas were published in newspapers in China and other developing countries.

I will give you data, very simple data, from a 3-year study. One group cooperated with U.S. scientists, and another two groups in our university studied crop modification benefits for 3 years. The Guokang is a variety [developed by CAAS] released in China, another is the transgenic cotton jointly issued by the Monsanto Company and local government, and a third is a domestic transgenic cotton Zhongmian released for field production by the Cotton Research Center.

There are 3 years of data which are basically very similar for the three varieties on the benefits going to farmers, the percentages, and also the profits to the multinational companies. Benefits go to both the multinational companies and to the farmers. From products of the Monsanto companies, about 83 percent of the benefits go to the farmers, and again, about 10 to 17 percent to the company because it has increased the price of seeds. The benefits still go to farmers—especially to poor farmers. No profit goes to the Chinese seed developers (from their lines released by the Chinese Academy of Agricultural Science) because we do not collect money from farmers.

A second argument says that there is almost no need for the transgenic crops, or that insect resistance will quickly develop, or that some other problems will arise. As some of you may know, over 40 to 50 thousand people are poisoned each year in China. These data have been published in a public database. Over 400 to 500 people die each year because of poisoning by pesticides in cotton and rice fields.

In the Hebei Province, I just mentioned that over 90 percent of fields were planted with transgenic cotton in the 3 years after plants were first released in the fields. This is a family-based economy, a family system. If the crop is not good, the farmer will not plant it. Planting decisions are not controlled by the Government but by each family.

The area in which transgenic cotton has been planted has increased rapidly since 1997. For the first release, we allowed the Hebei Province to plant only 2 hectares. By 2000, 220,000 hectares were planted. In Shantung Province, and in other provinces, cotton land has also increased dramatically. For pesticide use, we also have 3 years of data. The yield we received from Bt cottons substantially increased. However, for the pesticides used, you can see that on Bt cottons, pesticide use dramatically declined compared with non-Bt cotton. This cotton production is family based agriculture, I would like to emphasize. And thus the farmers appreciated the crop. The reason that over 97 or 99 percent of fields transgenic cotton has been planted in is that farmers know that less pesticides will be needed.

Now let me discuss environmental and health impacts, and this is, again, 3 years data from two groups. For Bt and non-Bt crop production, the number of people poisoned, as reported in hospitals and from villages, decreased quite dramatically in cotton fields. These data are for poisoning after applying pesticide in both transgenic and nontransgenic cotton fields.

Very similar findings are reported in rice fields. More people are poisoned annually in rice fields than in cotton fields. As you all know, insects get resistant to the pesticides and, as a result, farmers ask the pupils from elementary schools to pick the worms that were not killed by pesticides. Local citizens are no longer allowed to feed chickens with worms that were originally provided because the chickens will be killed by the contaminated worms. The worms contain large amounts of pesticides and are very poisonous.

Another concern is whether transgenic crops are safe, this is difficult to answer. But in China, we sometimes answer that over 200 million people have consumed transgenic crops for years, and zero cases of poisoning have been detected and no product has been revealed to contain a toxin. But again, significant research is being done in this area to analyze safety in feeding assays. We have tested safety of sweet peppers, tomatoes, and rice on a case-by-case basis. In the feeding tests, we detected no significant effects on animals just as has been reported in the United States. All the testing has been done in China.

Labeling, again, a difficult issue. I am sure labeling is also difficult for other developing countries, although it works in Europe and in Japan. Still it is a difficult issue. First, we all know the public has a right to be informed. Second, how many genetically modified (GM) products should be labeled, or should every GM crop or its products have to be labeled? Should content be labeled to 1 percent or 5 percent? And we all know that the cost will be increased dramatically for such labeled products.

We assessed the costs of labeling systems. We estimate an over 40 percent increase in production costs if we were to label transgenic foods. Because we have to separate the products, costs would be about 10 percent more for retail prices if we sold labeled compared with nonlabeled products in the supermarket. Even this might not be accurate because China

has a free market. Every morning, people, the farmers, bring the food to the city and sell in a free market. It would be very difficult for farmers to label food in a basket and to tell those professors that it's transgenic or nontransgenic.

A common feeling is that when you are concerned about the technology, both Western people and Chinese say, "Well, the stuffed people never understand the feeling of hungry people." That is really an ancient Chinese saying very similar to the one Western people repeat.

So we really feel that there needs to be international harmonization as a basis for national regulation. One country cannot establish regulatory policies alone. Regulation has to be international in scope, and to have a national policy on GMO trading the policy must be harmonized. The GMO labeling system somehow also has to have a harmonized component. For developing countries, identity-preserved output (IPO) will be a very important issue.

The EEU is a key market that will determine the future for biotechnology applications in the world. That is what the developing countries feel, and most of China feels, because of the problems associated with this region. Lastly, I would like to say that biotechnology is a promising technology. On the one hand, the farmers, and we, the developing countries, are waiting for this technology—rice, wheat, corn, and soybean. We need the technology. On the other hand, we have problems in exporting, and so we wait, we are waiting.

But the good news from Brazil and from this OECD organized meeting is that we recognize that biotechnology will be very important for poor countries, for developing countries. I attended a meeting in September of EEU ministers of agriculture in Brussels. For those 16 countries, the situation looks very promising, but there is still a long way to go. We all know that a discussion will be going on continually, but we hope that the GM technology can be assessed by the poor farmers in developing countries.

Thank you again for the invitation.

Session 2: The Practice of Environmental Assessment

Session 2A—Risk Assessment Issues: Mechanisms of Assessment; Baselines; Appropriate Date Sets

Risk Assessment for LMOs: A European Perspective

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Introduction

My purpose here is to describe the principles and philosophy that guide the process of risk assessment for the release and marketing of Living Modified Organisms (LMOs) in the European Union (EU). To do so I must first outline the key features of the EU regulatory framework, which I will illustrate mainly by reference to its implementation in the United Kingdom. Secondly, I will characterise the actual process of risk assessment, and finally I will discuss one or two current issues and future challenges. Limitations on space dictate that this presentation is less than comprehensive, and the perspective is somewhat personalised.

The Regulatory Framework

Release and marketing of LMOs in the EU are controlled under an EU-wide European Council directive. In February 2001, a new directive (2001/18/EC) was adopted, replacing the one that had been in force for 10 years (90/220/EEC). European Union member states now have a deadline of October 2002 to introduce national regulations that will implement the new Directive. In Great Britain, Directive 90/220 has been implemented by Part VI of the Environmental Protection Act 1990 and Genetically Modified Organisms (Deliberate Release) Regulations 1992 amended in 1995 and 1997 (there is equivalent separate legislation in Northern Ireland).

The essential point about this legal framework is that releases and marketing of LMOs can only take place in the EU with the explicit consent of the regulatory authorities (the body of specific legislation for genetically modified (GM) crops contrasts with some other countries such as the United States that have dealt with GM crops, for example, under existing legislation). The EU Directive covers both small-scale trials for Research and Development (under Part B) and the "consent to place on the market" in Europe (the so-called Part C releases). In the latter case member States evaluate the application for market release only after it has been assessed as low risk by the member State to which the application was originally

made. Since 1993 the United Kingdom has dealt with almost 200 consents for releases under Part B of the Directive, and 18 products have been approved for commercial release in the EU. These include four GM maize types, oilseed rape, carnations, and chicory. The oilseed rape, soya, and maize have approval for import into Europe for processing and animal feed use.

At the heart of all applications providing the basis on which risk assessment is made is a technical dossier describing the proposed release in detail (some features of the dossier are discussed later). Figure 1, simplified somewhat for clarity, tracks the movement of such a dossier in the United Kingdom and helps to highlight the main features of the regulatory mechanism. Central to this process is the reliance on an independent scientific advisory committee, in the United Kingdom this is the Advisory Committee on Releases to the Environment (ACRE). Other member States have a similar system. The U.K. application is made to the Joint Regulatory Authority (JRA), which consists of science-trained professionals in a Government department and also provides the secretariat for ACRE. The JRA then distributes the application to other departments, including statutory consultees such as the Health and Safety Executive and the wildlife conservation agencies (English Nature, acting on behalf of U.K. National agencies); others include the Department of Health and the Department of Trade and Industry. Once the JRA is broadly satisfied with the application, going back where necessary to the applicant for clarification, it is passed to ACRE which usually meets to discuss each application. If the application is a product for human food or for animal feed, other advisory committees under the aegis of the Food Standards Agency (the Advisory Committee on Novel Foods and Proteins and the Advisory Committee on Animal Feeding Stuffs) may be involved. Similarly, whenever an agrochemical may be part of the crop's management, appropriate advice is sought from pesticide specialists. On the basis of all this advice, ACRE will then advise the relevant Government ministers on the risks associated with the release and whether consent should be issued.

The Advisory Committee on Releases to the Environment is an independent, statutory science and technical committee. It currently comprises 12 members with a range of expertise, including leading academics and researchers in the fields of molecular biology and genetics, plant physiology, biochemistry, ecology and virology; an expert in sustainable agriculture; and a practising farmer. Unlike some other committees that advise government, there is no lay member or expert on ethical issues. In addition to advising on particular LMO releases, ACRE reviews developments in biotechnology, often commenting on particular publications, advises on the deliberate release of nonnative organisms (e.g., for biological control or conservation), and identifies research needed to inform risk assessment. From time to time the committee has established subgroups to provide strategic advice and specific guidance. Recent examples of this include a guidance note on the potential impacts of LMOs on biodiversity and farmland ecology and a document establishing some general principles of best practice in the design of GM crops (ACRE Guidance Note 13, 2001, - www.defra.gov.uk/environment/acre/ bestprac/guidance).

The European regulatory system strives to be as open and transparent as possible (within the limits of commercial confidence) and is becoming increasingly inclusive (see later). For example, ACRE places its agenda and minutes on the World Wide Web and publishes an annual report and all members declare their interests.

The Risk Assessment Process

General Features

Although much has been written on the subject of risk and risk assessment, it is perhaps worth listing below the main features of risk assessment as it relates to releasing LMOs in Europe.

1. The assessment is science based, utilizing both quantitative and qualitative evidence and data.
2. The assessment is comparative, that is the risks of releasing an LMO are compared with those of releasing its nonmodified equivalent under similar conditions (thus recognizing of course that absolute risk is difficult to define).
3. The approach is precautionary. The starting point for each assessment, as in most scientific inquiry, is complete skepticism, and all applications are subject to detailed scrutiny with the onus being firmly on the applicant to provide the evidence demonstrating that a release poses a negligible or low risk.
4. Each application is assessed individually on a case-by-case basis. Coupled with this is a stepped approach that exploits the increasing familiarity with each particular crop or construct as it passes from contained use, to glasshouse cultivation, to trial and unto commercialization.
5. The process responds to new information. It is iterative and continuous, requiring the applicant to forward any new information relevant to the risk assessment and the regulatory authorities to revisit earlier assessments in the light of such information.

Finally risk assessment follows a logical sequence of steps (of which there are arguably five or six) arriving at an assessment of the overall risk of a particular release. These are as follows:

1. Identify potential adverse effects (hazards) however rare these may be.
2. Evaluate the consequences of the adverse effects being realized, i.e., assess the magnitude of harm.
3. Evaluate the likelihood of the adverse effects being realized (a measure of exposure).
4. Estimate the risk (a function of the two preceding steps).
5. Assess any proposed risk management strategies.
6. In the light of the preceding step determine the overall risk of the release.

Despite the universal acceptance of these steps it is not uncommon in the wider literature to see hazards (e.g., harm to Monarch caterpillars from Bt pollen) treated as risks with no estimate or measurement of the degree of exposure.

Baseline Information

As mentioned earlier, applicants wishing to release LMOs in Europe must provide detailed information to the appropriate regulatory authority, usually in the form of a scientific dossier. Whilst the detail varies between member states (in the United Kingdom an applicant is required to address a series of 41 questions), the essential information required for a small-scale trial

under the EU directive covers the LMO, the proposed release and receiving environments, plans for monitoring and control of the release, and a statement evaluating the risks to the environment and human health. With regard to the LMO itself, information must be provided on the characteristics of the recipient organisms, the details of the modification, and the way in which the modification has altered the organism (i.e., what effect it has had on performance). The information about the environment in which the release will take place and the proposals for monitoring the release, including postrelease monitoring to ensure material from the trial is disposed of, must address ways of reducing risk if these are necessary (e.g., removing flower heads, establishing borders of nonGM barrier plants, minimizing cross-pollination with other crops of the same species by maintaining agreed separation distances).

The new EU Directive (2001/18) has introduced several key, novel elements for assessing marketing releases as well as calling on member States to harmonize their approach to risk assessment such that decisions are more obviously consistent and transparent. Particularly important are the need to consider possible longer term, indirect, delayed, and cumulative effects on the environment and the requirement for applications to include a postmarket monitoring plan (a program of monitoring following market release to confirm the assumptions of the risk assessment and identify unanticipated events). Both elements present something of a challenge to applicants and regulators alike. The new Directive also covers issues such as the requirements for traceability and labeling of LMOs and products derived from them, the provision of accessible information to the public about LMO releases, the methods of public consultation on releases, and the use of antibiotic resistance markers (target dates of 31 December 2004 and 31 December 2008 for part C and part B releases, respectively, have been set for phasing out antibiotic resistance markers, which may have adverse effects on human health and the environment).

Returning to the current process of risk assessment, let me briefly consider the type of baseline information that experience has taught us is required for an effective risk assessment. Whilst it is difficult to be prescriptive without a specific example, the technical dossier—at least for GM crop plants—must provide adequate data to address, where appropriate, the following issues:

The Genetic Modification—

There is absolutely no doubt that a well-conducted molecular analysis forms the basis for good risk assessment and helps to speed the application through the risk assessment process. The details required include the transformation method, the nature and source of the vector, and the size and source of donor organism(s) and intended function of each constituent fragment of the region intended for insertion. One expects well-characterized data on the trait and sequences actually inserted or deleted, including any extraneous or vector DNA, copy number, and location in the cell as well as information on the stability and expression of the insert throughout the plant's life cycle (and whether there is any unintended expression of flanking genes or junction sequences). The Advisory Committee on Releases to the Environment has recently offered some draft guidance on best practice for the presentation of molecular data in submissions for release of LMOs (www.defra.gov.uk/environment/acre/molecdata).

The Effect on the LMO's Persistence and Invasiveness—

Data that consider the effect of the insert on the biology of the plant should include an assessment of comparative performance in agricultural and peri-agricultural environments—in particular, the extent to which the modification may enable the plant to be more persistent, possibly creating a "volunteer" or weed problem, or more invasive, leading to the establishment of persistent feral populations. Analyses of changes in plant fitness are not trivial undertakings as evidenced, for example, by the extensive studies on herbicide-tolerant oilseed rapes to compare modified and unmodified plants (see Gray and Raybould 1999). Where a problem is identified, it is important to give details of procedures to minimize or manage the risk (e.g., use of an alternative herbicide).

Gene Flow and Hybridization—

The risk assessment clearly needs to address the issue of gene flow—especially the potential for cross-pollination and hybridization with wild relatives—but also in Europe the issue of crop-to-crop gene flow is one of emerging concern. Most crops (e.g., 12 out of the 13 most important world crops by area [Ellstrand et al, 1999]) hybridize with wild relatives, often antecedents, somewhere in the world, but modern agriculture and plant breeding have led to growing many crops considerably outside their native areas or centers of genetic diversity. Thus, the problem of gene flow to wild relatives is largely regional. In Europe it is not an issue for crops such as maize and potatoes but is to a varying degree for sugar beets and oilseed rapes. The potential for gene flow from crops grown in the United Kingdom, the Netherlands, and Switzerland has been assessed by analysis of their wild flora (Raybould and Gray 1993, de Vries et al., 1992, Jacot and Ammann 1999).

The consensus among scientists advising the Government is that, where hybridization and introgression are possible, the risk assessment should assume that they will happen and therefore address the question of the consequences (the so-called "So what?" question). The effect on the fitness of genes conferring tolerance to a herbicide is likely to be very different from that of genes coding for say virus or insect resistance. Understanding the impact on wild and feral plant fitness of traits acquired by gene flow requires research that, in my view, lies along the critical path of risk assessment. The issue of crop-to-crop gene flow has gained importance in Europe as part of the debate on traceability and the separation of the GM and non-GM food chains.

Target and Non-target Organisms—

When the LMO has been engineered to express an antifeedant or insecticidal protein, a whole raft of issues arises in relation to the potential environmental impact. They range from the possible evolution of resistance in the target pest to the direct and indirect effects on nontarget species. Where such a risk can be identified e.g., the evolution of resistance to Bt in a target lepidopteran pest, the dossier should propose measures for managing or reducing the risk. As stated earlier in relation to the Monarch butterfly research, it is important to move from laboratory-based studies that identify possible hazards, particularly harm to nontarget species, to more field-based assessments of the organisms' exposure to such hazards. Effects on nontarget species may be subtle and indirect and difficult to measure in the short term (e.g., reduction or removal of prey of beneficial insects), but the commonsense approach to date has been to assess risk within a comparative framework, that is, alongside current agricultural practice.

Biogeochemical Processes—

The possible impact of GM crops on soil processes and biodiversity has raised several concerns, and the research base to help address some of these is the subject of other contributions to this conference.

Crop Management—

When applying for consent to place an LMO on the market, the applicant's risk assessment may need to address questions that arise from the way the crop is managed. Of current concern in Europe in this respect is the potential impact of crops that are tolerant to broad-spectrum herbicides. In addition to issues of safety, the possibility that such crops might exacerbate the decline in farmland biodiversity has led in the United Kingdom to the establishment of a series of farm-scale trials to compare the effects on biodiversity of three herbicide-tolerant crop species (maize and winter- and spring-sown varieties of oilseed rape tolerant to glufosinate ammonium and sugar and forage beets tolerant to glyphosate) with their conventional counterparts. These trials, the U.K. Farm Scale Evaluations, are described in detail in the proceedings of this conference (Firbank et al. 2002), and the first results will be reported in 2003.

Human Health, Animal Health and Food and Feed Issues—

Issues relating to food and feed safety are outside the scope of this meeting and presentation. However, data may be required to assess environmental risks to human health from exposure to novel proteins by perhaps harvesting or handling the LMO or breathing in pollen. Thus, the risk assessment must indicate what is known about the allergenicity of any such proteins.

The preceding examples illustrate the type of baseline information an acceptable risk assessment should contain. Not all issues will be relevant to all releases, and the technical dossier is likely to vary considerably from application to application, thus emphasizing the importance of the case-by-case approach.

Current Issues and Future Challenges

Assessment of the environmental risks posed by any new technology must be viewed as an evolving process. It is important to build on experience and to share information and data on an international scale. That process is happening, not least through meetings such as this one. Nevertheless, scientists charged with making evidence-based assessments of risk can expect to deal in the future with novel areas of uncertainty and to be asked questions that increasingly challenge their understanding of natural systems.

For the ecologists there is the challenge of assessing the potential environmental risks from the so-called second generation of LMOs engineered to tolerate a range of stresses such as drought, salt or frost, and altered Darwinian fitness. Additionally, the development of

nonfood crops producing oils, plastics, or pharmaceuticals will bring new challenges. We are already dealing with the first of what may be a rising tide of requests to release Living Modified Micro-organisms into the environment for a variety of purposes ranging from bioremediation through veterinary medicine to human clinical trials that may involve the shedding of live, disabled, genetically modified viruses.

Arguably, the major current issues surrounding LMOs in Europe are not concerned with risk assessment but with risk perception and with public acceptance and confidence. This reality is reflected in the revised EU Directive with its emphasis on transparency, accessibility, and inclusiveness. The need for scientists and regulators alike to communicate perhaps more clearly than they have in the past includes the responsibility to deal in an open way with the problem of uncertainty. At some point along the road that charts the scientist's desire to know everything about every possible effect of a release, harmful or beneficial, a decision must be made about what is an acceptable risk or course of action. For some that point is sooner than for others. In my view that decision should also factor in any potential benefits of the release of the LMO and a range of other factors that lie outside the regulatory framework.

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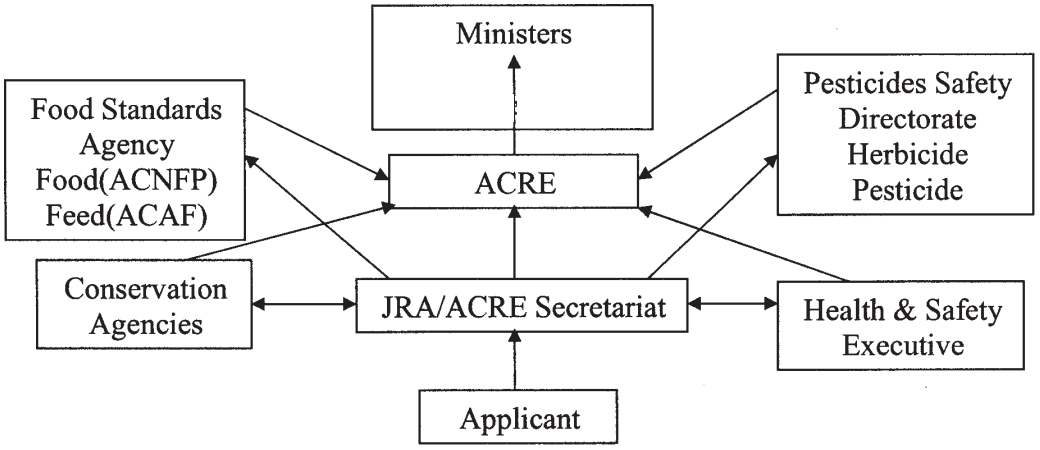

Figure 1

Simplified diagram of the links in the UK regulatory mechanism for assessing the risks from releasing LMOs (see text).
JRA = Joint Regulatory Authority
ACRE = Advisory Committee on Releases to the Environment

Gene Flow and Transgenic Crops—How Can Potential Impacts on Fitness Be Assessed?

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Introduction

Gene flow rates from crops to crops and from crops to wild plants have been measured over the past 10 years. This research has shown that gene flow at a relatively low level takes place by pollen transfer over long distances—sometimes up to several kilometers. The research has been prompted by concerns that transgenes might move from transgenic crops to conventional varieties, or to wild relatives of transgenic crops, or to both. The answer to the concern of "Does it occur?" now seems clear: gene flow is inevitable from those crops that naturally outcross both to conventional varieties of the same crop and to a small number of wild relatives, although this latter phenomenon is usually a rare event. However, for ecologists and agronomists the key question is "Does it matter?" More specifically, does outcrossing of transgenes affect fitness of recipient offspring in both natural and agricultural ecosystems?

This is a key issue because, if the transfer of specific transgenes to conventional crops and to wild relatives increases fitness, there is the possibility that the offspring of recipient plants will become either agricultural or ecological "weeds", potentially disrupting natural ecosystems. This is because some of the desirable traits in transgenic agricultural crops confer the ability to be tolerant to insect, fungal, and viral attack and to be resistant to cold, drought, and salinity, which are all traits that could increase fitness (Cooper and Raybould 1997). Although some of these traits may exist naturally, transgenic technology can introduce them to plants with such genes absent from the gene pools of the crop–ancestor complex. Perhaps the most immediate issue is whether there could be increased fitness of the offspring of some agricultural crops that appear later in crop rotations as "volunteer" plants. Unless some volunteer crops (such as oilseed rapes and beets and some transgenic grasses) can effectively be controlled, they may become "weeds" in other crops. until recently there has been little research into impacts of gene transfer on the population dynamics and habitat requirements of recipient crops and wild plants and still less on the possible implications for farmland and natural ecology. The lack of research on this topic has partly been the result of regulatory difficulties in obtaining consent for experimental releases of transgenic crops and especially for hybrids between transgenic crops and wild plants. There has also been considerable, but as yet unresolved, debate in scientific circles about methodologies to assess fitness in plants containing transgenes.

Case-By-Case Approach

Generalized statements about the impacts of transgenic plants and transgenes are confusing and unhelpful in the debate about biosafety. So far as the potential impact of gene flow is concerned, each genetic transformation carries different potential risks. These stem from the species and variety of plant transformed and the nature of the transgene (and associated genes such as promoters and markers) inserted into the transformed plant. Gene flow between transgenic crops and conventional crops and wild plants can only normally occur if they are sexually compatible in nature and grown in close enough proximity for pollen transfer to take place. Potential impacts of gene transfer will depend on the effects (if any) of the specific transgene on the plant phenotype as a whole. It is essential therefore, that any assessment of the potential impacts of gene flow be made on a case-by-case basis. As new methods of plant breeding based on genomic knowledge are developed, there may be a need to extend case-by-case risk assessment to this sector.

Assessing the Likelihood of Gene Flow

The inherent characteristics of a crop and its proximity to closely related plants are some of the factors that determine the likelihood of gene transfer to other plants. The key to understanding gene flow is knowledge of the sexual compatibility of the crop with other species growing in the same landscape. For example oilseed rape (canola) *Brassica napus* growing in Europe is sexually compatible with several other species, some of which are wild (such as *B. juncea* and *Raphanus raphanistrum*) and others of which are probably derived from crop plants such as wild turnip (*B. rapa)*. Research (e.g., Scheffer and Dale 1994 and Thompson et al. 1999) has shown that, whilst several commercial varieties of this crop freely cross and may be artificially crossed with several related species in the laboratory, in nature this crop forms hybrids with very few wild relatives. These hybrids are only rarely found and may not be fully fertile (Raybould and Gray 1993). However some hybrids have been found in the wild (e.g., Wilkinson et al. 2000 and Chevre et al. 2000), and thus it may be assumed that transgenes from oilseed rape can be transferred into some wild relatives with the risk presumably increasing in proportion to the area of transgenic crop being cultivated. In contrast, crops such as maize have no wild relatives in Europe, and so the risk of gene transfer is zero.

What is the Gene of Interest? Possible Fitness Effects

If gene transfer does occur, the key questions for regulators are, "What will be the effect on the phenotype of the recipient plant?" and, "Will any effect change the fitness of the recipient?" This is not only an important issue for those charged with protecting wildlife resources in the landscape, but also a key issue for agriculture. Not surprisingly, many wild relatives of crops and feral populations of different varieties of the crop grow in close proximity to farmland, often sharing the field margins with the crop. Wild beet (*Beta vulgaris*) and sea beet (*Beta vulgaris* ssp *maritimum*) are sexually compatible with commercial beets and can be found in field margins and coastal fringes (Bartsch and Pohl-Orf 1996), whilst in North America wild sunflowers occupy the same habitat as the commercial hybrid crop (Snow 2002). If these species were to have increased fitness as the result of gene transfer from

transgenic plants, then they could become weeds of agriculture or might change their population dynamics in natural ecosystems. This risk also applies to crosses between transgenic plants and conventional crops. Increased fitness could also lead to the transgenes going to fixation in recipient populations.

Risk Assessment

Assessment of risk from gene transfer is a twofold process. Firstly, an assessment can be made of whether the transgene is likely to transfer to wild relatives. This is relatively straightforward and can be done in the field by estimating gene flow to wild plants using markers. Rates have been found to vary greatly, depending on the crop variety and factors such as distance from wild relatives, presence of pollinators, and weather conditions (Department of the Environment 1995, European Environment Agency 2001). The second part of risk assessment should be estimation of the impacts of the transgene on the fitness of recipient plants. This is much more difficult to predict and relies on the development of protocols for estimating fitness in the habitats where the recipient plants are likely to survive. This latter factor is notoriously difficult to predict—even for alien species that could potentially invade new habitats (Williamson 1996). Changes in the fitness of plants owing to the acquisition of new genes can enable them to colonize new habitats. One of the best examples can be found in the *Rhododendron* complex of species (Ellstrand and Schierenbeck 2000), where hybridization in Western Europe between species imported for ornamental purposes (*R.catawbiense* from North America and *R. ponticum* from Iberia) led to the acquisition of cold tolerance genes that allowed *R. ponticum* to invade, and in some cases overwhelm, native oak woodlands and wet heaths in oceanic regions of France and the United Kingdom. Because it is very difficult to predict the environment that might be favored by a plant acquiring new genes, regulators may need to draw upon experienced botanists to make a "best guess".

Fitness Estimation

Theoretical assessments of the impacts of gene introgression on fitness are very risky—but not only because we cannot be certain of the ecological context into which a transgenic hybrid might spread. At present we do not have enough knowledge of the relationship between the plant and its habitat at the molecular level. This may improve as more research into environmental genomics emerges. For some transgenes such as cold, drought, and salt tolerance, it is also difficult to predict what the effect of the transgene might be on the recipient phenotype because the genetic background into which the transgene moves may be different from that of the original transformed plant.

Given the uncertainty surrounding the theoretical prediction of fitness impacts there is a need for experimental work to assess fitness of crop–wild plant hybrids containing transgenes. Perhaps the most obvious way to approach this research would be to construct transgenic crop–conventional crop and crop–wild plant hybrids artificially and then backcross them to conventional crops and wild plants to yield populations of plants with and without the transgene within the same genetic backgrounds. There would need to be properly designed experiments i.e. placing plants in relevant ecological situations, where the "best guess" would place the new plant in the ecological landscape. In many cases this would be the field margin and

disturbed ground habitat. Experiments will need to be closely controlled and inherently safe—possibly by recreating suitable habitat in contained conditions or by placing experimental plots in remote conditions where the plants in question could not survive naturally. There is an important role for regulatory systems to ensure that risks from such experiments are minimized.

Measurement of Key Fitness Components

Fitness experiments such as those described above would be assessing the relative fitness of two plant populations: those containing the transgene compared with those that do not. Fitness is defined as genetic fitness, that is the ability of a plant to reproduce relative to the nontransgenic population. There is often confusion about defining fitness. It is not simply variation in plant vigor, although this may be a component of fitness. In some habitats, especially those with harsh windswept conditions and poor nutrient status, high plant vigor is negatively correlated with fitness. Plants living successfully in these conditions put more resources into reproductive structures and less into vegetative vigor.

The key factors in any assessment of fitness will focus on those characters that impact on reproductive success. In plants these include the following:

- Identification of the habitat into which the plant is likely to spread. This is perhaps the most difficult and arguably most important part of any risk assessment.
- Consideration of plant survival to seed production stage from germination to adult plant. It is important that early stages of development be included because most mortality may take place at this time.
- Number of flower heads.
- Number of seeds per head.
- Seed viability and size.
- Predation of seeds on and off plants—mollusks, arthropods, fungi, mammals.
- Seed survival over winter which is important if cold tolerance and other genes are introduced.

Importance of Relating Results to Population Dynamics of Plants in Typical Habitats

If sufficient data are obtained by field experiments, it should be possible to model whether the gene in question would be likely to go to fixation. The population dynamics of plants can be predicted and documented by gathering sufficient ecological data to construct life tables that capture the survival of plants at the population level during all stages in the development of the plant. Changes in fitness detected experimentally can be used in conjunction with life tables to predict what effect any fitness change might have on the population dynamics of the plant in specific habitats. The choice of habitats is crucial and for crop plants may include not only field margins but also disturbed ground habitats that may be similar in character. These could include coastal and cliff areas, erosion areas, and fluvial margins. For hybrids between transgenic crops and conventional crops, field margins and disturbed track margins are the obvious choice. Where risks from transgenic hybrids with wild plants are concerned, this approach may reveal whether the hybrid is capable of surviving or increasing in the

defined habitat. It may then be possible to make estimations of potential effects on all populations of the plants in question within a specific biogeographic area.

Although the preceding protocol may seem excessive and burdensome for any regulatory system, it should be stressed that it would only be necessary to embark on such an approach if there were a reasonable risk of gene transfers leading to impacts on fitness from the introduction of transgenic plants into a biogeographic area. For many transgenic crops there may be no risk that gene transfer to wild plants can occur because sexually compatible wild relatives do not grow in the area. For many transgenes, there may be a vanishingly small risk that gene transfer would increase fitness in recipient plants. If those involved in the production of transgenic plants were to incorporate gene restriction mechanisms such as those suggested by the U.K. regulatory body Advisory Committee on Releases to the Environment (ACRE) (DEFRA 2001), then risks of gene transfer from transgenic crops would be greatly reduced and in some cases could be eliminated, making estimation of fitness impacts unnecessary.

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The Use of Biological Databases to Assess the Risk of Gene Flow: The Case of Mexico

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Abstract

Gene flow from living modified organisms to their wild relatives is one of the risks associated with genetically modified crops—especially when the crop spontaneously hybridizes with its taxonomically related species. In countries like Mexico, which is a megadiverse country and a Vavilov center of origin where many wild relatives of the major crops can be found, proper assessment of this risk is very important. We outline the methodology to assess the risk of living modified organisms (LMOs) developed by the National Commission for the Knowledge and Use of Biodiversity (CONABIO) in Mexico. We highlight the importance that biodiversity databases have in the context of developing countries.

Introduction

It is known that living modified organisms (LMOs) may represent environmental risks. These risks depend on the new genes they contain in their genomes, the technology used to transform the organism, the features of the parent crop such as the reproductive biology, ecological parameter and genetic variation, and the specific ecological situation in which the LMO is released (Persley et al.1993).

Commonly mentioned risks include the LMOs will become invasive (Wolfenbarger and Phifer 2000, Royal Society of Canada 2001) or cause geneflow to wild relatives (European Commission 2000, Ellstrand 2001), which may decrease their genetic diversity (Ervin et al. 2000), transfer weedlike traits to wild relatives (Rissler and Mellon 1996, Warwick et al.1999) or simply alter their original genetic constitution; or have unintentional effects on nontarget species (Ellstrand 2001, Obrycki et al. 2001); or induce new viral diseases (Wolfenbarger and Phifer 2000).

To assess all the theoretical risks that releasing LMOs may pose for the environment systematically is a daunting task. In megadiverse developing countries comprehensive assessment of the risks is simply impossible because of the intrinsic complexity of the ecological factors and the incipient or nonexisting technical capacities. However, this difficulty has been acknowledged even in the developed world: "Given the complexity of biodiversity, the assessment of environmental impact of LMOs can only be completed indirectly" (CFIA DIR-94-08).

The countries in the North American Free Trade Agreement (NAFTA) recognize gene flow to wild relatives as one of the risks associated with field releases of LMOs. Although this risk is particularly significant and relevant in centers of origin of cultivated species in megadiverse countries, other countries have developed protocols to assess the risk of gene flow. An example of these is the NAFTA countries (Canada, Mexico, and the United States), which have such methodologies, although only one (Mexico) is megadiverse as well as a Vavilov center of origin (Vavilov 1951). Therefore, Mexico has special interest in the development of practical procedures to prevent such gene flow, including assessment methods, legislation, and policies.

Among the Mexican institutions that oversee different aspects of LMOs, there are specialized subcommittees for specific matters like science and technology, agriculture, health, environment, and industry. As a part of the group of institutions in charge of dealing with risks related to LMOs, the National Commission on Biodiversity, CONABIO, provides the risk assessment of gene flow from a biodiversity perspective.

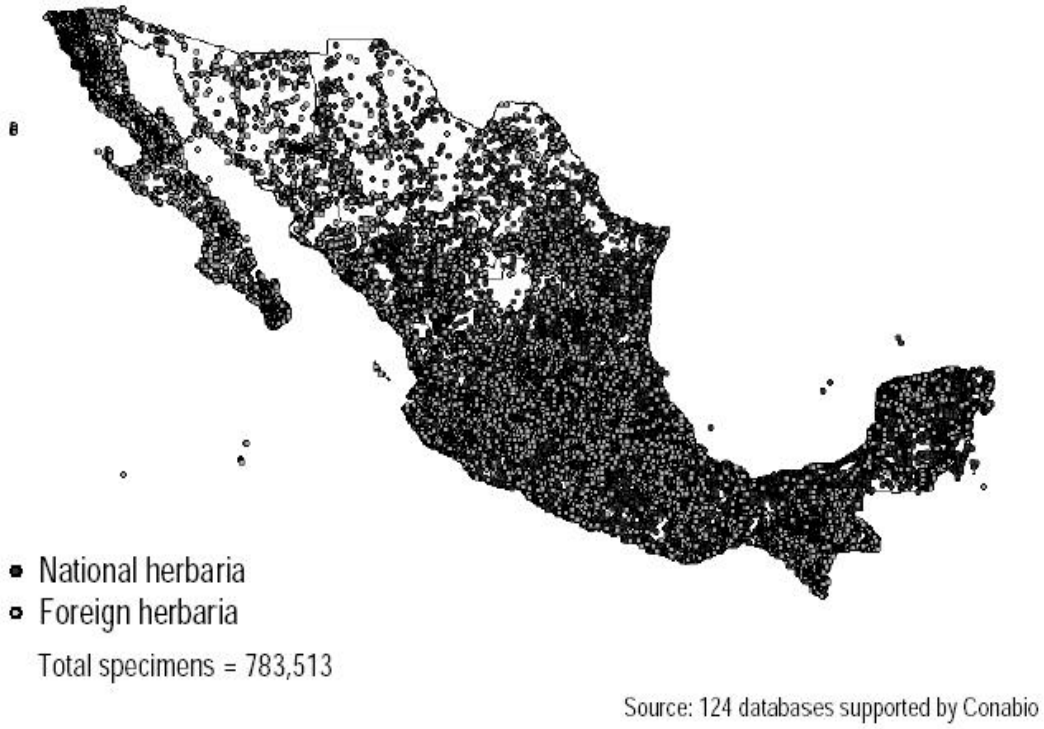
Since CONABIO was created (1992), most of its budget has been directed to support studies and projects related to biological inventories and databases. By these means, CONABIO has computerized the main Mexican zoological collections and herbaria. Specifically, at this moment the database for vascular plants includes 836,600 specimens from herbaria and museums in Mexico (57 collections) and abroad (87 collections; see figure 1 for an example).

Assessing the risk of gene flow

There is evidence of gene flow between crops and their wild relatives, suggesting that even the most domesticated plants will hybridize naturally with their cross-compatible wild relatives when they come into contact (Ellstrand et al. 1999). The level of gene flow is highly variable and depends on a variety of spatiotemporal factors. To assess the risk of gene flow it is necessary to have biological information of the species concerned such as population and species variation parameters, the potential and current spatial distribution of populations of wild relatives, and the spatial location of the LMO site.

In addition, specific and detailed information about the reproductive biology of both the wild relatives and the LMO, in as many experimental or field situations as possible (NOM—056–FITO–1995) is needed to determine the possibility of gene flow.

Figure 1. Location on Mexican vascular plants specimen in foreign and national databases



Information about the proximity of LMOs and wild relatives is highly important. The three North American countries request different information about proximity in their respective regulations. Canada asks for the "geographic scope" of the effects of releasing LMOs (CFIA DIR 94–08); the United States requires "a detailed description of the intended destination" of the LMO (7CFR340), and Mexico requires information on the "wild relatives and their distribution" (NOM–056–FITO–1995), among other information important for the risk assessment. The requirements of information are established by the Mexican regulation NOM–056–FITO–1995.

In view of theese requirements, every application for a permit to release LMOs in Mexico is evaluated using the following information to develop the risk assessment to wild relatives:

Taxonomy of LMOs and Wild Relatives and Known Geographical Distributions.

The Organization for Economic Cooperation and Development (OECD) reports 94 plant species that have been genetically modified (OECD, BioTrack database of field trials). Of these, Mexico has 889 species that are congeners to those LMOs. After checking for correct taxonomic identification, a search of databases is done to obtain georeferenced localities for the species taxonomically related to the LMO (www.conabio.gob.mx/remib).

Bioclimatic Modeling to Obtain Regions of High Ecological Similarity to the Known Localities.

The specimen points provide insufficient and biased estimates of biological distributions. To infer the potential distribution of species we first evaluate the geographical expression of the fundamental niche of the species (Mac Arthur 1972). This is done using an artificial intelligence algorithm called GARP (Genetic Algorithm for Rule Production; Stockwell and Peters 1999) and Geographic Information System (GIS) technology. Application of the algorithm creates GIS coverages of high similarity of physical attributes (climate, soil, slope, etc.) to the data points where the wild relative has been observed. This geographical coverage is interpreted as the area in the country where the fundamental niche of the species is present.

Predicting Distributions from Niches.

To predict species distributions we "cookiecut" the GIS coverages generated with the GARP algorithm by first using biogeographical coverages to include only the GARP regions belonging to the historical distributions of the species (thus discarding regions of high niche similarity but low "historical" or biogeographical affinity) and then using primary vegetation obtained from recent satellite images (Landsat ETM 1999–2000). In the final step, we consult experts to validate the resulting maps. These maps provide information about the likely presence of wild relatives. The current technology has a resolution of pixels of about 4 km. This technique has been evaluated for several taxonomic groups in Mexico, and it has been shown to have a good predictive capacity (A. T. Peterson and K. P. Cohoon 1999, Sanchez-Cordero and Martínez-Meyer 1999, Feria 2001).

Literature and Database Search to Obtain Reproductive Biology Criteria Regarding Likelihood of Gene Flow Given Proximity.

Of the 94 LMOs reported by OECD and their wild relatives in Mexico, we have databased the biological information from scientific sources for 28 species. This database is a growing body of information maintained by full-time staff. We include information about the descriptions of the novel trait of the LMO, comparative descriptions of the LMO and its counterpart, and information related to reproductive biology like pollinators, seed dispersal, pollen movement, genetic variation, and hybridization and gene flow. One of the important features of this database is that the biological attributes may be associated with the species or populations at a specific point in space and time.

On the basis of reproductive biology information in the database, we determine the risk of gene flow, assuming that the LMO and the relative are in close proximity. We also obtain estimates of how close the proximity should be to present a significant risk based on the presence of their wild relatives and biological features like movement of pollen.

Overlap of Data and Regions of Intended Introduction of the LMO

In the distribution maps for the wild relatives generated with GARP algorithms, we overlap the release location of the LMO. In these maps we observe if a given location is inside or close to a "risk area" that would allow gene flow with wild relatives. The determination of the risk is based on the biology and potential distributions of wild relatives of the LMO.

Since 2000, the preceding procedure has been applied to 105 introductions of different LMOs, including *Gossypium hirsutum*, *Glycine max*, *Cucurbita pepo*, *Carthamus tinctorius*, *Cucumis melo*, *Musa acuminata*, *Nicotiana tabacum*, and *Zea mays* ssp. *mays* (only to transport seeds between two research centers). The risk assessment of gene flow is performed on a case by-case basis (table 1).

Table 1. Number of requests evaluated following the procedure developed by CONABIO

Scientific Name	Number of requests
Gossypium hirsutum	70
Glycine max	21
Cucurbita pepo	6
Carthamus tinctorius	2
Cucumis melo	1
Musa acuminata	3
Nicotiana tabacum	1
Zea mays ssp. *mays*	1

This methodology has been presented to scientists, non-governmental organizations (NGOs) and members of the private sector. It appears now to be accepted as a way of highlighting regions of high risk, where field research is indispensable, as well as zones of very little risk, where the LMO can be released with low or no risk to wild relatives.

Conclusions

The approach of CONABIO for the assessment of gene flow is feasible for developing countries and provides a quick assessment, which is nevertheless based on large quantities of scientific information. The accuracy of this methodology largely depends on the availability of data collections and on biological information of species. Sharing the "presence" information of wild relatives from museums and herbaria is something reasonably cheap and very useful.

We also require reproductive biology databasing and much more research on the population biology of LMOs and their relatives.

The extrapolation algorithms to generate the distributions of the species are predictive at mesoscales (about 10 km^2) thus, we need to improve the technology to increase the resolution. High resolution also means that the proposed sites for release of LMOs must be known with precision.

In the midterm, CONABIO intends to make all the databases and algorithms available through its Web site (www.conabio.gob.mx).

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Transgenic Rice and Gene Flow Assessment to Wild and Weedy Rice Species in Costa Rica

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Abstract

Costa Rica has made strategic decisions to develop agricultural biotechnology tools over the past 10 years. Development of transgenic rice lines was part of the effort to obtain local rice varieties resistant to the hoja blanca virus disease (RHBV) and to the herbicide phosphinothricin (PPT). However, deployment of transgenic crops in biodiverse tropical ecosystems raises several concerns. Conscious of this situation, we had identified and characterized potential *Oryza sativa* transgene recipients: native wild *Oryza* species populations and the weedy rice complex associated with rice cultivation.

This paper describes the advances obtained by developing an integrated strategy for the assessment and management of gene flow from transgenic rice lines to the closely related wild relative of rice, *Oryza glumaepatula* and to the weedy rice complex that contaminates rice fields. Future aims include promoting the conservation and utilization of wild rice populations and their ecosystems and providing science-based information on this strategy to local rice growers, policy makers, community leaders, and the international community.

Introduction

Costa Rica is one of the 20 countries with the greatest biodiversity, comprising 5-percent of the world biodiversity, with an estimate of more than 11,000 species of plants. As part of a national policy to preserve its biological resources, 25-percent of the territory has been protected through the Siculma Nacional de Areas de Conservación. In addition, a systematic national inventory has been taking place for the past 12 years as part of an effort to obtain information about the biological diversity of the country. More recently, public and private institutions have been engaged in finding uses for this biodiversity in the agricultural, pharmaceutical, and chemical industries. The country has also established laws for the appropriate use of its biological resources. Furthermore, the Government has invested in research development, supporting the establishment of research institutes in public universities and autonomous institutions for the past 25 years with the purpose of developing biotechnology to solve regional problems. In addition, the University of Costa Rica has developed the capacity for crop improvement by genetic engineering. Small biotech companies are also emerging, particularly for micropropagation of species of economic importance.

On the other hand, the National Biosafety Committee (NBC) has developed regulations, granting permits to agribiotech companies for transgenic seed increase for nearly a decade. Although the NBC has considerable experience in this area, no transgenic products have yet been released for commercial purposes in Costa Rica. Costa Rica is a small country of 51,100 km^2 of which one-fourth of its territory is devoted to national parks; therefore, the potential for expansion of its agricultural boundaries is very limited. In addition, the improper use of the land, the abuse of toxic agrochemicals, and low productivity are some of the factors that contribute to a nonsustainable agriculture. To reduce the impact of such human activities on the environment, it is necessary to introduce important changes in the agricultural practices. The development and utilization of transgenic crops, as part of an integrated pest management program, may contribute to a more sustainable agriculture.

It is important to stress that there is lack of information about the impact that transgenic crops may have in tropical environments, which are centers of origin for many plants. There is also lack of knowledge among consumers about living modified organisms (LMOs), their production, commercialization, consumption, and related food safety issues. Public perception is an important issue in Costa Rica for the acceptance of transgenic products in the country. Although general information has been broadcast in the mass media and debates organized by academic institutions, no data are available about public perception of LMOs in Costa Rica. Other constraints involve the negotiation of licenses and freedom to operate from patent holders of the proprietary technology used in the genetic transformation of the new varieties as well as the establishment of mechanisms for production and distribution of transgenic seeds among farmers. Unless these constraints are properly resolved, they may prevent the use of improved varieties by genetic engineering in Costa Rica and other developing countries.

The Case of Transgenic Rice in Costa Rica

Rice is a very important staple crop in Costa Rica, providing approximately 25-percent of the daily caloric intake to the population. Currently, rice production faces several phytosanitary constraints, which include the rice hoja blanca virus disease (RHBV) among others. The distribution of this viral disease is limited to tropical America, and there is no natural resistance to RHBV among *indica* rice varieties. Therefore, an alternative approach is to use nonconventional strategies such as the genetic transformation of commercial rice varieties with RHBV antiviral or insecticidal genes against the virus insect vector. The Centro de Investigación en Biología Celular y Molecular (CIBCM) of the University of Costa Rica has produced transgenic rice lines of Costa Rican cultivars CR–1821 and CR–5272 containing fragments derived from RHBV RNA–3 (Muñoz 2000).

Parallel to the development of transgenic rice lines, CIBCM has mapped and characterized wild *Oryza* species throughout the country. This study demonstrated that Costa Rica is home for three of the four wild *Oryza* species native to tropical America: *O. latifolia, O. grandiglumis,* and *O. glumaepatula* (Zamora 2001). *O. glumaepatula* is the most closely related to cultivated rice, *O. sativa*, sharing an AA-type genome, whereas the others are allotetraploid with CCDD genomes. The genetic proximity of *O. glumaepatula* to cultivated rice raises concerns about gene flow from cultivated rice to these natural populations, particularly northwest of Costa Rica in the Los Chiles wetlands, where there is proximity of this species to rice-growing areas. CIBCM has also conducted an exhaustive inventory of weedy rice biotypes associated with rice fields. Weedy rice is a complex of rice plants showing characters of *O. sativa* and other wild relatives of rice with different degrees of seed shattering, seed dormancy, phenology, outcrossing rates, and productivity. Weedy rice biotypes are the most likely potential recipients of transgenes if genetically modified rice lines are deployed in the field. Risk assessment and gene flow analyses should be focused on these potential target populations. In the case of transgenic rice lines produced by CIBCM, field tests were established under the supervision of the NBC. Public concerns and attitudes towards biotechnology and agriculture also need to be addressed properly before genetically modified crops are adopted by our society.

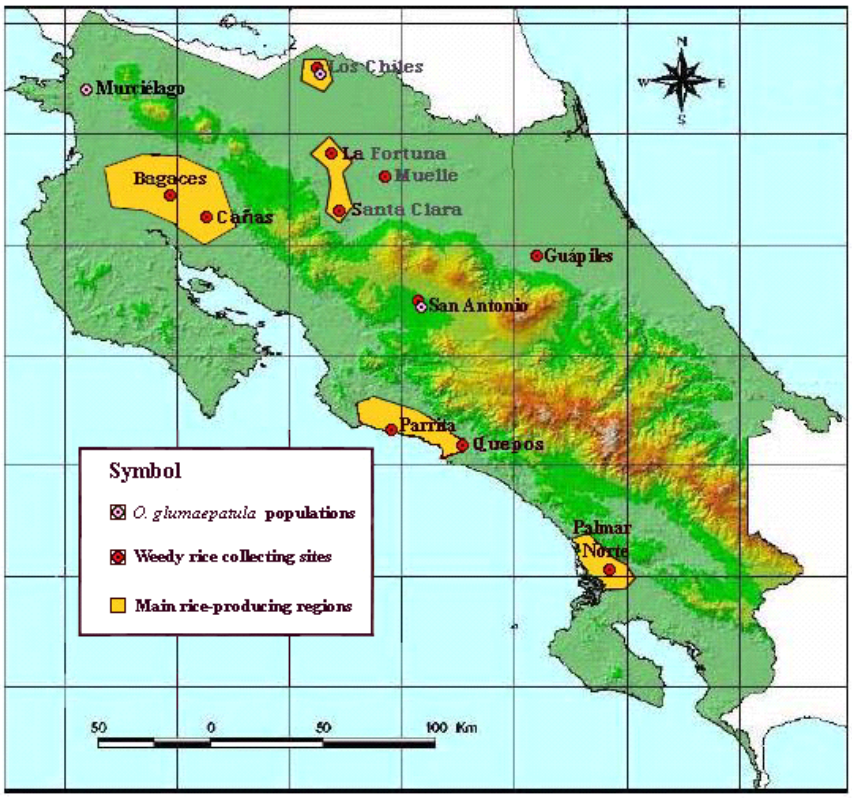
Our working hypothesis is that baseline studies about the distribution, population genetic structure, reproductive biology, and phenology of the wild and weedy *Oryza* species could help to design strategies directed to mitigate or delay gene flow from transgenic rice lines to closely related species. At the same time, such studies would increase the lifespan of new transgenic varieties thorough the implementation of science-based management strategies. This knowledge will also help to promote an inclusive assessment through the conservation and utilization of wild rice populations and their ecosystems, involving rural communities and farmers. The purpose of our research is to develop an integrated strategy for the assessment and management of gene flow from transgenic rice lines to the closely related wild relative of rice *O. glumaepatula* and to the weedy rice complex that contaminates rice fields. In addition, the studies promote the conservation and utilization of wild rice populations and their ecosystems by providing information to local rice growers, policymakers, community leaders and the international community.

Material and Methods

Confined Field Trials of Transgenic Rice Lines:

Two field trials of the transgenic rice lines containing RHBV-derived sequences and the *bar* gene conferring resistance to the herbicide PPT as a selection marker were performed in San Antonio, Alajuela (Central Valley, 900 meters above sea level), under the supervision of the NBC (figure 1). The lines were tested for RHBV and herbicide resistance and were also used for seed increase. The first trial involved 36 T1 lines that contained the RHBV coat protein gene in sense and antisense orientation or flanked by nuclear matrix attachment regions as well as 3' and 5' fragments of this gene. The progeny of those plants (T2) were evaluated in the greenhouse for selection of homozygous lines for the herbicide-resistance trait. The herbicide-resistant T2 lines were transplanted to a second confined field trial and are being evaluated for agronomical performance through an assessment of plant morphology and phenology.

Figure 1. Map of Costa Rica showing the country's main rice-producing regions, weedy rice collecting sites and the location of *O. glumaepatula* populations, that provided the material used in this study.



Morphological Analyses of the Weedy Rice Complex:

Over 1,200 samples of weedy rice, commercial varieties, and landraces in the plant maturity stage were collected from the main rice-growing areas of the country (figure 1). Biotypes were classified and coded according to awn presence and color, color of the apiculus, and lemma and palea color. Twenty-one morphological traits were then evaluated based on previously established descriptors (IRRI 1980; UPOV 1985). The morphological variables were evaluated by a multiple discriminant analysis (Systat 8®). A classifying function was established based on the morphological characteristics of the commercial varieties of rice. The coefficients of the resulting function for the varieties were used to calculate the discriminating points for each weedy rice specimen and to separate it from the commercial rice varieties.

Phenological Analyses of the Weedy Rice Complex:

The growth cycles of 27 weedy rice biotypes collected from Guanacaste (North Pacific) and Parrita (Central Pacific) (Sánchez 2001), 5 Costa Rican commercial varieties, 18 landraces and 2 wild *Oryza* species were compared in a field trial in San Antonio (figure 1). The following characters were evaluated: number of days from seeding to 50-percent of seed emergence, percentage of total emergence; number of days from seeding to 50-percent of tillering, booting, anthesis, heading, and maturity. The duration of anthesis was also recorded. Plant size, number of tillers, and number of leaves per plant were evaluated every 15 days during the vegetative cycle.

Optimization of Molecular Analyses of the Weedy Rice Complex:

DNA extraction from leaf tissue of 1-month-old plants was performed on samples of all weedy rice biotypes, landraces, commercial rice varieties, *O. glumaepatula, O. glaberrima,* and *O. rufipogon.* The extraction method by Lodhi *et al.* (1994) was modified to eliminate polyvinyl pyrrolidone (PVP) and mercaptoethanol. Polymerase chain reaction (PCR) was performed on a subsample of the preceding materials using 14 microsatellite primers: RM22, RM41, RM11, RM230, RM20, RM19, RM1, RM222, RM167, RM200, RM164, RM5, RM168 and RM123 (Mappairs®). PCR amplification was visualized in 1-percent agarose gels stained with ethidium bromide.

Flowering, seed set and sample collection of *O. glumaepatula*:

Flowering periods were monitored in three locations of the country: two natural populations in Los Chiles and Murciélago and a field trial used for seed increase in San Antonio, Alajuela (figure 1). Seeds from individual panicles along with their respective flag leaf were collected randomly throughout the area covered by *O. glumaepatula* in Los Chiles (figure 1). The seeds were labeled and kept for later germination and the flag leaf was stored separately at -30°C to conduct progeny studies.

Collection of Wild Oryza Species for Organoleptic Studies, Industrial Processing and Nutritional Analyses:

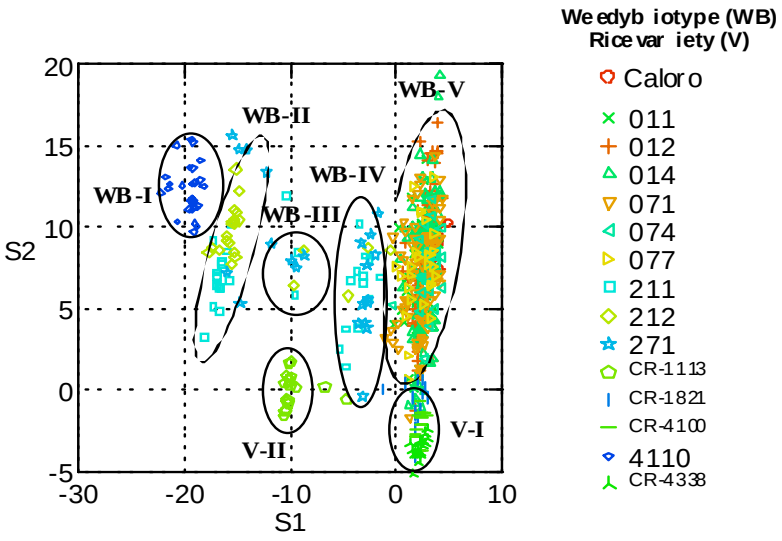
Seeds of *O. glumaepatula* were collected from three localities: two natural populations in Los Chiles, Alajuela and Murciélago, Guanacaste (figure 1)., and a field trial used for seed increase in San Antonio, Alajuela, Seed samples of *O. latifolia* were collected from two localities on the province of Guanacaste: Bagaces and San Miguel, Cañas (figure 1). The seeds were stored at room temperature with low humidity. Seed availability of *O. grandiglumis* in the Caño Negro wildlife refuge was also monitored.

Results

In the first field trial for the evaluation of transgenic lines, T1 seeds were tested for PPT- and RHBV-resistance. Herbicide resistance was segregated in Mendelian fashion, and some lines were resistant to virus infection. Interestingly, neither RNA nor coat protein was detected. The T2 generation was planted in the greenhouse and the seedlings were evaluated for their PPT resistance 4 weeks after germination. It was observed that, as occurred in the T1 generation, the *bar* gene is active in the T2 transgenic lines and that these were resistant when PPT was applied in the recommended dose for weed control (1 l/ha). On the basis of these results, homozygous T2 lines were identified for herbicide resistance, and a replica of these lines was planted in a field trial for evaluating their agronomic performance and selection of true-to-type lines. This study is still in progress and the results are expected to be complete in the following months.

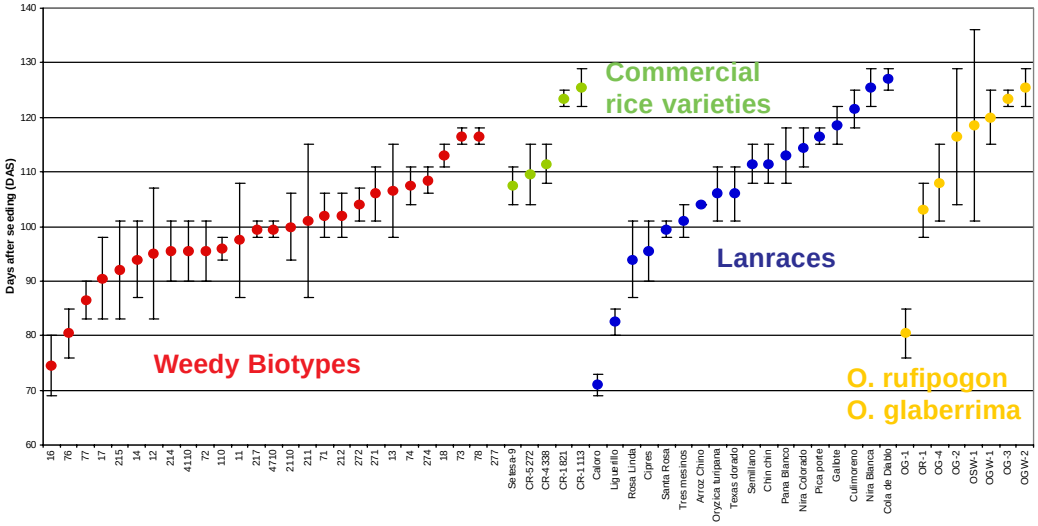
Twenty-seven weedy biotypes (WB) were identified according to the morphological characteristics of the mature grain. The discriminant analyses revealed that the most useful traits to separate the groups, were awn presence, color and distribution, total culm number, total number of culms with panicles, plant height and panicle exsertion. Using these variables, we grouped the commercial rice varieties into three clusters: V–I (varieties CR–1821, CR–4110, CR4338, CR 5272 and Camago 8); V–II (variety CR–1113, which shows awned grains and low number of culms); and V–III (landrace Caloro, which is taller than the others and has a lower average exsertion when compared with the commercial varieties). These same analyses discriminated the weedy rice population in five clusters: Group WB–I is constituted by one biotype (4110, identified as *O. rufipogon*), WB–II to WB–IV are conformed by the 7 awned biotypes separated according to awn distribution, length, and color. Finally, WB–V groups the 12 awnless weedy rice biotypes that have different plant heights: tall (> 150 cm), intermediate (100 to 150 cm), and small (65 to 99 cm) (figure 2).

Figure 2. Discriminant analyses of commercial rice varieties (V) and weedy biotypes (WB). S1= Total culm number, total culms with panicle, awn color and distribution. S2= Culm length and panicle exsertion



The phenological analyses of the weedy rice complex indicated that 24 weedy rice biotypes germinated between 6 and 9 days after seeding (DAS). These germinated earlier than commercial varieties and landraces that required 9 to 20 DAS. In general, weedy rice biotypes reached 50-percent booting several days earlier than commercial varieties. It was observed that the weedy rice biotypes from Parrita significantly required fewer days to reach 50-percent booting than those from Guanacaste. The weedy rice biotypes were classified into four groups depending on the days to reach 50-percent anthesis: I. 90–100 (2 biotypes); II. 100–110 (5 biotypes), III. 110–120 (14 biotypes) and more than 120 (4 biotypes). Flowering time overlaps occurred between the commercial variety CR–5272 and fourteen weedy rice biotypes and three landraces. Nevertheless, for the same trait the rice varieties CR–1821 and CR–1113 overlapped with only one biotype (figure 3).

Figure 3: Days to reach 50% heading of weedy biotypes, rice varieties and wild species



Optimization of molecular analyses of the weedy rice complex included the development of a DNA extraction protocol that preserves DNA quality for PCR amplification and that allows the processing of a large number of samples in a short time. PCR amplification of the following microsatellite primers were positive for all samples: RM22, RM230, RM20, RM19, RM167, RM164, RM5, and RM168. The amplification of primers RM222, RM200, RM123, RM11 and RM1 was negative for at least one of the wild *Oryza* species evaluated but positive for all the weedy rice biotypes and commercial varieties. No amplification was observed on any sample for primer RM41. Other primers remain yet to be tested.

Flowering and seed set monitoring of *O. glumaepatula* revealed that the flowering of *O. glumaepatula* occurred simultaneously from October to December 2001 in the populations growing at Los Chiles, Murciélago, and a field trial in the San Antonio. Approximately 192 progeny groups were obtained randomly at the "El Muro" population in Los Chiles along with the flag leaf of the respective mother plant. Seeds are currently undergoing humidity reduction for storage and future germination, and flag leaf samples were stored at -30°C. Molecular progeny analyses using microsatellites will be performed in the following months, and the results are expected to provide information about the genetic structure of this population as well as on its reproductive biology.

Seeds of *O. glumaepatula* and *O. latifolia* have been collected and stored for organoleptic, industrial processing, and nutritional analyses. *O. grandiglumis* began the flowering period in the first weeks of December, and thus mature seeds were available in January. The following analyses will be performed proximately: carbohydrate content, starch, total protein content, dietetic fiber, cooking and milling properties, and flavor and aroma quality.

Discussion

Transgenic plants were resistant to both RHBV and to the herbicide PPT. This demonstrated that rice genetic transformation has been successful in Costa Rican varieties. In the field trial of the T1 lines, neither RNA nor coat protein was detected, indicating the effect of gene silencing for the viral protein. The herbicide resistance trait was observed in the T1 generation and was inherited in Mendelian fashion in the progeny (T2). The PPT resistance of the T1 and T2 transgenic lines indicated that the *bar* gene was expressed in the transgenic lines, and the enzyme phosphinothricin-N-acetyltransferase reached sufficiently high concentrations to detoxify PPT when used in the recommended dose for weed control (1 l/ha). This allowed the selection of homozygous PPT-resistant lines for the depuration of this trait. Morphological and phenological analyses of the T2 plants are yet to be performed and will provide valuable information for the selection of true-to-type herbicide-resistant lines. Some of these lines will also be useful for performing crosses with other elite commercial varieties. The location of the field trials in the Central Valley was chosen because it has adequate climatic conditions for rice development and is devoid of natural wild rice populations, and the nearest rice plantations are about 100 km away.

The morphological characterization of weedy rice populations allowed the identification of 27 biotypes based on mature grain characteristics. Previous publications have classified weedy rice according to lemma and palea color (Smith 1981, Montealegre and Vargas 1993). In this study, additional characters were included to obtain a broader morphological characterization mainly because weedy rice populations are highly polymorphic, and grain characters alone would not be sufficient (Noldin *et al.* 1999, Galli *et al.* 1982, Lago 1982). This method allowed the identification of clusters within a highly polymorphic weedy rice population and the separation of weedy rice from the highly related commercial varieties (Cuevas-Pérez *et al.* 1992).

The results obtained in the phenological analyses suggest that the fast and early emergence of weedy rice seeds indicate that these do not exhibit dormancy. However, early seed emergence may be helpful for weedy rice control because selective practices can be performed before the emergence of commercial varieties (Diarra *et al.* 1985). A wide heterogeneity on flowering periods was observed on landraces and weedy rice biotypes. The information on the overlapping of flowering periods between weedy biotypes and commercial varieties will be useful to select the weedy rice biotypes that may be used in field experiments for assessing gene flow from transgenic rice to weedy rice populations. Other characters such as the crossing compatibility between weedy rice and commercial rice varieties, plant height, similarity of grain size and color, panicle shattering and susceptibility to the herbicide PPT must also be considered. Because much of this information is still unknown, future experiments will be performed to answer these questions.

Modifications of the DNA extraction protocol allowed obtaining DNA with adequate quality for PCR reactions that did not require the use of organic solvents in the protocol, possibly owing to its plant age and the low presence of secondary compounds in rice. The low amplification efficiency of microsatellites observed in wild rice species may result from rice microsatellite primers obtained from cultivated rice varieties (Chen *et al.* 1997, McCouch *et al.* 1997), and the primer annealing may be affected in wild species due to its specificity to rice cultivars. Nevertheless, under these conditions at least eight primers can be used for analysis in all

available material. An additional five primers can be used for the analysis of weedy rice biotypes and commercial varieties, though modifications of PCR conditions may allow the amplification of the wild rice species. More microsatellite primers are yet to be evaluated.

O. glumaepatula flowering occurred simultaneously during October and November in all three sites evaluated. During these months, the daylight time is 30 minutes shorter in comparison with the longest days of the year. This change in photoperiod seems sufficient to trigger flowering in *O. glumaepatula* in the three locations because these sites have different climatic conditions. In addition, these regions have adequate environmental conditions for rice cultivation. Therefore, the annual flowering period of *O. glumaepatula* is important to define the rice-sowing cycles in areas close to these natural populations, and consequently minimize the possibility of gene flow between these species. Another possibility for minimizing gene flow is to provide additional options to rice cultivation in the area such as the use of wild rice species as alternative sources of income that may substitute for the cultivation of *O. sativa* in the area. The analyses of the nutritional, organoleptic, and milling properties of the wild species of rice could provide valuable information towards exploring the possibility of using these species as "gourmet" rice. This would also involve the rural communities in the conservation of the natural habitats of wild *Oryza* species.

Conclusions

The results and strategies presented represent a unique contribution in which the development of transgenic rice lines has paralleled a baseline study for obtaining useful information needed for the deployment of new genetically modified rice varieties. Weedy rice and *O. glumaepatula* are the most likely potential transgene recipients if genetically modified lines are deployed in the field. Therefore, the baseline studies aim towards the characterization of rice-related populations and are focused on their distribution, genetic structure, and reproductive biology. In addition, this study will help determine the magnitude of gene flow between transgenic rice and its wild and weedy relatives before the crop is commercialized.

The case of transgenic rice in Costa Rica is an example of progress in developing science-based information for the deployment of modified crops to local farmers. In this paper we presented results on environmental impacts, and ecological risk assessment, public perception, food safety, and intellectual property rights (negotiation of proprietary technology, protection of intellectual property, and freedom to operate) as well as food safety and organoleptic studies. We are also preparing information for the general public to generate objective facts about biotechnology practices that could provide a base for the future incoroation of transgenic organisms may be incorporated in the agriculture of the country.

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Gene Flow Assessment of Living Modified Organisms in the Neotropics

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Abstract

Transgenic plants, or living modified organisms as currently known (LMOs, according to the Cartagena Protocol), may offer improved traits and benefits for agriculture and consumers in the tropics; however, their introduction may also entail potential risks. Hybridization between crops and their wild relatives sometimes brings novel genes into wild populations, occasionally resulting in the evolution of aggressive weeds or endangerment of rare species. Widespread deployment of transgenic crops could also lead to similar outcomes, but only limited information is available regarding gene flow and distribution of wild populations in crop areas that might lead to the prediction of such outcomes. The likelihood of crop-to-wild hybridization depends on the outcrossing rate and on distance and direction of wild and crop populations. A careful assessment of potential impacts of gene flow from LMOs on population genetics of natural crop plant biodiversity is needed to design strategies for the safe use of LMOs in the Neotropics.

Introduction

Neotropical biodiversity has contributed by the mechanism of human domestication up to one-third of all plant crops grown worldwide. Mesoamerica, the Andean region, and the Amazon have been the centers of origin or diversification of well-known crops such as maize, beans, potato, sweet potato, tomato, cassava, groundnut, pineapple, cotton, cacao, and chili peppers (Harlan 1992). Many landraces still exist there, as well as most of the ancestral wild relatives. Gene flow usually occurs across the primary gene pool of wild relatives (i.e., genetically compatible), and its derived cultigens, to maintain genetic diversity and thus to ensure survival and adaptation to changes. More than 70 percent of plant species may be descended from hybrids of wild species ancestors. Nonetheless, even if hybridization is common, it is not ubiquitous (Ellstrand et al. 1999). Hybridization between crops and their wild relatives sometimes can also bring genes into wild populations, occasionally resulting in the evolution of aggressive weeds or

endangerment of rare species. The likelihood of crop-to-wild hybridization depends on the outcrossing rate, and on the distance and direction of wild and crop populations (Ellstrand and Hoffman 1990).

Transgenic crops offer an alternative for introducing traits that can reduce the need for chemical pesticides and fertilizers and can improve agronomic performance. This technology could contribute to a decline in the conversion of currently unused land (which bears areas of biological diversity) into new agricultural lands. Just as is true for the introduction of any foreign trait, so also may transgenic crops pose four potential types of adverse consequences of gene flow into the wild and weedy relatives (Ellstrand and Hoffman 1990). The foremost issue is the possibility that the traits inserted and expressed by the wild or weedy relatives might increase their aggressive weediness. A second issue is the possibility of diversity reduction in the wild or weedy gene pool, affecting their fitness and thus long-term survival. The third is the possibility of disturbing ecological relationships within natural communities. The fourth consequence is the possibility of unexpected pleiotropic effects associated with the introduced gene. There is a need to evaluate the potential effects of using LMOs under tropical conditions where there is continuous cropping and where pest, disease, and weed problems are higher.

Risks associated with gene flow presuppose physical proximity of the crop to its wild relative(s), or among varieties or landraces of the crop itself, so that pollinating agents can effect gene transfer. A second important assumption is the genetic compatibility of the crop and its immediate wild relative(s), which may or may not be fertile. In the former case, accurate mapping of the crop and above all the location of its different wild relative(s) having genetic compatibility is a prerequisite for the introduction and management of transgenic crops. With few exceptions (teosinte, wild potatoes) the range of distribution and ecology of wild relative(s) of several neotropical crops are still only partly documented. These deficiencies are true also for the limited numbers of American species of rice. If creation of transgenic varieties of principal tropical crops is expected, then the mapping of the genetically compatible wild relative(s) is a basic step towards their sound management.

The likely consequences of gene transfer to other crops or to wild and weedy relatives, including impacts on biodiversity, depend on both the specific genes and the environment. To address these questions, we are using beans and rice as models. Beans have a center of origin and biodiversity in the neotropics. Rice is an introduced species from Africa and Asia but with wild and weedy relatives that include wild native species in Central and South America. The aims of this work are as follows:

1. To analyze the gene flow from transgenic crops to wild and weedy relatives in crop centers of diversity using beans and rice as models

2. To monitor changes due to transgenes in population genetic structure and dynamics of wild and weedy relatives under confined field plots and local agricultural field conditions

3. To develop management practices for the use and handling of transgenic crops in the tropics

4. To advise biosafety entities of neotropical countries on the safe use and management of transgenic crops

Discussion

Bean Crop-Wild-Weedy Complex in the Neotropics

Phaseolus beans and wild relatives have their center of origin and diversity in Central America and the tropical Andean countries, they display a spectrum of reproductive biology, lifespans and agro-ecological niches (Debouck and Smart 1995). The common bean is usually reported as an autogamous species; however, rates of outcrossing up to 30 percent and above have been reported in subtropical environments (Wells et al. 1988). High temperatures might be directly or indirectly involved through higher insect activity (bees and bumblebees) acting as pollinators (Debouck et al. 1989). The wild relative of the common bean might have slightly higher rates of outcrossing in comparison with its derived cultigens (Triana et al. 1993). Traditional bean landraces are grown sympatrically with their direct wild ancestors in many places of Latin America—especially in Mexico (Delgado Salinas et al. 1988), Guatemala (Gentry 1969), Colombia (Debouck et al. 1993), Peru (Berglund–Brücher and Brücher 1976), and Bolivia (Freyre et al. 1996). Crosses have been shown to occur between the bean crop and populations of wild relatives in many places of their wide range of sympatric distribution (Beebe et al. 1997). In certain places in Latin America, the hybrid swarms resulting from such crosses are used by farmers—either as additions to their original seed stocks or as emergency food just in case of a crop failure (Debouck et al. 1989). The presence of a specific type of phaseolin (a seed storage protein) from the Peruvian wild *P. vulgaris* gene pool in the cultivated bean in Colombia suggests that gene flow from wild and weedy beans may have occurred before pre-Colombian times (Beebe et al. 1997). The extent of such wide crosses between bean landraces and wild forms, in terms of geographical range and timespan, as well as their significance for the maintenance of genetic diversity in bean landraces and for increased fitness of farmers' mixtures need to be quantified (Beebe et al. 1997). Crosses between landraces have also been reported (Paredes and Gepts 1995).

Natural variation in seed storage proteins has been exploited in studies on bean evolution (Gepts and Bliss 1988). One group partly related to the lectins is arcelin, which confers high levels of resistance to pests of stored grains: the bruchids (Cardona et al. 1990). Bruchids exist on wild and cultivated *P. vulgaris* crops in the Americas from Mexico to Argentina. Arcelin proteins are not known to occur naturally outside Mexico (Acosta-Gallegos et al. 1998). There are several variants of arcelin protein known so far, and they do not confer even levels of resistance to bruchids (Cardona et al. 1990). Currently, we are conducting gene flow analysis of bean crop-wild-weedy complexes under local agricultural field conditions at the Central Valley of Costa Rica. Populations of the three target species—*P. vulgaris, P. polyanthus*, and *P. costaricensis* as well as cultivated beans had been mapped to specific locations. Simulation experiments under confined experimental field plots are also underway. To determine the gene flow rate, selected materials were planted in specific designs for the simulation experiments. A wild bean accession containing an arcelin type with almost no insecticide activity against bruchids is being used. It would thus behave neutrally if this arcelin type were to migrate through gene flow into the commercial varieties planted adjacent in the external concentric squares. Various bean varieties differing in flower color are also used. Hybrids are identified using the arcelin gene and segregation for flower color.

Rice and Wild and Weedy Diversity in the Americas

Cultivated rice, *Oryza sativa* L., is an autogamous plant, with a low outcrossing rate of 0–1 percent (Roberts et al. 1961). Such low outcrossing rates are not, however, typical of the wild relatives of rice. Outcrossing rates can be as high as 56 percent (Roberts et al. 1961). Several genome combinations are found among *O. sativa* and its wild relatives. Hybridization can be expected within the genomic group that includes *O. sativa*, namely, the AA group. Recent reports indicate the presence of rice wild relatives in Central and South America and the diversification of an American AA genome wild *Oryza* species, *O. glumaepatula* Steud, in Brazil, Colombia, Costa Rica, and Venezuela (Vaughan and Tomooka 1999). Some taxonomist have considered *O. glumaepatula* the American *O. rufipogon* Griff (*O. rufipogon* is of Asian origin), and its classification is still confusing in some Latin American countries, such as, Venezuela (Vaughan and Tomooka 1999). The wild relatives of the AA genome, which are found in Central and South America and may hybridize with the rice, include *O. rufipogon* (AA, hybrid seed set 19 percent without and 73 percent with embryo rescue), and *O. glumaepatula* (AA, hybrid seed set 39 percent without embryo rescue) (Chu and Oka 1970, Vaughan and Sitch 1991, Vaughan and Chang 1992). Gene transfer from *O. sativa* to *O. rufipogon* under field conditions has been documented in Asia. Spontaneous intermediates between cultivated rice species and their wild relatives occur frequently in and near rice fields when wild taxa are present. The intermediate plants usually appear as hybrid swarms. Natural rates of hybridization can sometimes be substantial, and the hybrids usually show hybrid vigor (Sitch 1990). Natural hybridization with cultivated rice has been implicated in the near extinction of the endemic Taiwanese taxon *O. rufipogon* ssp. *formosana* (Ellstrand et al. 1999). Throughout Asia, typical specimens of other subspecies of *O. rufipogon* and the wild *O. nivara* are now rarely found because destruction of natural habitats and extensive hybridization with the crop (Ellstrand et al. 1999). Recently, knowledge of the *Oryza* species in Latin America has increased greatly since the series of germplasm-collecting missions in Brazil, Paraguay, and Argentina and subsequent research on collected germplasm from Colombia, Costa Rica, and Venezuela (Vaughan and Tomooka 1999). *O. rufipogon* is abundant in the middle reaches of the Orinoco—particularly in Apure and Guarico States. Considerable variation is apparent from specimens, and *O. rufipogon* is found as a weed of cultivated rice. The biodiversity erosion of Asian *Oryza* species highlights the relevance of documenting the Latin American *Oryza* diversity, which may represent new sources of genes of interest for breeding that have not yet been used.

The weedy red rice is also readily found with the cultivated crop in Latin America. Red rice (*O. sativa* f. *spontanea*) is a weedy rice with a red pericarp and dark–colored grains. Its seeds shatter readily and possess dormancy characteristics; the plants typically are tall and late maturing and have pubescent leaves and hulls (Langevin et al. 1990). In contrast to Asia ,where manual transplanting is still predominant, in tropical America direct seeding of red rice-contaminated seed is common for a high proportion of rice farmers in Latin America, ensuring field reinfestations and making it one of the most serious weed problems in this region (Fisher and Ramírez 1993). There are indications that genes placed in cultivated varieties of rice have transferred quickly into red rice in Asia (Clegg et al. 1993). In the United States, an allozyme progeny analysis of experimental mixed stands of the rice crop and the red rice weed indicated that the natural rates of hybridization could range from 1 percent (with early season variety, flowering at 72–76 days) to 52 percent (with late season variety, flowering at 82–86 days) (Langevin et al. 1990). Thus, cultivated varieties that flower and mature late, like those mainly grown in Latin America, may enable hybridization with red rice to occur throughout several generations (Langevin et al. 1990).

Studies to define the red rice and rice wild relatives complex in the crop contact zone would likely be important to design biosafety guidelines for the neotropical region. Current work conducted by our group on the characterization of the red rice biotypes found in the major rice-cropping regions of Colombia and Costa Rica suggests differences between red rice populations that are associated with the crop history of each field. Some of the red rice populations are clearly distinct from the rice variety crop in the plot and resemble the wild species *O. rufipogon*. Other red rice populations are more diverse. Although some biotypes are not significantly different from *O. rufipogon*, others look like the variety grown in the plot. Some biotypes phenotypically fall in between *O. rufipogon* and the cultivated variety. Complete characterization of these populations is underway to identify potential indicators of gene flow between rice and red rice.

Tracing Gene Flow

Measuring hybridization rates is critical for the assessment of the risk of weediness or extinction by hybridization. The appropriate way to assess hybridization rates under field conditions is to create experimental stands of the crop and wild or weedy taxon under conditions comparable to those under which the crop and the wild or weedy taxon will coexist when field release occurs. Progeny testing of the wild or weedy taxon for crop-specific genetic markers can then be used to measure gene flow (Ellstrand et al. 1999). A more precise estimation of gene flow is obtained by using specific molecular markers. Of the molecular markers available nowadays, microsatellites are valuable genetic markers because they are simple and codominant, allow detection of high levels of allelic diversity, and are easily and economically assayed by polymerase chain reaction (PCR) (McCouch et al. 1997). Spatial distribution of alleles can be used to study local gene flow, including pollen dispersal distances. Microsatellite markers have been used to detect polymorphism within crops, to detect population expansion, and to trace crop-to wild gene flow and wild-to-crop hybridization rate under confined experimental settings as well as under natural conditions (Guadagnuolo et al. 2001).

Our research group has used bean microsatellites to characterize the diversity of the different bean gene pools (unpublished). Clear differences were noted between the Mesoamerican and Andean gene pools. Gene-pool-specific microsatellites were identified. Results suggested that, although gene flow between cultivated and wild bean species occurred in natural environments, no indication of erosion of diversity of the wild pool was noted owing to gene flow. The diversity of the bean crop was rather narrow in contrast to the wild bean gene pool, which was widely diverse. At this point, intervention and destruction of the natural habitats may be a more important cause of diversity erosion. In the case of rice, a set of microsatellite markers is being used to detect polymorphisms between different rice varieties, wild species, and red rice. Genotype-specific markers have been identified and selected, allowing the identification of handmade crossed hybrids from individual genotypes. This set of microsatellites is being used to characterize the genetic structure of the experimental populations before gene flow and to detect outcrossing rates in the field. The spatial distribution of alleles is used to study local gene flow, including pollen dispersal distances. Microsatellites are used to trace crop-to-wild or to red rice gene flow and red rice or wild-to-crop hybridization rates under confined experimental settings as well as under natural conditions. Similar analyses were conducted to assess transgenic-to-non-transgenic variety gene flow.

Conclusions

The quantification of gene flow from the transgenic crop plants to the related weeds and wild species, its effect(s) on the population genetic structure of the recipient species, and maps describing spatial distribution of potential areas of gene(s) movement in the targeted countries are key elements to design strategies for the safe use of LMOs in the neotropics. Besides the mapping of crop and wild or weedy populations in the study sites, it is necessary to analyze the genetic structure of the wild or weedy relatives before and after gene flow. In this case, data analysis of gene flow under the controlled conditions of confined field plots and under local agricultural field conditions should be seen as complementary. A Geographic Information System facilitates fine mapping of wild or weedy diversity distribution in the region and helps target areas with risk potential for gene flow. The information should be translated into procedures and protocols for risk assessment and made available to regional developing countries. Research and monitoring of gene flow and introgression using non-LMOs will give us a suitable base line. Case studies making a comparison of LMOs and non-LMOs carrying the same trait (i.e., herbicide resistance) will serve as a base line to elucidate the effects due to the trait itself. For that purpose equivalent counterparts should be used which that be identified through microsatellite molecular markers and micro-array analysis.

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Practice of Risk Assessment

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Abstract

In this paper we describe the general methodology of risk assessment for living modified organisms (LMOs) as it is outlined in several internationally agreed documents such as Organization of Ecomic Cooperation and Development recommendations, the United Nations Environmental Program Technical Guidelines, and the Cartagena Protocol on Biosafety as well as the day-to-day practice of applying that methodology. Risk management is discussed along with the writing of a concluding evaluation of environmental impacts. This contribution is part of a training manual developed for training workshops on the development and implementation of biosafety frameworks. The training workshops are part of the project "Implementation of Biosafety Frameworks in Preaccession Countries of Central and Eastern Europe," which is funded and implemented by the Dutch Government. The complete training manual and background information about the project can be found on the Central and Eastern Europe CEE Biosafety Web site (www.biosafety-CEE.org; sub page "Events, Links and Projects," under "Matra project").

Introduction

Risk assessment in the field of biosafety is a scientific process used to identify and evaluate the impacts that activities such as releases into the environment with genetically modified organisms (GMOs) may have on the environment, including humans. Risk assessment can be carried out by those who plan to accomplish those activities with GMOs as well as by authorities with responsibilities to regulate and assess such activities. To provide a meaningful tool for decisionmaking, risk assessment needs to be practiced in a scientifically sound and transparent manner and needs to make use of the best up-to-date scientific knowledge and experience.

Although the details of a risk assessment vary from case to case, the overall methodology followed in doing a risk assessment for GMOs usually involves several systematic steps. An outline of this overall methodology can be found in a variety documents, including the following:

- UNEP International Technical Guidelines for Safety in Biotechnology,[1]
- The Biosafety Protocol (Annex III),[2] and
- EC Directive 2001/18/EEC (Annex II).[3]

As these documents show, the steps taken in a risk assessment are as follows:

1. Identification of potential adverse effects[4] on the environment, including humans.
2. An estimation of the likelihood that these adverse effects, will be realized.
3. An evaluation of risks based on the evaluation of the likelihood and of the consequences of the identified adverse effects of being realized.
4. Consideration of whether any identified risks are acceptable or manageable, including, where appropriate, an identification of risk management strategies.
5. Assessment of the overall potential environmental impact.

In addressing these steps, the relevant characteristics of the following are taken into account:

- The recipient organism,[5]
- The inserted genes and other relevant sequences,[6]
- The resulting GMO,
- The application (e.g., small-scale field trial or marketing),
- The receiving environment, and
- The existing situation, including consideration of the use of the nonmodified recipient organism

Practice

How is the methodology described above applied in practice in countries where biosafety frameworks have been in place for many years? This section focuses on risk assessment for the release of genetically modified plants into the environment. The reason for this focus on plants is that currently the bulk of requests for permits deal with releases of genetically modified plants. However, the methodology presented can, to a large extent, also be applied to releases of other genetically modified organisms.

The practical approach described below follows two steps:

1. Preparation of a cover note for the request and the dossier,
2. The actual risk assessment

Preparation of a Cover Note

As a first step in the risk assessment it is useful to 'set the scene' of the assessment by listing the following on a cover note:

- the name of the applicant,
- the type of application (e.g., field trials under controlled conditions or a commercial release),
- the name of the recipient organism, including whether the recipient plant can cross fertilize with wild flora with cultivated, or both, crops in the receiving environment;
- the inserted genes or sequences

The last part of the cover note is a list of the inserted or modified genes and sequences, and—where known—the corresponding traits for which these genes code or may code. What is important in this stage is to get a complete list of any inserted genes or sequences regardless of whether the genes are actually expressed in the plant.

It is recommended that the assessor note the pages of the request on which relevant information is found. Assessors should be aware that in some requests the relevant information about inserted genes may be given in different places within the request. Applicants should be urged to concentrate similar types of information when possible in one part of the request. Experience shows that the use of such a cover note facilitates the risk assessment and in fact the entire handling of the request. An example of such a cover note is attached as "worksheet A" to this article.

The Actual Risk Assessment

Once the main elements of the request are included in a cover note, the actual risk assessment can start. The risk assessment starts in a systematic way whereby for each of the inserted genes and sequences the questions described above are addressed:

1. Identification of potential adverse effects.
2. An estimation of the likelihood that these adverse effects will be realized.
3. An evaluation of the identified risks.
4. Consideration of risk management.

After this systematic gene-by-gene assessment, a broader and more holistic approach follows whereby the potential impacts of the genes together are evaluated with a view to an assessment of possible synergistic effects. Finally, the overall environmental impacts are evaluated. These steps are discussed below.

Identification of Potential Adverse Effects—

The risk assessment process starts with the identification of potential adverse effects that will be considered in the risk assessment. This is done in a systematic way by identifying each of the inserted genes or sequences of genetic material that have been introduced. Any

resulting changes in the plant metabolism are examined along with any resulting new or changed traits (phenotype), taking into account that gene products through their interaction with the physiology of the host may cause multiple traits that may differ from the traits expressed in the host organism.

Unlike risk assessments for chemicals, there is not yet a fixed "cookbook recipe" for the identification of potential adverse effects related to a gene or sequence. Whether or not a particular gene or sequence may have the potential to cause adverse effects depends on the characteristics of the gene, of the gene product, of any resulting changes in the phenotype, of the receiving environment, and of the type of application.

In identifying potential adverse effects, the following types of questions are addressed on the basis of the case:

- Can the inserted gene or sequence cause the recipient plants to become more persistent in agricultural habitats or more invasive in natural habitats (weediness) with the related potential adverse effects of changes in management of weeds, changes on population level, or both in natural populations? An inserted gene may confer a selective advantage or a change in survivability.
- Can the inserted gene or sequence cause the recipient plant to be toxic, allergenic, or both to humans or animals?
- Can the inserted gene or sequence cause changes in susceptibility of the recipient plant or—after outcrossing—of other plants to pathogens, which in turn can cause the dissemination of infectious diseases and creating new reservoirs or vectors?
- Can the inserted gene or sequence cause negative effects on populations of nontarget organisms, including indirect effects on population level of, where applicable, predators, competitors, herbivores, symbionts, parasites, and pathogens?
- Can the inserted gene or sequence cause unintended effects on the target organisms (e.g., resistance development)?
- Can the inserted gene or sequence result in a change in management of the genetically modified crop plant that has a negative impact on the environment?
- Can the inserted gene or sequence cause changes in biogeochemical processes?
- Can the inserted gene or sequence cause other unintended side effects such as
  - the potential reduced effectiveness of an antibiotic used in medicine as a result of horizontal transfer of antibiotic-resistance genes?
  - the development of new virus strains owing to the introduction of viral sequences in a plant genome and possible recombination of genetic material?
  - potential insertion effects?

In this stage of the risk assessment it is important to consider the potential adverse effects that are scientifically conceivable on the basis of the gene characteristics involved regardless of whether it is likely that this effect actually would occur during the proposed activities. The question of likelihood will be addressed in the next stage of the risk assessment. In the process of identifying potential adverse effects it should also be remembered that such effects can be direct, indirect, immediate, or delayed[7]. Adverse effects may occur directly or indirectly through mechanisms such as

- the spread of the GMO(s) in the environment
- the transfer of the inserted genetic material to other organisms
- phenotypic or genotypic instability
- interactions with other organisms
- changes in management, such as agricultural practices

The identification of potential adverse effects to be considered in the risk assessment can be addressed in a way that is scientifically sound as well as transparent to the public. The scenario in which this potential adverse effect might occur should be described sequentially, that is, beginning with the causal steps that could culminate in the adverse effect. The scenario should begin with the trigger: What is the scientific reason to assume that a certain adverse effect may occur? The scenario should show the chain of causal events that may lead to its occurrence. As with all scenario writing, this is a creative process, which in this case also requires a rigorously scientific imagination.

It is also important to formulate clearly which potential adverse effect is being considered. For example, the mere mention of the "horizontal gene transfer" of an antibiotic resistance gene does not clarify the potential adverse effect. Transparency is established when the assessor identifies potential adverse effects of reduced effectiveness of an antibiotic used in medicine that might arise as a result of horizontal transfer of antibiotic-resistance genes to pathogenic micro-organisms. Sometimes it may be useful to indicate whether the adverse effect, should it occur, is deemed to be either severe or insignificant.

Although assessments are done on a case-by-case basis, information and analyses from previous assessments can be very useful. There are many such sources of existing knowledge and experience such as

- decision documents of earlier cases, which can be found on the Web sites described under topic 4c;
- search engines such as the SWISS-PROT/TrEMBL Full text search (http://www.expasy.ch/cgi-bin/sprot-search-ful) and the ICGEB database on risk assessment (http://www.icgeb.trieste.it/biosafety/rasm.html)
- OECD consensus documents on traits (http://www.oecd.org/ehs/cd.htm) and related documents (http://www.oecd.org/En/home/o,,en-home-528-nodirectorate-no-no-no-27,ff.html).

As was noted earlier, it is strongly recommended that the risk assessment be started systematically, focusing on each of the genes or sequences separately and listing for each gene or sequence any potential adverse effect or effects that the assessor may wish to consider in the risk assessment. Here too, a cover note has proven to be a useful tool. An example of such a cover note (worksheet B) is attached to this article.

Estimation of Likelihood—

Once a potential adverse effect has been identified for inclusion in the risk assessment, the next step is estimating the likelihood that the identified potential adverse effects will actually occur in the proposed application. This stage follows the same systematic approach. For each of the identified potential adverse effects of each of the inserted genes or sequences, an

estimate is made within the proposed application of the likelihood that particular potential adverse effect will actually occur. Here the term "estimation" is chosen, because, given the "nature of nature," exact numbers of the frequency with which something will happen in nature can rarely be given. Therefore, terms are used such as likely, unlikely, and negligible or effectively zero (or 'zero' for that matter, but many scientists are uncomfortable using the "zero" in the context of risk assessment).

The likelihood that a certain inserted gene or sequence will actually result in a potential adverse effect is influenced by many different factors such as the following:

- The characteristics of the inserted gene. For example, a gene that is not involved in toxicity of the donor organism is very unlikely to cause the recipient organism to be toxic. On the other hand, it is likely that a gene product known to be toxic for one insect, such as the endotoxins produced by *Bacillus thuringiensis*, will also be toxic for other closely related insects. Assumptions related to toxicity or allergenicity can usually be verified with the information presented in the request or dossier as in feeding studies.
- The characteristics of the recipient organism. For example, the potential for outcrossing with wild relatives is negligible for sterile plants or in regions where no relatives exist but is likely for fertile plants in an environment where wild relatives are present in the environment.
- The characteristics of the size or the scale of the application. For example, the likelihood of a genetically modified plant with a certain built-in pesticide resulting in the development of resistance by the target organism is negligible in a small-scale field trial but can be quite likely in a commercial application if no resistance management is applied.

Several tools are available that can provide useful information on the characteristics of recipient organisms such as

- the OECD consensus documents on the biology of plants (www.oecd.org/ehs/service.htm),
- the so called botanical files (De Vries et al. 1992, Van den Meijdan 1994)
- files on the biology of several crop species (see www.aphis.usda.gov/biotech)

In cases in which the estimation of the likelihood does not result in the conclusion "negligible" or "effectively zero", the risk assessment continues with the next step described in the next section. In cases in which the estimation of the likelihood does not result in a clear conclusion, it is sometimes recommended to proceed with the next step of the assessment by assuming a certain effect will occur. For example, rather than spending much time and effort to determine the frequency of outcrossing, it is assumed that if the plant can outcross, then it will outcross. The attention is then focused on the next step in the risk assessment, that is, the potential consequences of such a transfer.

Another example is the assessment of the possible transfer of antibiotic resistance genes from plant material to microbial organisms. In case there is no scientific consensus about the likelihood of the transfer from plant material to microorganisms, then it may help to continue the risk assessment by asking what the consequence would be if such a transfer would occur. (See next section).

Evaluation of the Identified Risks—

In the cases where a potential adverse effect has been identified and the estimation of the likelihood did not lead to the conclusion "negligible" or "effectively zero", the risk assessment proceeds to the next step, namely, the evaluation of that particular risk. Note that at this point the term used is "risk" instead of "potential adverse effect". Risk is the combination of a potential adverse effect and the likelihood of it[5] occurring. Here too, it is recommended that the assessor follow the same systematic approach as before. For each of the identified risks (i.e., the cases in which the likelihood of an identified potential adverse effect is not negligible or effectively zero) of each of the inserted genes or sequences, an evaluation is made of the actual consequence on a component of the environment.

It is important to differentiate between risks related to human health and risks related to the environment. Key issues in risks to human health are toxicity and allergenicity. For required toxicity data, experimental tests are often available. For allergenicity, a specific risk assessment, including specialized assays, is required because allergenicity can usually only be definitively assessed by patients who have the allergic reaction.[8]

For an evaluation of the potential consequence of possible toxicity or allergenicity, the type of application is taken into account. For applications such as small-scale field trials in which the material resulting from the field trial is not consumed by humans or animals, toxicity and allergenicity would generally be of no consequence. For large-scale and market releases, toxicity and allergenicity would be of consequence and would therefore need to be addressed. It is for this reason that, in requests for market approvals, the results of toxicity and allergenicity tests are usually included. Assessors should bear in mind that there is a difference in looking at toxicity in terms of food safety for which it is assumed that large quantities may be consumed frequently (i.e., scenarios in which even low levels of toxicity may have a consequence) and toxicity in the context of environmental safety for which the focus is on the effects of incidental consumption.

Evaluating the impacts that the introduction of a genetically modified plant may have on the environment is less straightforward for several reasons:

1. The different types of effects that can be considered such as weediness, susceptibility to diseases, effects on nontarget organisms, effects on target organisms, and changes in agricultural management differ markedly.
2. Agricultural and natural ecosystems are very dynamic systems in which many changes occur constantly.
3. Every agricultural activity has an impact on the environment in which it takes place. For example, a straightforward agricultural practice such as ploughing and tillage in general has a severe impact on the soil organisms. However, natural processes such as immigration of soil organisms restore these impacts usually quite quickly.

In order to evaluate the possible consequences of the introduction of a GMO in the context of these dynamic processes, the concept of a "baseline" plays an important role. The assessment of the transfer of antibiotic resistance genes from plant material to microbial organisms can serve to illustrate this. Apart from the discussion of whether or not it is likely that such genes present in decaying plant material can be taken up by bacteria so that the gene will still function in the bacterium, one could assess the consequences for a bacterial population that received the transgene.

For the previous case it is important to identify the baseline. What is the existing presence of antibiotic resistance genes in the soil population? It is known that certain antibiotic resistance genes, such as kanamycin resistance, are so abundantly present in the environment that any addition would theoretically make no measurable difference (i.e., would be of no consequence). Some other antibiotic resistance genes, on the other hand, are not present in the environmental isolates of relevant species at such high numbers, and in those cases a (hypothetical) transfer of antibiotic genes could have a measurable consequence such as on medically important micro-organisms. This example illustrates that the assessment of antibiotic resistance gene presence cannot be done in a generic way but depends on the type of antibiotic resistance involved.

Consideration of Appropriate Risk Management Strategies—

In the previous step of the risk assessment, whether the introduction of a GMO would have a measurable adverse impact in the background of the baseline of the existing situation was evaluated. In cases in which this is true, the risk assessment continues with the next phase, which is a consideration of whether the identified risk is acceptable or manageable,[9] that is, a consideration of appropriate risk assessment strategies.[10]

It should be emphasized that the term "acceptable" plays a role twice in the evaluation of a proposed activity with GMOs, but in different ways. First, it plays a role in this phase of the risk assessment when the risk management strategies that would be appropriate are considered. Second, it plays a role in the final decisionmaking when an identified risk for the environment or human health is compared and weighed against any potential benefits that the proposed activity may have for the environment or human health.

In this phase of the risk assessment, the question of whether risks are identified that require additional risk management measures is addressed and, if so, a risk management strategy is defined. This step should also be conducted in the systematic gene-by-gene and potential adverse effect by potential adverse effect way, as described previously. For cases in which a risk management strategy has been identified, the risk assessment "loops back" to the earlier steps in the risk assessment to check whether the proposed risk management strategies sufficiently reduced the likelihood or the consequences. This is why risk assessment is often called an iterative process. There are many different strategies for risk management of genetically modified plants, including reproductive isolation by removing of flowers, use of isolation distances or border rows, and reduction of the size or duration of an application. Annex 5 of the UNEP guidelines gives examples of risk management strategies.

Assessment of the Overall Potential Impact: Conclusion—

After the systematic gene-by-gene assessment described in the previous steps, a broader and more holistic approach follows whereby the potential adverse effects of the genes together are evaluated with a view to possible synergistic effects. Finally, the overall environmental impacts are evaluated by placing any identified risks in the context of risks posed by the nonmodified recipients and by taking into account any beneficial effects the proposed activities with GMOs may have on the environment.

Synergistic Effects

New traits may enhance or suppress each other. This may have effects on the overall behavior of the genetically modified plant. This is why after the systematic gene-by-gene approach two more questions are considered in the risk assessment focusing on the GMO as a whole. The first question is, Do the introduced genes or traits have characteristics that may enhance the effect of the GMO in the environment? For example, a plant with one newly introduced abiotic stress resistance trait, such as drought resistance, may behave differently than a plant with several different abiotic stress resistance traits. Whether this is the case depends on the type of traits introduced and on the biochemical pathways involved. The second question is, How does the GMO behave in practice? For this part of the assessment, data obtained from greenhouses, field trails, and attempts to market the GMO in other countries are often included in the request. Assessors should be aware that, although the GMOs that have been developed to date are usually relatively simple constructs with one or sometimes two new traits, more complex cases will likely be offered for assessment in the near future.

Overall Environmental Impact—

In the last step of the risk assessment, the overall environmental impact is evaluated. Note that at this point there is a change in terminology. Although in the previous steps the focus was on potential adverse effects, in this last step the focus is on the overall environmental impact, that is, consideration and comparison of potential adverse effects as potential beneficial effects on the environment. This is done by placing any risks identified in the context of risks posed by the nonmodified recipients and taking into account any beneficial effects the proposed activities with GMOs may have on human health or the environment.

The risk assessment usually ends with a summary or a conclusion. It should be emphasized that this is not the same as the final decision. The summary or conclusion will "spell out" the type of risks that the proposed activity with GMOs may have, including, where appropriate, proposed risk management strategies. The summary also describes any potential beneficial effects the proposed activity with GMOs may have on the environment or human health. It is usually up to the decisionmakers to weigh these potential risks and benefits.

Endnotes

1 http://www.unep.org/unep/program/natres/biodiv/irb/unepgds.htm
2 http://www.biodiv.org/biosafe/protocol/protocol.html
3 http://europa.eu.int/eur-lex/en/oj/2001/l10620010417en.html
4 In some countries and documents the terms "potential harm" or "hazard" are used.
5 In some documents the term "host organism" is used. Both these terms refer to the organism in which genetic material from a donor organism is introduced.
6 With the "other relevant inserted sequences", reference is made to inter alia (a) open reading frames (ORFs) that code for proteins (i.e., that encode a protein in the host from which the sequence has been derived); (b) promoter, terminator, and enhancer sequences; and (c) sequences that code for RNA transcripts that are not functional in translation (e.g. anti-sense RNA).

[7] For example, Directive 2001/18/EC describes these terms as follows:
- "Direct effects" refer to primary effects on human health or the environment that are a result of the GMO itself and do not occur through a causal chain of events.
- "Indirect effects" refer to effects on human health or the environment occurring through a causal chain of events, through mechanisms such as interactions with other organisms, transfer of genetic material, or changes in use or management. Observations of indirect effects are likely to be delayed.
- "Immediate effects" refer to effects on human health or the environment observed during release of the GMO. Immediate effects may be direct or indirect.
- "Delayed effects" refer to effects on human health or the environment that may not be observed during the release of the GMO but become apparent as a direct or indirect effect either at a later stage or after termination of the release.

[8] See also http://www.who.int/fsf/GMfood/ConsultationJan2001/report20.pdf made after the 2nd Joint FAO/WHO Consultation on Foods Derived from Biotechnology, Allergenicity of Genetically Modified Foods, 22–25 January 2001, Rome, Italy.

[9] See for example, annex III of the Biosafety Protocol.

[10] See for example, annex II of Directive 2001/18.

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WORKSHEET A (Cover note)

Applicant (dossier number)

……

Type of use: field trial / commercialisation.

Host plant: ……

- **Potential for outcrossing**
  - **With wild relatives ……..**
  - **With cultivated relatives ……**
- **Potential for persistence in the environment ……..**

Inserted genes and sequences:

- ……..
- ……
- ……..
- ……

WORKSHEET B (ASSESSMENT PER GENE)

Dossier/Applicant: ……
Type of use: ……
Plant: ……
Gene: ……

Potential adverse effect	Estimation of likelihood	Evaluation of identified risk	Consideration of risk management	Assessment of overall impact
OVERALL CONCLUSION FOR THIS GENE:				

Session 2: The Practice of Environmental Assessment

Session 2B—Risk Management Issues

Resistance-Breaking Pathogen Strains and Identification of Mitigation Measures

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Abstract

Traditional pathogen resistance genes usually are effective for only a short time. The breakdown of resistance is an expected consequence of the release of resistant varieties. Durable resistance remains a goal that is yet to be achieved for most plant–pathogen systems. Traditional pathogen resistance genes are also usually strain specific. Varieties are released with the recognition that they are not resistant to all strains and that new strains existing in areas where a variety has not been tested might have the capability to overcome the resistance gene(s) possessed by the variety. Transgenic pathogen resistance is expected to exhibit the same characteristics as traditional genes in terms of limited time of use and strain specificity.

The most extensive experience to date has come from transgenic virus-resistant crops because these have already been commercialized. Evidence from the past experimental literature has revealed the strain specificity of engineered virus resistance, which parallels that of traditional virus resistance. Strain specificity has been noted for currently commercialized transgenic squash as well. Consequently, the detection of a field isolate that appears to overcome coat protein-mediated resistance in commercial transgenic squash is consistent with expectations. It is not known whether this strain has appeared as a consequence of selection caused by the presence of the resistant variety or whether it is an established, preexisting resistance-breaking strain.

The plant breeder's response to strains that overcome resistance genes has typically been to seek new, more effective genes that can be bred into new resistant varieties. The availability of transgenic strategies to incorporate resistance to new strains could make this approach more effective. Continued commercial use of transgenic strategies to mitigate the effect of resistance breaking pathogen strains will require the rapid and cost effective introduction of transgenes. Regulatory policies that enable these conditions to be met will ensure the continued development of pathogen resistance traits in transgenic plants.

Introduction

The development of crops resistant to pathogens is one of the most important applications of crop genetic engineering—particularly for developing countries. Pathogens destroy a significant portion of crop output and are a major cause of the variability of crop yields from year to year. Resistance genes have been introduced in many crops, and the development of pathogen resistant varieties is an ongoing goal of traditional plant breeding.

The extensive history of breeding for pathogen-resistant varieties has shown at least two characteristics of traditional resistance genes:

1. Resistance genes are usually not durable; their effectiveness against target pathogens is often short-lived. One reason for this phenomenon is that, for many pathogens, the number of generations per unit time is significantly greater than that of the host. This fact provides the pathogen with a greater opportunity to generate mutations for overcoming resistance. In other words, the pathogen has the potential for evolving more rapidly than the host.

2. Resistance genes are usually strain specific. A resistance gene rarely confers resistance to all pathogen genotypes.

Results

Examples of Traditional Fungal Resistance Genes

Traditionally bred fungal resistance has often proven to lack long-term effectiveness. For example, the wheat cultivar gene, was resistant to the fungus, *Mycosphaerella graminicola* when it was released. However, after only 3 years of use, the resistance in this cultivar deteriorated (Cowger et al. 2000). In beans, the pinto bean cultivar pinto olathe, containing the rust resistance gene Ur-6 was released in 1981. The resistance in this cultivar was overcome by the target pathogen, *Uromyces appendiculatus*, within 10 years (Steadman et al. 2001). Finally, data from a recently completed 2-year study in Ohio indicate that the soybean resistance genes Rps1a, Rps1b, Rps1c, Rps1k, Rps3a, and Rps6 conferring resistance to specific strains of *Phytophthora sojae*, are losing effectiveness against this economically important pathogen (Pollock 2001).

The multiplicity of resistance genes in soybean highlights the second characteristic of traditional genes mentioned above, namely, their strain specificity. Although the Ohio survey indicates that the resistance genes studied are losing effectiveness against strains to which they conferred resistance in the past, these genes were not effective against all strains in the first place. For example, Rps1, Rps3, Rps4, Rps5, and Rps6 of the soybean can be defeated by race 7 of *Phytophtora sojae* (Young et al., 1994).

Another example of strain specificity is the apple Vf gene, which confers resistance to *Venturia inaequalis* races 1–5. This resistance gene has been found to be overcome by *V. inaequalis* race 6 in some apple varieties (Parisi et al. 1996). Another study indicates that other resistance genes residing in apples confer varying degrees of resistance to different *V. inaequalis* field isolates (MacHardy et al. 2001).

It is important to note that the existence of a multiplicity of strains of this and other pathogens makes it difficult to distinguish between selection for a mutant that is able to overcome the resistance and the selection of an already established ("preadapted") strain that might predominate in a particular geographic location and then spread to a new location because resistance genes eliminate competing strains. Indeed, these two possibilities are simply two sides of the same coin.

Examples of Traditional Bacterial Resistance Genes

Traditional bacterial resistance genes follow the same pattern as that described for fungal resistance genes. For example, the resistance gene Rb in cabbage, conferring resistance to race 1 of *Xanthomonas campestris* pv. *campestris*, can be overcome by race 0 of the same pathogen, thus demonstrating the strain specificity of this particular resistance gene (Dzhalilov et al. 2000). In a field experiment illustrating the evolution of resistance breaking as well as strain-specificity, Leach et al. (2000) showed that in the case of rice possessing the resistance R genes Xa4, Xa10, or Xa7, which confer resistance to *Xanthomonas oryzae* pv. *oryzae* several new strains could be selected that overcame these resistance genes. All selected strains were capable of overcoming Xa4 resistance, whereas all strains derived from one specific clonal lineage overcame resistance R gene Xa10, and only a few strains of that same lineage overcame resistance R gene Xa7.

Examples of Traditional Virus Resistance Genes

As with fungal and bacterial resistance, virus resistance genes are also eventually overcome. Furthermore, as with fungi and bacteria, multiple strains of virus exist. Virus resistance genes are not effective against all of these strains.

Aside from the potential that several rounds of viral replication (several "generations") will occur for each generation of host plant, thus providing viruses with a better opportunity for generating diversity that can include resistance-breaking mutants, the replicating mechanism of ribonucleic acid (RNA) viruses in particular affords additional potential for generating high diversity. First, RNA-dependent RNA polymerase (RDRP) possesses no editing function. This lack of editing leads to a high mutation rate among RNA viruses. For example, the mutation rate for tobacco mosaic virus (TMV) has been calculated to be 0.15 per genome (García Arenal et al. 2001). Thus, if the number of viral particles per cell is 10^6 (a conservative estimate), a potential exists for at least 10^4 mutants per cell in an infected plant. On the basis of the number of infected cells within a single plant, there is a high potential for the generation of mutants, some of which might be able to defeat a resistance gene.

In addition to the high error rate it causes during RNA replication, RDRP also exhibits a high frequency of strand switching during this process, thus producing a high recombination rate. Estimates range from 10^{-4} to 10^{-8} per nucleotide (García-Arenal et al. 2001). For a

member of the Potyviridae, with an average of 10^4 nucleotides per genome, and again on the basis of the conservative estimate of 10^6 molecules per cell, between 10^2 and 10^6 recombination events per cell can occur. This potential is borne out well by the observation that RNA molecules arising from infectious transcripts of cloned viral cDNA are highly variable (Schneider and Roossinck 2000, Ambrós et al. 1999, Kearney et al. 1999, Palukaitis and Roossinck 1996, Kurath and Dodds 1995, Kurath and Palukaitis 1990, Kurath and Palukaitis 1989).

Examples of the consequence of this variability in viral genomes include the following:

1. The use of tomato mosaic virus resistance in tomatoes selected for mutants that overcome the resistance gene (Pelham et al. 1970),
2. The lettuce gene mo12 conferring resistance to lettuce mosaic virus, is overcome by one strain, LMV-E (German-Retana et al. 2000),
3. The tomato spotted wilt virus (TSWV) resistance gene Sw-5 in tomatoes is resistant to isolate D but susceptible to isolate A (Moyer et al. 2001),
4. The Cry locus in cowpeas confers resistance to CMV–Y but is overcome by CMV–L (Karasawa et al. 1999).

Because there has been greater success in engineering effective resistance against viruses than against either fungi or bacteria, there is a better opportunity to compare the performance of these engineered resistances to viruses with traditional resistance genes. With respect to the two characteristics mentioned thus far, the performance of transgenic resistance is identical to that of traditional resistance genes. First, as with traditional virus resistance, transgenic resistance is strain specific. For example, the coat protein gene of papaya ringspot virus (PRSV) confers resistance to the Hawaiian strain (PRSV–HA) in transgenic papaya but not to strains from Mexico, the Bahamas, Florida, Australia, Brazil, China, Ecuador, Guam, Jamaica, and Thailand (Gonsalves and Slightom 1993). This strain specificity is also observed in transgenic plants engineered with genes other than the coat protein gene. Transgenic plants expressing the nucleocapsid protein gene (N gene) of the BL strain of TSWV are resistant to that strain but not to the Arkansas, 10W Pakchoy, or Begonia strains (Pang et al. 1992). Finally, resistance to cucumber mosaic virus (CMV) conferred by the expression of a replicase gene was shown to be overcome by a genotype belonging to CMV subgroup I (Hellwald et al. 1999). Selection specifically for a genotype that can overcome resistance has been shown expeimentally by Moyer et al. (1999), who were able to select a resistance-breaking genotype that could overcome transgenic N-gene resistance against TSWV.

Strain specificity is true of virus resistance genes now in commercialization. Initial work with the CMV–C coat protein presently in commercial virus-resistant squash (*Cucurbita pepo*) hybrids containing the constructs ZW20 or CZW3 (marketed by Seminis Vegetable Seeds) was shown in a tobacco model system to be resistant to another strain in the same subgroup (CMV–Chi) but not to a strain in the other subgroup (CMV–WL) (Namba et al. 1991, Quemada et al. 1991). More extensive studies of the coat protein genes in squash itself corroborated the results in tobacco. For example, transgenic line ZW20 was challenged with various isolates of zucchini yellow mosaic virus (ZYMV). The results of these experiments, summarized in table 1, show that at least one isolate is capable of overcoming the transgenic resistance. A study of the transgenic line CZW3 summarized in table 2 similarly shows the strain specificity of resistance against CMV, ZYMV, and watermelon mosaic virus 2 (WMV2).

Table 1. The resistance or susceptibility of transgenic squash line ZW20 to different geographic isolates of ZYMV.

ZYMV isolate	Reaction
California	Resistant
Connecticut	Resistant
Florida	Resistant
Egypt	Resistant
China	Susceptible

Table 2. The resistance or susceptibility of transgenic squash line CZW3 to different geographic isolates of CMV, WMV2, and ZYMV.

Virus	Isolate	Reaction
CMV	Carna-5	Resistant
	New York	Resistant
	China	Resistant
	California	Susceptible
	V33	Susceptible
WMV2	California	Resistant
	New Jersey	Resistant
	New York	Susceptible
ZYMV	California	Resistant
	Connecticut	Resistant
	Florida	Resistant
	Egypt	Resistant
	China	Susceptible

These studies of field isolates in greenhouse inoculations therefore lead to the prediction that other virus genotypes capable of defeating the transgenic resistance will be encountered upon deployment of transgenic squash over an increasingly wide area. This prediction has apparently been fulfilled after only a few years of commercialization. Figure 1 shows the results of inoculation of a transgenic hybrid, Destiny III, with a virus strain isolated from an infected field of transgenic squash growing in southern Illinois. The virus, which appears to be an isolate of WMV2, is capable of overcoming the resistance conferred by the WMV2 coat protein gene.

Figure 1. Transgenic hybrid Destiny III showing symptoms after inoculation with a southern Illinois isolate of WMV2.

Discussion

The evolution (or detection) of strains that can defeat specific viral resistance genes was not unexpected by the developers of transgenic squash and should be expected by developers of future crops engineered to be resistant not only to viruses but other pathogens as well. To mitigate the breakdown of resistance, a strategy of pyramiding genes was foreseen and should be incorporated into the plans for maintaining any long-term benefits of transgenes against pathogens. Breeders of traditional resistance genes have followed this strategy, but the use of transformation technology has the potential for making it an even more effective means of developing crops with enhanced disease resistance.

As applied to coat protein-mediated resistance, the pyramiding strategy is simple: one has merely to isolate the coat protein gene(s) of new strains that are encountered and add them via transformation to the array of resistance genes already present in a plant. This strategy allows the incorporation of genes that may be modified based on new information, thus adding more effective and broader resistances. More important, this strategy allows the incorporation of resistance gene constructs that better address safety concerns such as recombination and transencapsidation.

The pyramiding strategy also permits incorporation of genes that confer resistance not only against new viral strains but also against new virus problems that might arise either because of expansion of cultivation into an area where new viruses are encountered or because new viruses take the place of those that have effectively been eliminated by the resistance genes. A similar approach can be envisioned for genes that might be deployed in the future against fungal or bacterial disease.

The effective execution of a gene-pyramiding strategy requires that at least two conditions be met: (1) the introduction of new transgenes must be sufficiently rapid to respond effectively to new strains or new viruses, and (2) the incremental cost of introducing new genes should decrease, to allow their introduction to be economically feasible. Neither of these conditions exist today—especially for the "minor crops"—that is, the crops other than soybeans, corn, and cotton. Consequently, disease resistance is not being pursued vigorously by industry,—particularly that segment concentrating on "minor crops". Data for the United States from the Information Systems for Biotechnology (ISB) field test database (http//www.isb.vt.edu/cfdocs/fieldtests1.cfm) for the period 26 November 2000 through 25 November 2001 provide evidence for the low level of industry activity. Figure 2 shows the proportion of notifications and field test applications for all pathogen-resistant transgenic crops filed by the public sector and by industry. The majority of activity appears to be in the public sector. This disparity of activity is even greater when corn and soybeans are eliminated from the data (no notifications or applications for disease-resistant cotton were filed during the period studied). Figure 3 shows that for crops other than soybeans and corn, roughly 75-percent of the development activity is being carried on in the public sector. This same proportion is seen for virus-resistant minor crops (figure 4). These statistics signal that the industrial sector, which is more sensitive than the public sector to the costs versus economic gain of developing a crop, realizes that the cost and time required to develop and maintain the effectiveness of transgenic pathogen resistance are often not economically feasible.

Figure 2. The proportion of notifications or field test applications for all pathogen resistant plants filed by the public sector versus industry for the period 11/26/00-11/25/01.

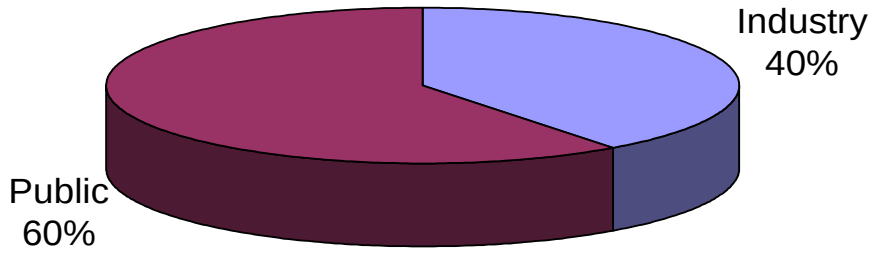


Figure 3. The proportion of notifications or field test applications for pathogen resistant plants, except corn and soybean, filed by the public sector versus industry for the period 11/26/00-11/25/01.

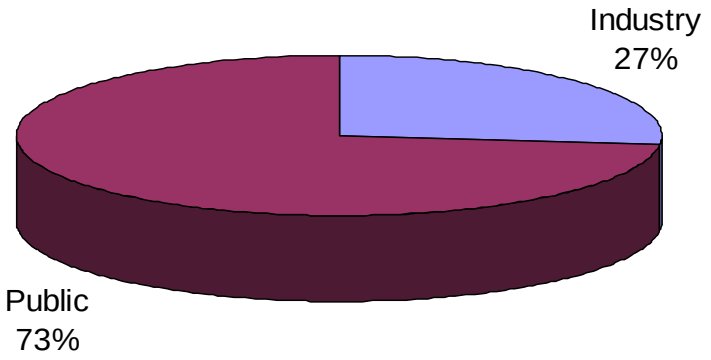
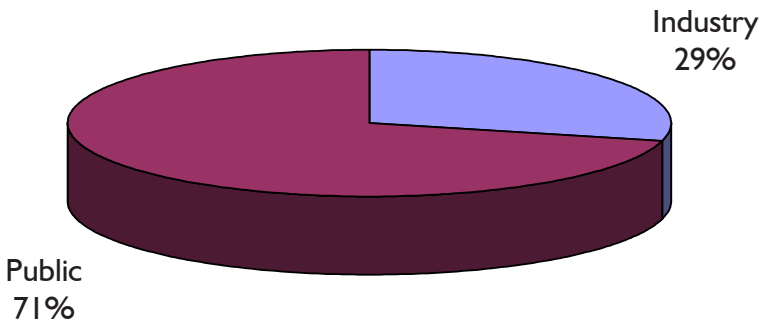


Figure 4. The proportion of notifications or field test applications for virus resistant plants, except corn and soybean, filed by the public sector versus industry for the period 11/26/00-11/25/01.



The cause of the cost and time problems does not appear to be technical. The ability to transform various crop species increases each year, and the efficiency of this technology likewise improves. The involvement of public institutions in the United States and of publicly funded research institutes in developing countries is testimony to the relatively low cost involved in accomplishing the basic technical tasks required to develop and deploy pathogen-resistant crops. Rather, the primary constraint appears to be the regulatory hurdles that prolong the development time and increase cost.

Conclusions

Because publicly funded institutions in the United States and other parts of the world appear to be the principal means by which pathogen-resistant crops will be developed, the cost of fulfilling regulatory requirements must be considered in any plans to apply this technology. Public institutions must recognize that they will have to bear those costs in addition to those they have already borne for the technical development of the crop. In many cases, given the current regulatory framework, the regulatory costs could account for the more significant portion of the total project funds.

Funds are rarely set aside in public projects for fulfilling regulatory requirements. If the regulatory framework requires excessive expense and development time, so that transgenic pathogen resistance cannot be deployed by even publicly funded institutions, then the benefits of this technology will be lost to those who are in the most critical need of this technology—the developing countries.

Developed countries can better afford to implement traditional solutions to crop disease. If transgenic pathogen resistance were not developed, farmers would be able to return to their reliance on traditional resistance genes; they could shift areas of production to new disease-free areas; and they could grow different crops not susceptible to prevailing diseases. Furthermore, farmers could continue their reliance on traditional chemical means of control: fungicides, antibiotics, and insecticides or other chemicals to kill or inhibit disease vectors. The harm of some of these alternatives, especially chemicals, has been clearly established—particularly by data presented at this conference. The real potential for transgenic technology to reduce this demonstrated harm needs to be weighed against its postulated risks.

Acknowledgments

Dr. Rosario Provvidenti of Cornell University conducted most of the strain inoculations shown in Tables 1 and 2. The author also wishes to acknowledge the help of Dr. Alan S. Walters of Southern Illinois University, who located virus-infected transgenic squash fields in Illinois.

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Young, B. A., St Martin, S. K., Schmitthenner, A. F., Buzzell, R. I. and McBlain, B. A. 1994. Absence of residual effects of defeated resistance genes on phytophthora rot of soybean. Crop Science 34, 409-414. Table 1. The resistance or susceptibility of transgenic squash line ZW20 to different geographic isolates of ZYMV.

Risk Management from a Developing Country's Perspective

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Abstract

Risk assessment and management in South Africa is the responsibility of the National Department of Agriculture under the Genetically Modified Organisms (GMO) Act. The Minister is advised by an executive council consisting of officers from the six departments involved. A Registrar administers the Act, and an advisory committee, consisting largely of academics experienced in working with living modified organisms, considers all applications for releases and advises the registrar. An example of risk assessment and management in the case of cotton resistant to cotton bollworms will be given. In addition, an example of trade barriers to export from an African country to Europe will be discussed. Risk assessment and management legislation in other sub Saharan African countries will be mentioned. Finally, research needs to improve risk assessment and management will be presented. These include the development of insect resistance, effects on nontarget insects and on other animals and birds, socioeconomic impacts, and environmental benefits.

Introduction

This paper will deal mainly with risk assessment and management in South Africa. Before the introduction of the Genetically Modified Organisms (GMO) Act in 1997 and its implementation in 2000, living modified organisms (LMOs) were handled by the South African Committee on Genetic Experimentation (SAGENE). This was a governmental statutory body that handled requests for contained use, field trials, or general releases of LMOs. Although compliance with SAGENE regulations was voluntary, no known violations were perpetrated. The author was a member and former chair of this committee. After the 1994 elections in South Africa, the Government decided that legislation was required to enforce compliance with regulations. This paper will deal with risk assessment and management after the implementation of the GMO Act.

Discussion
South Africa

The GMO Act was passed by the South African parliament on 23 May 1997. However, it took until November 1999 for the regulations to be approved. Hence, the Act was only implemented at the beginning of 2000. The Act stipulates that there will be an Executive Council, a Registrar, and an Advisory Committee. Their composition and functions are as follows:

Executive Council

The executive council consists of one officer from each of the National Departments of Agriculture (which administers the Act), Arts, Culture, Science and Technology, Environment, Health, Labour, and Trade and Industry. These officers should be knowledgeable of the implications of the GMO Act with respect to their individual departments. The Executive Council decides on the issue of permits (on the basis of advice from the Advisory Committee via the Registrar), oversees the office of the Registrar, is involved in intercountry liaison, advises the Minister of Agriculture, and ensures law enforcement under the Act.

Registrar

The Registrar, who is appointed by the Executive Council, is responsible for administering the Act. He or she issues permits, acts on contraventions of the Act, appoints inspectors to do site inspections, and ensures that the conditions of permits are complied with.

Advisory Committee

The advisory committee consists of up to eight members knowledgeable in the field of GMOs. It includes two persons from the public sector with knowledge of ecology and GMOs. Among the areas of expertise represented are biochemistry, biotechnology, cell biology, ecology, entomology, microbiology, molecular biology, and plant pathology. The functions of the advisory committee are to advise the Minister of Agriculture and the Executive Council (via the Registrar) of the environmental impacts of introducing GMOs; the contained use, import, and export of GMOs, and regulations and guidelines concerning all of these.

Figure 1 shows the process followed when the Registrar for Genetic Resources receives an application for a trial or commercial release. He or she chooses a member of the Advisory Committee to chair an ad hoc subcommittee to review the application. This Chair chooses two or three members of the South African scientific community skilled in the particular application under consideration from a list of names supplied by the Registrar for this purpose. All relevant documentation is supplied to the subcommittee, which is required to submit its recommendations within 2 months. These recommendations are summarized by the subcommittee Chair, who then submits a report to the Registrar. This report is sent to all members of the Advisory Committee for comment. The Registrar then compiles a final report for submission to the Executive Committee.

Table 1. Risk assessment of Bt cotton in South Africa

Environmental Impact	**Finding**
• Effect on sustainable agriculture	• Positive; less input and 'peace of mind' management
• Effect on soil, water, and air	• Positive; less pesticide load
• Socio-economic effects	• Benefits rural, small scale farmers
• Stability	• Stable for 10 years worldwide
• Other specific concerns (e.g., development of insect resistance)	• Compulsory integrated pest management to minimise development of resistance
• Spread of gene (pollen, seed, or vegetative propagation)	• No negative impact
• Out crossing to weeds or natural flora	• No compatible local relatives; not invasive
• Effect on insects, birds, and other consumers	• Only lepidopterans affected; renews biodiversity (insects and birds) in and around crops due to reduced use of insecticides

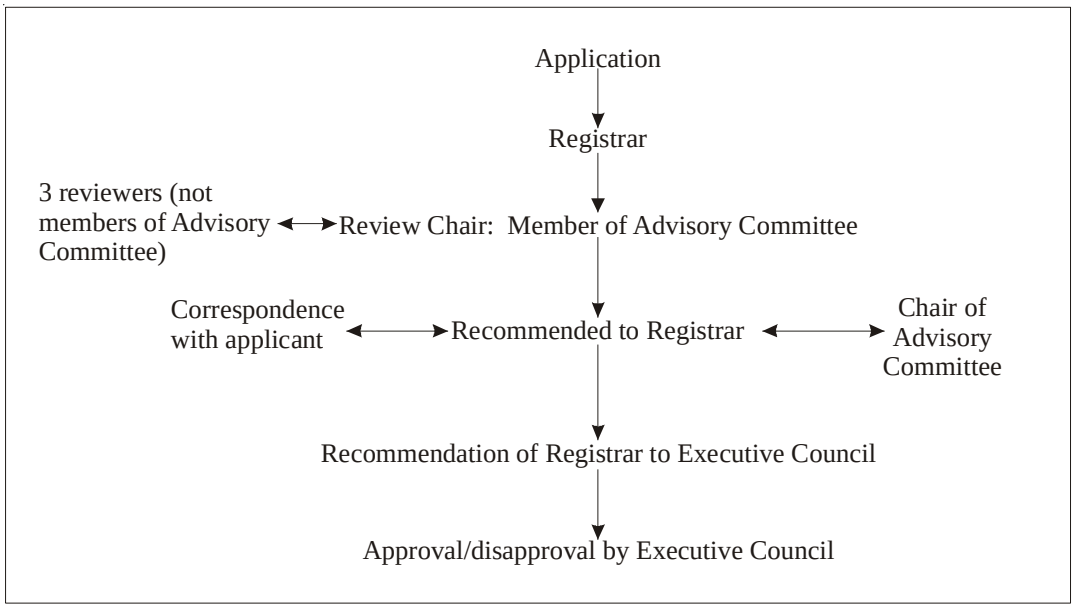

Figure 1. The process followed when the Registrar for Genetic Resources receives an application for the trial or commercial release of a LMO

Before an applicant can submit a request to the Registrar for a field trial or commercial release of a GMO, public notification has to be given in three different newspapers in the geographical area affected. Copies of such notifications have to accompany the application. Comments or objections are submitted by the registrar to the Executive Council, which will take these into account when deciding whether or not to award a permit. It is at this stage that socioeconomic impacts of such permits are considered.

Should the Executive Council approve a permit, the Registrar appoints one or more inspectors to ensure that the trials are carried out in accordance with the GMO Act. Inspectors maintain records and issue warrants for violations of the Act. The inspectors conduct routine and surprise inspections.

Organizations or companies conducting the trials are required to ensure that measures are taken to avoid adverse impacts on the environment, and they are responsible for any damages. Conviction of offenses carries penalties, including fines or imprisonment.

A summary of the applications for trial releases, commercial releases, and commodity imports in South Africa is shown in figure 2.

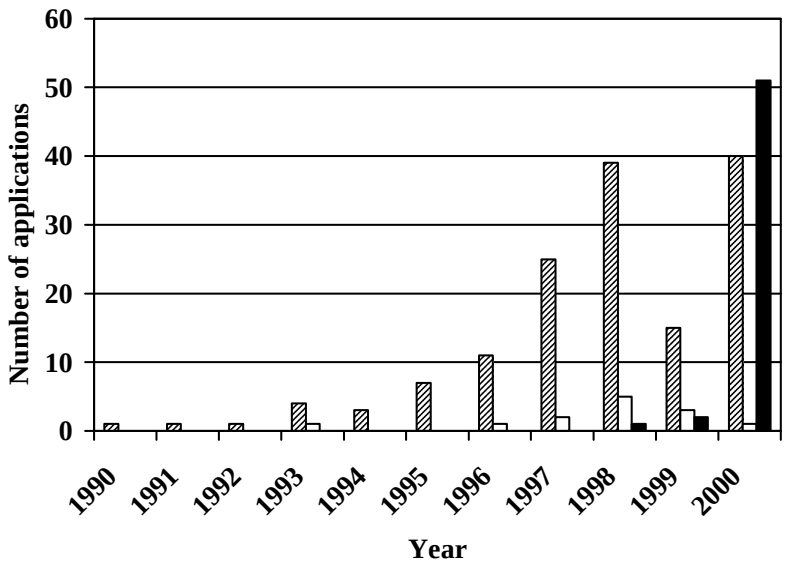

Figure 2. Applications for trials and releases in South Africa from 1990 to 2000. ▨ trial releases; □ commercial releases; ■ commodity imports

Risk Assessment in South Africa

Risk assessments and risk management are currently both the responsibility of the Department of Agriculture. It is hoped that in time the Department of the Environment will become more closely involved. An example of risk assessment leading to risk management is shown in table 1 for cotton resistant to cotton bollworm species (*Helicoverpa armigera, Diperopsis castanea, Erias biplagar* and *E. insulana*). This crop expresses the gene encoding the *cry*1Ac gene of *Bacillus thuringiensis* and is known as *Bt* cotton.

As a result of the preceding risk assessment, the following risk management procedures are being implemented:

The Development of Bollworm Resistance to the Bt toxin—

Commercial farmers will plant the required percentage of non-*Bt* cotton to prevent the development of insect resistance. Originally it was considered feasible to sell small-scale farmers a mixture of non-*Bt* and *Bt* cotton to provide suitable refuges in situ. However, data presented by Janet Anderson of the U.S. Department of Agriculture at this conference showed that this could, on the contrary, speed up the development of insect resistance. Instead, a procedure is recommended whereby a group of farmers join to form a consortium and together set aside a given area of land in which to plant non-*Bt* cotton in order to provide the required refuges.

Effects on Nontarget Insects and Other Animals—

An international research grant has been applied for to determine the effects that *Bt* cotton might have on nontarget insects. This research will be carried out among both small-scale and commercial farmers.

Socio-economic Impacts—

Ismael et al. (2001) recently published a study of the socioeconomic impacts of growing Bt cotton by small scale farmers in South Africa. They showed that farmers who adopted the *Bt* cotton variety in the 1998 and 1999 seasons benefited from the new technology according to all the measures used. Average yield per hectare and per kilogram of seed was higher for adopters than for nonadopters. The increase in yields and reduction in chemical application costs outweighed the higher seed costs, and thus gross margins were also considerably higher for adopters in the second season. This was a bad year owing to unusually heavy rainfall, and the *Bt* adopters suffered far less fall in yields than those who did not adopt.

Because yields and gross margins are only partial measures of efficiency in that they fail to take account of inputs such as labor, the preceding data were supplemented with other studies. These found that *Bt* cotton adopters were considerably more efficient than those who used non-*Bt* varieties. For 1998 the adopters averaged 88 percent efficiency compared with 66 percent for nonadopters. The relative numbers for 1999 were 74 percent and 48 percent.

A similar risk assessment was carried out for *Bt* maize grown in South Africa. At present this is only yellow maize used predominantly for animal feed. Risk management scenarios are much the same as for *Bt* cotton except for the following economic implications. Namibia exports most of its beef to Europe and imports almost all its maize feed from South

Africa. Europe will not accept any beef from Namibia fed with GM maize. One of the reasons for this is that GM maize carries a gene coding for antibiotic resistance. This, however, is a spurious argument, for the *Bt* maize grown in South Africa does not carry an antibiotic resistance gene. Therefore, Europe is excluding Namibian beef solely on the basis of trade barriers.

Sub-Saharan Africa

South Africa is currently the only country in Africa with GMO legislation in place. However, several countries have drafted legislation, and these are in various phases of implementation. These countries include Namibia, Zimbabwe, Zambia, Kenya, Uganda, Cameroon, Nigeria, and Egypt. Geneticaly modified crops trials are, however, underway in Zimbabwe, Zambia, Kenya, Uganda and Egypt.

Conclusions

The situation in South Africa is reasonably acceptable. However, we need research into the following:

- Insect resistance
- Effects on nontarget insects
- Effects on other animals and birds
- Socioeconomic impacts
- Environmental benefits.

The situation in other African countries is quite variable, and they need support to develop biosafety guidelines and regulations for the import, trial, and commercial releases of LMOs.

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Current Status of Biosafety Framework in Brazil

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Biodiversity, a resource that has proven essential for human survival, comprises the wealth of organisms that are a source of food, medicine, and shelter among other essentials. The economic importance of biodiversity has significantly increased with the development of modern biotechnology because sexual barriers have been bypassed, and thus genes discovered in diverse biota can be expressed in genetically modified organisms (GMOs). Brazil is a country rich in genetic resources with its diverse ecosystems, harboring close to 20 percent of the planet's species and the highest number of plants and amphibians besides abundant species of birds, reptiles, and mammals (Groombridge 1992).

In 1992, Brazil hosted the Rio Conference (UNCED) when Agenda 21 and the Convention on Biological Diversity (CBD) were signed, international instruments which were later ratified by 170 countries. The CBD emphasizes the preservation and sustainable use of biodiversity and also recognizes the state's sovereign right to its own genetic resources and the share of benefits generated by the use of biodiversity in a fair and equitable way. The concept of safe use of biotechnology is stressed in the text of the CBD in article 8 (g) regarding the need to regulate, manage, or control the use and release of living modified organisms (LMOs) resulting from modern biotechnology. The focus is on those LMOs that are likely to have adverse effects on the conservation and sustainable use of biodiversity, but risks to human health are also taken into account. The intentional transboundary movement of LMOs is addressed in article 19 (3) of the CBD in which the need to develop a protocol setting appropriate procedures for the safe transfer, handling, and use of LMOs that may have adverse effects on biodiversity is stated. Such a protocol was finalized and adopted in Montreal in January 2000, and it is known as the Cartagena Protocol.

Brazil is a CBD member State, and it has adopted national policies toward the conservation of biodiversity and the sustainable use of genetic resources. Biosafety policies have been addressed by the establishment of a legal regulatory framework. Significant investment is being made in capacity building, biotechnology research, and development programs. The country participates in the discussions for the implementation of the Cartagena Protocol, although it has not yet ratified the instrument. In this paper we report the main features of the Brazilian Legal Biosafety Framework and make a brief evaluation of the operability of the system and the current status of genetically modified (GM) crops.

National Legal Biosafety Framework

In Brazil, a Biosafety Legal Framework has been in place since 1995 (Law 8,974/95, Decree 1,752/95), complemented by other legal instruments (MP 2,237–9/01 and Norms) that set the standards for controlling the use of genetic engineering techniques in the construction, cultivation, manipulation, transportation, marketing, use, release, and disposal of GMOs with the objective of protecting the life and health of humans, animals and plants, as well as the environment. All activities and projects, including scientific research and industrial production, are subject to regulation under such a framework. Activities with GMOs can only be performed by legally established institutions, not at the individual level. The Biosafety Law forsees, in case of non-compliance, the application of fines and penalties. Besides the specific Biosafety legislation, the Brazilian model also includes a harmonized approach with legal instruments, such as those originating in the inspection agencies of the Ministries of Agriculture, Health, and Environment. The competent authorities from other branches of government have to comply with the technical report originating in the National Technical Biosafety Committee (CTNBio), elaborated on a case-by-case basis.

Features of the National Technical Biosafety Committee (CTNBio)

The National Technical Biosafety Committee (CTNBio) is a Federal body consisting of 18 full members and their alternates with the following representation: 8 scientists presently working with biotechnology (2 in human sciences, 2 in animal sciences, 2 in plant sciences, and 2 in environmental sciences); representatives from the following ministries: Science and Technology (1), Health (1), Environment (1), Education (1), Foreign Affairs (1), and Agriculture, Livestock, and Supply (2); representative of an agency for the consumer's defense (1); a representative from the biotechnology business sector (1); and a representative from an agency for worker's health protection (1).

National Technical Biosafety Committee (CTNBio) members are designated by the Minister of Science and Technology from a short list recommended by the members of the Committee and based on recommendations received from scientific, public or private institutions and associations, or, in case of representatives from other ministries, by the respective minister of that organ. The Chair of the Committee is designated by the Minister of Science and Technology. The members have a 3-year mandate and can be nominated for another term. CTNBio deliberates with a minimum quorum of two-thirds of its members. Board members are not paid to work for the Committee, for it is considered an honorific duty to do so. Petitions and other biosafety related demands are initially analyzed by the members according to the issues and to their area of expertise and discussed within the specific

subcommittee (CSE—Human, Animal, Plant and Environmental), before a consensus or majority position is reached on the subject by the CTNBio board.

The CTNBio has the following legal responsibilities:

- To propose a national biosafety policy and a code of ethics on genetic manipulation
- To follow the developments in biosafety and related areas,
- To issue Biosafety Certificates (CQB) and to establish procedures for operating the Internal Biosafety Committees (CIBio),
- To classify the biosafety risk level of the genetically modified organisms (GMO) and determine the need for environmental impact studies,
- To issue expert technical reports on deliberate release of genetically modified organisms (GMOs) and projects involving pathogenic GMOs,
- To provide technical support to inspection agencies,
- To publish the petitions and expert reports in the official journal (D.O.U.),
- To request adhoc consultants,
- To propose changes to the biosafety law and norms, among other demands involving modern biotechnology.

Box 1- Norms (IN) issued by CTNBio:

- IN 1—The Certificate of Quality in Biosafety (CQB) and functioning of the Internal Biosafety Committee (CIBio).
- IN 2—Importation of GM Plants for Research. The CIBio issues expert reports on the importation of risk Group I GMOs and the CTNBio of risk Group II GMOs. Authorizations are issued by the Ministry of Agriculture.
- IN 3—Risk Assessment for Field Release of GMO (microorganisms, plants, and animals). Information required: taxonomy, objective of the release, location of the experimental area, habitat and ecology, GMO genetics, data on previous experiments, experimental design, monitoring, safety procedures, information to the public.
- IN 4—Transport of GMOs. Information on the GMO and a valid CQB are required.
- IN 5—Links importation of GMOs to the approval for field trial.
- IN 6—Classification of GM plants according to their risk groups and norms for the contained use of GM plants.
- IN 7—Classification and norms for the contained use of GM microorganisms. GMOs are classified under Group I (Risk Group 1) or Group II (Risk Groups 2, 3, or 4); work in Large Scale is not allowed with Risk Group 4 GMOs;
- IN 8—Genetic manipulation and human cloning. Genetic manipulation of germinal cells and radical cloning by any technique are not allowed.
- IN 9—Gene therapy. Genetic manipulation or gene therapy in humans is only allowed on somatic cells, respecting the Ministry of Health's Resolution 196/96 (ethics of research with human beings).
- IN 10— Fast Track rules for field release of GM plants that have been previously approved by the CTNBio according to IN 3,
- IN 11—Importation of GM microorganisms for contained use. the CIBio issues expert reports for the importation of Group I GMOs and the CTNBio for the importation of Group II GMOs,
- IN 12—Procedures for the contained use of GM animals. Establishes the requirements for work under Biosafety Levels 1 to 4,
- IN 13—Importation of GM animals for contained use. The CIBio issues expert reports for the importation of Group I, and CTNBio for the importation of Group II animals,

- IN 14—Establishes a 90-day period for institutions to comply with requirements for application for a CQB (complements IN 1),
- IN 15—Procedures for the contained use of nonmodified animals where GMOs have been introduced,
- IN 16—Maps and detailed location of field releases of GMOs (complements IN 3, IN 10),
- IN 17—Activities with products derived from GMOs that do not contain viable a GMO. Authorizations are issued by the competent authorities, and a CQB is not required,
- IN 18—Commercialization and environmental monitoring for Roundup-Ready Soybean,
- IN 19—Public Hearings promoted by the CTNBio related to field releases of GMOs,
- IN 20—Safety evaluation of GM plants and products thereof to be used as food and feed and for processing.

CTNBio's Activities

CTNBio had its first meeting in June 1996. Since then, the Committee had 57 ordinary meetings, which now take place once a month and 5 extraordinary meetings. The institutions working with GMOs in Brazil have been certified and visited by CTNBio members with the support of the Committee's Executive Secretary staff. Usually, an inspection agent of the competent area is part of the team. The CTNBio has issued 163 Biosafety Certificates (CQB) to institutions involved with GMO activities and has analyzed their annual reports.

As a rule, all petitions for importation or any other activity with risk Group II GMOs need to be evaluated by the CTNBio. The Committee has, so far, elaborated 20 norms (Box 1) to regulate different activities with GMOs. Additionally, CTNBio members have actively participated in meetings sponsored by other branches of the Government and acted as consultants in an attempt to harmonize the legislation concerning registration of products, labeling, importation, and compliance with international agreements pertaining to GMO activities.

Risk assessment for field releases and commercialization of GM crops

Over 1,000 field release proposals have been analyzed by the Committee using a case-by-case and step-by-step approach. The field releases of GM crops approved to date are listed in table 1. The proposals are evaluated for approval by CTNBio, and after a conclusion is reached a report is also submitted to the Committee. The main information required for analysis of petitions regarding deliberate field release of GM plants is listed in Box 2. The information required for analysis of a petition is based on norms established by the United Nations Environment Program (UNEP) guidelines (1995), on other relevant government documents, and on scientific literature. For the release of GM plants intended for use as pesticides or as biological control agents, in addition to CTNBio evaluation, the petitioner also needs to comply with further legal requirements from other Government agencies (Ministries of Health, Agriculture, and Environment).

To date, five petitions for the commercialization of GM crops have been submitted to CTNBio: one for glyphosate-resistant soybean, one for herbicide-tolerant corn, and three for insect-resistant corn. In 1998, the Roundup-Ready Soybean was approved by CTNBio for commercialization with a requirement to implement an environmental monitoring program

(Box 2). However, the transgenic seed product is not yet on the market owing to legal requirements that include registration and further environmental impact studies. The petitions for the commercialization of transgenic corn are under evaluation by CTNBio.

Food safety assessment

CTNBio is required to perform a safety evaluation of the production, importation and marketing of GM plants and their products, intended to be used as food or feed or in processing. Basically, the substantial equivalence concept is applied to the risk assessment analysis (Tomlison 2000). The main information required when a company submits a petition for analysis by CTNBio is indicated in Box 2. After evaluation by CTNBio, and according to Decree 3,871/01, all packed GM food or food products containing GMOs in the concentrations of 4 percent or higher should be labeled as "genetically modified (product)" or "contains genetically modified (ingredient)." The regulation applies to the unintended presence of GMO in food products. Labeling is perceived in this context as a consumer's right to have access to information, and it is not related to risk factors.

CTNBio analyzed food safety aspects of a commercial transgenic corn shipment intended for use in Brazil during an emergency shortage of feed. On that occasion, the Committee issued an expert report approving the importation based on food safety data provided by other countries that commercialized such products. The GM corn cargo was transported under the control and jurisdiction of the Ministry of Agriculture from the port of entry directly to the milling factory, avoiding accidental environmental release of the grain.

Capacity building

Board members are continuously updated on biosafety issues by attending courses, workshops, and conferences on both the national and international levels. The members are expected to deliver oral presentations on the Brazilian Legal Framework and risk assessment procedures when performing technical inspections on institutions requesting Biosafety Certificates. Board members also participate in scientific meetings on biotechnology, biosafety, and related areas to discuss the operational aspects of the Committee. CTNBio has organized a workshop on bioethics, sponsored several events organized by universities and scientific associations, and cosponsored several initiatives of the National Biosafety Association (ANBio). CTNBio members have been participating, as part of the Brazilian Delegation, in meetings for negotiation of the Cartagena Protocol among other international activities.

Operational aspects

The Executive Secretary of CTNBio is located at the Ministry of Science and Technology within a suitable environment for operating a multidisciplinary advisory committee. Administrative matters are efficiently handled by the Executive Secretary. Pitfalls in CTNBio's modus operandi could be stressed, including the difficulty in harmonizing legislation of other Government branches regarding regulation of GMOs. Another relevant drawback is the high turnover of members of the Committee, which is in part due to their work serving on a voluntary basis and not receiving compensation in any form for their activities; on the other hand, such professionals still have to fulfill their main job obligations. Furthermore, members may feel discouraged by the extremely polarized public perception and emotional debate on transgenic crops and food products, bringing constant visibility in the press and frequent legal obstacles.

BOX 2- Risk assessment information required for analysis of petitions on GM crops

a—Deliberate field releases

- Taxonomic characterization (subspecies level) of donor and recep tor organisms
- Classification of donor, receptor organism, and GMO into biosafety risk level
- Objective of the proposed release
- Detailed location of the experiment with information on vicinal habitats
- Habitat and ecology of the receptor organism and its interactions
- Genetics of the GMO, including sequences of inserted genes, origin, and methodology
- Vector, its restriction map, method of insertion, and host range
- Inserted gene products and their effects on humans and the environment
- Survival, dispersion, and gene transfer data on the GMO
- Measures for containment, safe disposal of the GMO, and monitoring of voluntary plants
- Field trials done in other countries and history of safe use
- Plant propagation mechanisms
- Indirect phenotypic effects
- Mitigation measures
- Information to the public excluding confidential data

b—Food safety information

- History of safe use as food of the receptor organism
- Toxicity, allergenic reactions, and metabolites affecting humans and animals
- Nutritional aspects and digestibility
- Possibility of gene transfer to microbiota associated with the intestines

c—Postcommercialization environmental monitoring (Roundup-Ready Soybean)

- Monitoring for 5 years, including annual reports
- Areas representative of soybean crop regions in Brazil
- Population dynamics of weeds and seeds in the soil
- Population dynamics of insects, plant pathogens, and microorganisms
- Gene transfer to compatible plants
- Gene transfer to soil microorganisms
- Environmental impacts of glyphosate

Table 1. Field releases of genetically modified plants in Brazil

GMO	Number	Area (ha)
Maize (*Zea mays*)	842	427
Soybean (*Glycine max*)	64	208
Cotton (*Gossypium hirsutum*)	52	97
Sugarcane (*Saccharum* sp.)	19	6
Beans (*Phaseolus vulgaris*)	2	0.3
Eucalyptus (*Eucalyptus* sp.)	2	2
Potato (*Solanum tuberosum*)	2	0.1
Papaya (*Carica papaya*)	2	0.6
Rice (*Oriza sativa*)	2	10
Tobacco (*Nicotiana tabacum*)	2	0.2
Total	**989**	**751.2**

Main Traits Inserted in GM Plants, CTNBio, 2002:
Herbicide tolerance (HT), Insect resistance (IR), (HT+IR), Virus resistance (VR)

Concluding Remarks

Brazil has an operational Biosafety Legal Framework compatible with both the development and use of modern biotechnology and the sustainable use of biodiversity, ecosystem preservation, and human health. The country has adopted a multidisciplinary biosafety committee model nominated to deliberate on all activities involving GMOs. The federal biosafety regulatory body (CTNBio) is part of the structure of the Ministry of Science and Technology, where regulatory and administrative matters are handled with efficiency and transparency. To date, all institutions involved in activities with GMOs in the country have been mapped and are certified, for new applications are analyzed promptly. This has been accomplished by CTNBio's applying an educational rather than a punitive approach because Biosafety is perceived as a new concept necessary for the safe use of modern biotechnology.

A relevant challenge faced by CTNBio and by other entities dedicated to the development of biotechnology in Brazil has been the negative public perception regarding transgenic plants. Intense publicity on the risks posed by biotechnology has not been matched by a comprehensive analysis of the benefits that can result for human health and the environment in comparison with conventional agriculture practices. Furthermore, agreement among different branches of the Brazilian Government on the legislation for commercialization of GM crops has not yet been achieved; nevertheless, efforts are in progress with the aim of obtaining a legal harmonization. Throughout the years of operation, a deficiency has been identified in CTNBio's predominantly consultative status. The Committee, not being an executive organ, has been challenged on the limits of its legal competence concerning GMO authorizations in Brazil. This has had the consequence of delaying the commercialization of LMO products owing to additional requirements for their approval.

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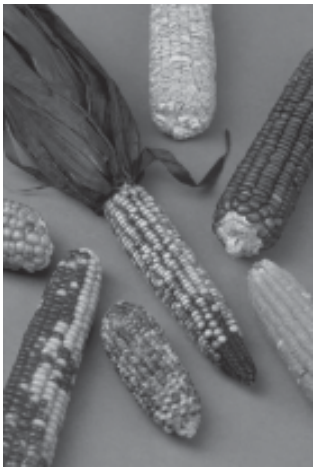
Risk Management Strategies for Living Modified Organisms that Take Uncertainty into Account



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Abstract

There are different types of uncertainty in risk assessment and of risk management. It is helpful to distinguish between a quantitative and a qualitative type of uncertainty. Quantitative uncertainty analysis addresses descriptive errors such as the variability in baselines or laboratory experiments. Qualitative uncertainty concerns ignorance and indeterminacy, which cannot be addressed through risk assessment but must be covered by appropriate risk management practice. Many of the previously unpredicted adverse effects of chemicals (e.g., DDT, methyl bromide) refer to the qualitative type of uncertainty. This paper outlines risk management strategies dealing with ignorance: the implementation of both an early warning system after the approval of the living modified organism and also an approach to finding precautionary criteria before the approval to avoid effects of substantial and unmanageable stressors due to the lack of mitigation measures.

Introduction—Why Uncertainty?

> "While the duty of preventing damage to the environment is based on a known risk, the notion of precaution is based on "lack of certainty"(OECD 2000).

All human activities have an impact on the environment. Some of the impacts can be addressed proactively by ecological risk or environmental impact assessment; others become visible after a substantial delay. Some impacts of human activities are impossible to identify owing to the complexity of ecosystems. The history of risk identification and regulation of different pesticides shows the following: from 1939 up to now the risk identification of new (previously unknown) harmful effects to humans and the environment continues to evolve. The depletion of the ozone layer by methyl bromide and the hormonal effects of many chemicals (for example Vinclozolin, see figure 1) are well known examples of these new risk identifications within the last two decades. Furthermore, the history of pesticide regulation shows the relevance of the following sequences of events:

- The time lag between introduction of a chemical and exposures in the environment;
- The occurrence of a harmful effect not immediately associated with the pesticide;
- The identification of that deleterious effect ;
- The scientific proof of the cause of that effect;
- The political reaction to that new scientific evidence;

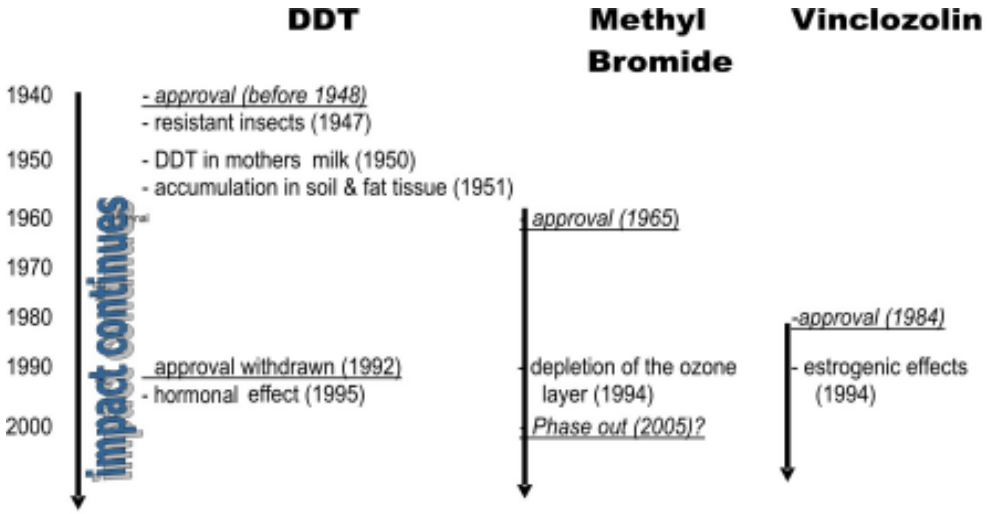

Figure 1: Historical review of the risk identification and regulation of three pesticides in Austria (Sources for the table: For DDT from 1947 to 1951 secondary references were used due to the lack of suitable databases for that time period. 1947 DDT resistant insects cited in Briejé 1957, 1950 DDT in breast milk cited in Heinze 1952, 1951 Accumulation of DDT in the soil cited in Heinze 1951b and in the fat tissue cited in Heinze 1951a, 1995 hormonal effect of DDT Kelce et al. 1995, 1994: depletion of the ozone layer by Methyl bromide WMO 1995, 1994: hormonal effect of Vinclozolin Kelce et al. 1997

Figure 1 gives a short review of these aspects for three examples.

Owing to the complexity of ecosystems the overall ecotoxicity can never be fully assessed. Risk assessment and risk management follows the precautionary principle only when it acknowledges the limits of knowledge (e.g., food web) and hence takes the possibility of error into account.

In the view of the U.S. Environmental Protection Agency (EPA), "Risk assessments explicitly evaluate uncertainty. Uncertainty analysis describes the degree of confidence in the assessment and can help the risk manager focus research on those areas that will lead to the greatest reductions in uncertainty" (U.S. EPA 1998, 7f). The U.S. Department of Energy (DOE) noted that

> the current Environmental Protection Agency (EPA) policy for risk characterization (issued by Carol Browner, EPA Administrator, in February 1995) requires all risk assessment to have the core values of transparency, clarity, consistency, and reasonableness. To attain these core values, Agency risk assessors and risk managers are instructed to have a full and open discussion of uncertainties in the body of each risk assessment, including a prominent display of critical uncertainties (U.S. DOE 1996, p.1)."

Apparently there is a need for more explicitly addressing uncertainty in risk assessment of living modified organisms (LMOs).

There are many papers regarding the uncertainty in risk assessment. Some of these documents (EU-Commission 2000, OECD 2000, UNEP 2000) deal with the question of how to apply the precautionary principle in the light of uncertainty in risk assessment. Other, more technical documents give examples of reasons for (or sources of) uncertainty and how to address uncertainty in the risk assessment (e.g., U.S. DOE 1996, U.S. EPA 1998, Warren-Hicks and Moore 1998a).

What is Uncertain?

The term "uncertainty" in the context of risk assessment has been used since the mid 1980s (Morgan and Henrion 1992). However, there is no common understanding of the use of this term. Covello et al. (1992) distinguished four primary sources of uncertainty in risk assessment and management:

- Uncertainties about definitions;
- Uncertainties about scientific facts;
- Uncertainties about risk perceptions and attitudes;
- Uncertainties about values.

Uncertainties about definitions derive primarily from disagreements about meaning and interpretation of key concepts such as probability. Uncertainties about scientific facts derive primarily from disagreements about failure modes, the probability and magnitude of adverse health or environmental consequences, cause and effect relationships, dose–response relationships, and exposure patterns. Uncertainties about risk perception and attitudes derive primarily from disagreements about what constitutes a significant or acceptable level of risk. Uncertainties about values derive primarily from disagreements about the desirability or worth of alternative risk management actions or consequences.

Very different from that are U.S. EPA definitions on sources of uncertainty (U.S. EPA 1998) as follows:

- Unclear communication
- Descriptive errors
- Variability
- Data gaps
- Uncertainty about a quantity's true value
- Model structure uncertainty (process models)
- Uncertainty about a model's form (empirical models).

The Scientific Committee of EEA (European Environmental Agency) (EEA 1998) distinguishes different basic types of uncertainty:

- Risk: Odds known
- Uncertainty: Odds not known, may know the main parameters.

  May reduce uncertainty but increase ignorance

- Ignorance: What is not known is not known. Ignorance increases with increased commitments based on given knowledge.
- Indeterminacy: Causal chains or networks open.

(For further definitions on uncertainty see, e.g., Hrudely 1998, Warren-Hicks and Moore 1998a, EU-Commission 2000).

From the perspective of reducing uncertainty it is possible to distinguish between two different groups of sources of uncertainty:

- A quantitative uncertainty (see U.S. EPA 1998 above) in comparison with the tools from QUA (quantitative uncertainty analysis), which are used to reduce uncertainty by Monte Carlo analyses, and Bayesian statistics, or both (e.g., Warren-Hicks and Moore 1998b; Warren-Hicks and Moore 1998a).
- A qualitative uncertainty (e.g., ignorance and indeterminacy), which cannot be reduced by QUA (quantitative uncertainty analysis) and other technical tools. Figure 1 reveals that most errors in risk assessment are caused by ignorance.

How to Address Ignorance

Quantitative uncertainty has to be addressed mainly during the risk assessment process. Ignorance, on the other hand, cannot be addressed during risk assessment but can be covered by risk management (which includes postapproval activities and activities before risk assessment, i.e., definition of hazard and thresholds). Risk assessment analyzes "how it is" and estimates "how it will be" and risk management aims at "how it should be" and "how to act" to achieve that goal (definition of harm and thresholds). There are two ways to address ignorance during risk management. One way is that of the "quick response" after the approval of LMOs supported by the implementation of an early warning system. The other way is to define precautionary criteria in advance for the risk assessment such as thresholds for persistence (see the section, 'Before Approval—Precautionary Criteria').

Post Approval—Early Warning System

Two different monitoring schemes exist within the European Union (EU): "case specific monitoring," which mainly focuses on the validation of case-specific hypotheses of the risk assessment, and "general surveillance" for "unanticipated adverse effects" of LMOs (EU-Parliament and Council 2000). Case-specific monitoring would assess, for example, the risk derived from a hypothesis that predicted a negligible impact for the release of Bt toxins in the soil. General surveillance has to be seen as an early warning system. Key problems for such a system are

- defining key parameters that would show major ecosystem disruptions with greatest sensitivity,
- describing sensitive "trigger points" or thresholds and appropriate methods to reduce the timelag between release of the transgenic organism and first identification of an exposure, and
- detecting adverse effects and implementing mitigation measures, (See, for example, the discussion about the F2 screen, which is the most sensitive method for monitoring changes in the frequency of resistance alleles in insect populations, and also other less sensitive monitoring schemes like the dose–response test (Roush and Miller 1986, Andow and Alstad 1998, Marcon et al. 2000).

To facilitate a quick response there is a need for clear responsibilities to ensure the implementation of mitigation measures without major delays. Furthermore, the newly detected adverse effects must lead to adjustments in the models of risk assessment. In addition, improved error reporting needs to be accomplished, a so-called soft factor in the improvement of the risk assessment process. A recent survey lists the following key soft factors used in highly reliable operations to manage unexpected events (Weick and Sutcliffe 2001):

1. Pay close attention to errors. Encourage reporting errors
2. View errors as a window to the system as a whole
3. Have clear instructions for how to reevaluate your risk assessment

Before Approval—Precautionary Criteria

In some cases the early warning system reveals new, unanticipated adverse effects without opportunities for effective mitigation of these effects. For example, if the seed bank in various soil ecosystems were contaminated with feral plants expressing transgenes (synthetic genes), long-term impacts would occur without easy remedies. The implementation of precautionary criteria is the only way to avoid unmanageable and long-lasting adverse effects.

The historical review (see figure 1) shows clearly that persistent chemicals—especially if they are mobile and can be accumulated—are major risk factors in a continuously changing environment. Owing to the complexity of ecosystems, the overall ecotoxicity can never be fully assessed. The persistence of chemicals is a central criterion for assessing ecotoxicity because exposure to persistent chemicals cannot be terminated or removed if new harmful effects are identified in the future (Klöpffer 1994). Because transgenes may be transferred to feral populations by outcrossing, their persistence may cause a more serious or more long lasting effect given the lack of knowledge about the half-life of a synthetic gene. This has to be taken into account in the risk assessment.

Analyzing and Identifying Uncertainty During Risk Assessment—a Brief Example

The traditional approach in assessing risks from outcrossing of transgenes asks, Is there any potential for an adverse effect (i.e., weediness) from the spread of, for example, a synthetic herbicide-tolerant (HT) transgene to wild relatives of canola? The answer of contemporary regulatory systems at present is no!. There is no selective

advantage of that gene that might allow plants expressing the HT gene to become more weedy as asserted in the following observation by the U.S. Department of Agriculture (USDA):

> In nature, the gene that results in accumulation of CP4 EPSPS and GOXv247 proteins will not provide glyphosate tolerant canola or its progeny with any measurable selective advantage over "nontransformed" canola plants in their ability to disseminate or to become established in the environment. There is no reason to believe that glyphosate-tolerant canola exhibits any increased weediness relative to that of traditional varieties. The use of glyphosate-tolerant canola or its progeny in agriculture will not lead to an increase in weediness in any plant with which it can successfully interbreed (USDA 1999).

While analyzing and identifying uncertainty during risk assessment, firstly the potential hazard (effect profile) and secondly the potential exposure (exposure profile) must be addressed. In analyzing the exposure profile, two areas must be investigated:

1. The potential exposure of the genetically modified organism (GMO) itself and
2. The potential exposure of the transgene (synthetic gene) or, in other words, What is the fate of the gene? Will it spread and persist in feral populations?

With respect to the fate of synthetic transgenes in feral populations, considerable evidence from computer modeling indicates that synthetic transgenes will persist in feral populations. At migration rates between 10 and 20 percent after positive selection, selectively neutral or even up to 20 percent selectively disadvantageous synthetic transgenes will be fixed in a feral receiving population at rates between 70 and 90 percent (Adam and Köhler 1996). Experimental data show that transgenes do not necessarily contribute to selective disadvantage. In some cases a slight fitness advantage for hybrids (carrying the transgene) has been detected. This leads to the conclusion that transgenes will likely persist for many generations in feral populations (Klinger and Ellstrand 1994, Arriola and Ellstrand 1997, Snow et al. 1999).

On the basis of polymorphism in allozymes, the theoretical foundation for assuming that "synthetic genes" act as selectively neutral traits and therefore will spread and persist in feral populations was laid down in 1968 by Kimura (1991a). In contrast to the Darwinian theory of evolution by natural selection, the neutral theory claims that the overwhelming majority of genes evolved by continued inputs of mutations are selectively neutral and therefore randomly fixed owing to random sampling drift in finite populations (Kimura 1991b). After changes in the environment, some of the genes turn out to be useful.

Intergroup competition and individual selection lead to extensive adaptive evolution. Nevo (2001) rejected Kimura's hypotheses. He declared that polymorphism can also be preserved in small, long-isolated populations by "stabilizing selection" or "cyclical selection." Both theories contribute to the same conclusions. Neutral transgenes are maintained in feral populations. The way genes are maintained is seen differently as occurring randomly or by "stabilizing selection."

After environmental changes, some "synthetic" transgenes may turn out to be useful. From the standpoint of uncertainty, the half-life of that gene is a key factor in assessing the degree of uncertainty. But there are limits in estimating the half-life or even the fitness of a gene. Because fitness is a function of an organism and its corresponding environment, lab

tests give quite limited security for extrapolations to a wide range of possible affected ecosystems. Figure 1 shows clearly that ecotoxicity of a chemical, and also for LMOs, can never be fully assessed in advance of a release. Therefore, more risk may be associated with outcrossing than weediness (e.g., extinction by hybridization; Rhymer and Simberloff 1996). Once a release occurs, there are limits in the ability to estimate the potential for weediness of a "synthetic gene" from lab experiments alone just as is true for an estimate of fitness.

Some scientists argue that crop genes derived by mutations or derived by genetic engineering are equal with respect to uncertainty and persistence. From an evolutionary perspective the creation of genes by enhanced induced mutation is "just" speeding up evolution 100–10,000 times faster than it would occur naturally. The creation of synthetic transgenes in plants with combinations of virus promoters, bacterial expression sequences, and so forth is not known to occur as a consequence of evolutionary forces. Persistence of synthetic transgenes must be considered a more serious hazard to biodiversity than persistence of crop genes derived by induced mutations simply because possible impacts of exotic genes may be highly uncertain.

The U.S. EPA (1998) recommends

1. To articulate major differing viewpoints of scientific judgments clearly;
2. To acknowledge uncertainties and assumptions in a forthright manner; and
3. To identify reasonable alternatives and conclusions that can be derived from the data.

These points should be incorporated into the risk assessment, especially when outcrossing may be at issue. The following short example should indicate specifically how risk assessment reports that consider outcrossing for decisionmakers could be improved:

Clearly Articulate Major Differing Viewpoints of Scientific Judgments:

There are different scientific judgments about the extent to which outcrossing must be seen as a risk in itself or not.

Acknowledge assumptions and uncertainty:

There are major restrictions in estimating the fitness and weediness of a "synthetic gene" because of the difficulties of performing fitness tests in a varied and continuously evolving environment. The ecotoxicity cannot be fully assessed. Persistence of transgenes in feral populations is likely to occur. Unpredicted long-term effects arising from persistent transgenes may be associated and cannot be excluded by current risk assessment methods. If adverse effects from persistent transgenes occur, no effective ways to mitigate adverse effects are known.

Reasonable alternatives and conclusions:

Some scientists conclude that outcrossing is a risk in itself. Genetically modified crops with the potential for outcrossing should not be approved because there would be no (or at least very limited) options for mitigation measures.

Conclusions

Acknowledging uncertainty in the risk assessment of LMOs should lead to new risk assessment frameworks as suggested by the U.S. EPA (1998) among other agencies. This should also lead to a redefinition of risk that might be represented as follows:

Risk = hazard * likelihood + uncertainty

Risk assessment reports should include the adverse effect, exposure, and uncertainty profile. The implementation of an early warning system and the definition of precautionary criteria like "persistence" should reduce the probability of major unanticipated adverse impacts that cannot be fully excluded by risk assessment methods.

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A Perspective of Civil Society

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Abstract

In Europe there is an intense debate about the use of transgenic plants in agriculture. An impression is conveyed that ecological aspects are neglected in the overall evaluation process and possible long-term effects are not taken into account sufficiently. There are strong hints that double standards are used when evaluating the evidence submitted in the context of risk assessment. Improvements in the risk assessment procedure are needed.

Introduction

I am here as a scientist and also as a representative of civil society. I would like to provide you with a different evaluation process for the biosafety of engineered plants and with viewpoints that have emerged specifically in Europe. I will contrast the views of those scientists working in the life science sector and industry on the one hand with those scientists representing quite often the majority of civil society on the other. The differences in viewpoints have much to do with an alternative weight given the associated risks of transgenic plants in the environment ,but, in addition, with a conflict or debate on the future directions for the development of agriculture. To frame it in popular terms, we deal with a conflict between different sets of shareholders and stakeholders.

Aspects of the Debate

Transgenic plants fit into the paradigm of an industrial agriculture based on a high-input, resource-intensive means of production. They are meant to optimize this form of agriculture. On the other hand, important international institutions, including FAO, the Food and Agriculture Organization of the United Nations, demand major changes and improvements as stated, for example, in their report *Towards 2010 —The Future Development of Agriculture* (1995). In the long run the agriculture that the industrial world has developed is destroying the resources on which it is built and on which it is depending (FAO 1995). This assertion refers to soil depletion, soil erosion, and loss of biodiversity as an overall loss and specifically as a loss in plant genetic and animal genetic resources as well as contamination of water and soils with pesticides and fertilizers.

Therefore, we deal with two sets of questions in the context of risk assessment:

- First: Do transgenic plants pose unprecedented short- or long-term risks, and may such plants contribute to or even aggravate the addressed problems?
- Second: Do trasngenic plants have the potential to optimize certain aspects of an industrial agriculture or even transform it into a sustainable form of agriculture without the negative side effects that are often cited?

There are serious doubts about the context surrounding both sets of questions.

For 20 years genetic engineering has been extensively discussed. Since the very beginning there have been serious concerns by those scientists involved in the first GMO experiments. Since then, billions of dollars have been invested in the development of different applications, and millions of dollars have been spent in public education and acceptance.

An international analysis of associated risk research, that is, research on possible ecological and health impacts (Sukopp and Sukopp 1997), came to the conclusion that less than 1 percent of the worldwide development budget has been used for research regarding safety effects. In other words, before the first commercial plantings in 1996, 10 years of field testing had been conducted without looking in depth into possible ecological consequences. That was also the outcome of an evaluation done by Mellon and Rissler (1995) published in *Nature Biotechnology* (table 1).

Table 1

• Since 1987:
–850 applications and notifications approved
–269 reports only 139 available to the public
–85 most recent reports analyzed

• Problem of weediness
–86% general observations
–14% aspect not mentioned

• Gene flow
–24 reports concerned crops with wild relatives in the U.S.
–23 reports did not address possible impact of gene flow

• Problem of virus recombination
–19 reports dealt with virus resistant plants; in no case were special experiments or monitoring done during the release—17 reports did not even mention the risks

• Nontarget effects
–15 reports dealt with insect-resistant plants
–failure to mention the possible adverse impact of nontarget effects

Conclusion by Mellon and Rissler (1995) Risk Assessment in Official Documents:
" the field tests do not provide a track record of safety but a case of 'don't look, don't find".**

Five years later a review published in *Science* came to nearly the same conclusion: "A review of existing scientific literature reveals that key experiments on both the environmental risks and benefits are lacking" (Wolfenbarger and Phifer 2000). In short, there has not been much progress. The consumer or the public as a whole feels more and more uncomfortable given these facts.

In dealing with risk assessment over the last 15 years there appears to be considerable disconnection between the emerging data and the handling of these data in the context of evaluation and decisionmaking. There are strong hints that double standards are used when evaluating the evidence submitted for market approvals. To arrive at the following summary I refer both to a study performed by Les Levidow and Susan Carr commissioned by the European Commission (Levidow and Carr 2000) and to our own study done for the German Technology Assessment Bureau (Vogel and Tappeser 2000). The main outcome of both studies is the following: studies or statements that underline the benefits are readily accepted by regulators in the U.S. and the European Union even if those studies are not peer-reviewed and rely only on laboratory experiments. Studies indicating risks and possible negative ecological or health impacts are heavily criticized no matter that they are peer-reviewed and published in scientific journals. These studies are criticized when they rely only on laboratory experiments.

In addition there has been a shift in judging certain impacts. For example, a central issue that has figured in the discussion on the cultivation of transgenic plants since its very beginning is that of outcrossing of such plants and the introgression of the recombinant genes into related weed and wild plants. It was more or less agreed at least in the beginning of the debate that pervasive spread of transgenes should be avoided if at all possible, for this may have problematic effects on species networks and on biodiversity in general. A point now attracting increasing attention is the implication of resistance development through outcrossing and the consequences of that development for agricultural land use systems. In Europe canola is at the center of interest because several related species are prevalent there. All experience and data gained in the course of the past years point to a high probability of transgenic rape populations becoming established outside cultivated areas and the subsequent possibility of gene flow into nontransgenic populations and related wild herbs. Nowadays, gene flow as such is no longer judged as being of special concern. It is said that gene flow only constitutes a risk when the outcome, the possible impact in the complex networks, can be described and the impacts are judged as having specific negative consequences. Otherwise such gene flow is qualified as a "so what" type of conclusion.

But the demand to describe the impacts of gene flow can only be met with a broad long-term research program because of the multiple knowledge gaps and uncertainties that exist. Given the current level of investments in the field of biosafety and assessment of ecological impacts, such a research program would extend into the next 20 years at least. But the decision to pursue such research has to be taken now.

I would like to develop a scenario describing the possible risks of deploying herbicide tolerant crops:

Nearly all of the world's major crop plants have been equipped with the same herbicide resistance genes. Their large-scale use will therefore produce an enormous selective pressure towards resistant weeds (Begon et al. 1991). Although those transgenic plants with wild and weedy relatives in a region will be the plants that initiate rapid resistance development via outcrossing, other plants expressing the same resistance genes but lacking crossable wild relatives in the region will promote, on a continuing basis, the one-sided selection of these weeds. I would dare to say that the use of herbicide-resistant plants may even accelerate resistance development compared with conventional agricultural practices. Furthermore, the cloning of different resistance genes into one and the same crop species also gives related wild herbs the opportunity to acquire multiple resistance traits. In Canada, double- and triple-resistant canola have already developed and are qualified by some as superweeds (Orson 2002, Hall et al. 2000).

This development may also be accompanied by a further impoverishment in farmland-associated floral species and insects because of the constantly increasing usage of broad spectrum herbicides instead of selective herbicides. The additional weed shift to less sensitive species will further contribute to a diversity-poor agricultural ecosystem with less stability and much more need of additional management inputs.

If that is a scenario you are willing to accept along with a short-term reduction in pesticide use—although this claim of benefits is challenged, too (Benbrook 2001 EU; Directorate-General for Agriculture 2000)—the long-term outcome of herbicide-resistance may be further biodiversity loss and the next round in the chemical treadmill.

Conclusions and Recommendations

I elaborated on this example of canola to provide some additional background for the mixture of conclusions, demands, and open questions with which I would like to finish:

- Risk assessment has been done on too narrow a basis.
- Risk assessment needs other scientific competencies than those necessary for the development of transgenic organisms; interdisciplinarity has to be strengthened in the risk-assessment procedure.
- The datasets are inappropriate. The main focus of evaluated data has been on the agronomic aspects of the transgenic plant. There are only sparse data on ecological impacts.
- The significance of, and the relationship between, laboratory experiments, greenhouse experiments, and field experiments are not clear, especially when there are data that question the use of transgenic plants as an unproblematic issue.
- Possible long-term systemic effects and effects due to changes in management practice and parallel use of different transgenic crops have not been elaborated.
- There is no consensus about the baseline, and there is no consensus about the environmental goals in agriculture. Maybe we have to accept that there are different options and goals and should shift part of our discussion to the goal of making it possible to follow different roads—that means differential requirements for segregation, traceability, and labeling.

- The framework of a risk–benefit analysis has to be defined thoroughly and the evaluation has to follow scientific principles.
- Transparency and public participation has to be improved.

And last but not least;

- How much uncertainty is acceptable?
- What is enough certainty to decide not to accept or use a certain type of transgenic plant?

Climate, soils, and ecosystems but also the tradition of agriculture are very different in various regions of the world. This diversity is part of our heritage and the riches of the Earth. Risk assessment and the decisions based on the risk assessment have to take that into account and may therefore have different answers in the different regions.

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Modern Biotechnology in Agricultural Development: A Latin American Perspective

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Abstract

The countries of Latin America and the Caribbean have many needs for the development and adoption of biotechnological strategies to improve agricultural production. The introduction of national regulatory authorities and the training of interdisciplinary assessors will be needed before the appropriate risk assessment can be done.

Introduction

The Latin America and the Caribbean Countries (LACC) are strategically placed centers for global food security. Three of the 12 global centers of origin for crops of major socioeconomic importance are found here, and their enormous biodiversity is highly significant (Leon 1987). Although representing only 7-percent of the earth's surface, the LACC contain a large amount of the planet's biodiversity. These resources are concentrated primarily in 18 countries, 9 of which are in the American hemisphere (Alarcon et al. 1998).

Recent studies by the World Bank estimate that more than 70-percent of the nearly 500 million inhabitants of the region live in urban zones and daily dispose of over 250,000 tons of waste. Less than 55-percent of this garbage is treated, which in turn contaminates surrounding water bodies. Almost one-third of the population lives in levels of absolute poverty, and more than 40 million indigenous people are excluded from the development process. These populations do not have access to basic public services such as education, health, and social assistance. From this perspective, the region is significantly challenged to find a suitable economic development plan that will also foster social equilibrium as well as the sustainable use of this region's biodiversity.

The agroindustrial sector contributes slightly more than 25-percent of the region's gross domestic product (GDP). Therefore, the consequences of the agricultural advancements derived from research and technological innovation are of the utmost importance for the region. The general consensus is that conventional technologies themselves will not provide a sufficient increase in the quantity and quality of food production to satisfy a population that is estimated will double in the next 50 years.

The Food and Agriculture Organization (FAO) has projected that over the next 25 years the population of the LACC will increase from 490 to nearly 680 million. It is possible that more than 30-percent of the cereal consumption of the LACC will be imported by 2020. The same FAO studies predict that the arable land in the region could be expanded by only 12-percent at acceptable economic and environmental costs (although such expansion would inflict damage to the remaining biodiversity). The increase in food demand expected to occur in the region during the same period is 61-percent. In the LACC the only potential cultivable lands are the Brazilian Cerrados and the Llanos of Colombia and Venezuela (Kendall et al. 1997), which may be marginal areas without the need for substantial improvements needed for agricultural production.

The Developing Issues

The challenges and opportunities for the LACC are large, given the high participation of the agricultural sector in the region's GDP. In addition, the LACC possess a rich base of flora, fauna, and micro-organisms essential to obtaining new products for the pharmaceutical and food industries.

The scenarios for the agricultural production of the region are not homogeneous. Those in the temperate zones of the north and south differ from the scenarios for those of the high mountain plains. The wet and dry tropical lowlands and medium-elevation hillsides, such as those in Central America, the Andean countries, and some Caribbean nations present yet a different scenario.

Technological engagement in temperate agriculture by industry and Government is greater than that occurring in the tropical areas. The biotechnological expertise of other countries has been consequently deployed in the LACC. In the LACC, for example, in the case of soybeans and wheat, a transgenic "RR soybean" has recently been imported. In tropical areas, there is no available technological counterpart for the region, although transgenic rice could be imported. Consequently, the technological gap with the world's leading countries is widening with respect to many crops (see tables 1, 2).

Table 1. Basic Grains. Current yields in LACC and leading countries of the world

Products	Average current yield in the LACC (ton/ha)	Current yields of world leaders (ton/ha)	Annual growth rate in the LACC 1985–97(%)
Rice	3.2	6.2	2.9
Bean (Dry)	0.6	1.8	0.6
Corn	2.7	7.7	2.9
Wheat	2.4	6.7	1.8

Source: IICA, Technical Management, Area II. Supported data from FAO. STAT.

Table 2. Main Crops. Average current yields in LACC , South American, Colombia and USA countries. Year 2000.

Crops	LACC (ton/ha)	South America (ton/ha)	Colombia (ton/ha)	United States (ton/ha)
Total (cereals)	2.79	2.99	3.05	5.86
Wheat	2.67	2.52	2.17	3.82
Rice	3.60	3.58	4.77	7.04
Barley	1.87	1.94	2.17	4.29
Corn	2.72	3.12	1.75	8.60
Rye 1.28	1.28	1.17	1.79	
Oat 1.67	1.68	ND	2.30	
Millo	1.52	1.52	ND	2.11
Sorghum	2.86	3.16	3.17	3.82
Quinua	0.69	0.69	ND	ND
Triticale	1.38	1.39	ND	ND
Roots and Tubers	12.63	13.23	12.20	42.79

Source, FAOSTAT, 2000

As we can conclude from analyzing the data in the tables, the Latin American region urgently needs improved agricultural biotechnology to increase food production. In the LACC, progress in biotechnology research has been particularly rapid for some of the most valuable crops of the region. Scientists hope that the development of transgenic plants will help to alleviate both the heavy use of pesticides and the susceptibility of traditional cultivars to many biotic and abiotic stresses.

Conclusions

The characteristics of modern biotechnology provide both opportunities and challenges. If the LACC are able to build capacity for their national research systems, biotechnology holds the promise of supporting national efforts towards food security and sustainable development in the region as well as increasing the export potential.

The issues of agricultural biotechnology are being actively debated—but mostly in the rich industrial world. However, it is in the developing world where the greatest value of this new technology may lie. Consumers in the industrial world can afford, if they wish, to take a highly skeptical view toward this new technology. A majority of farmers and consumers in the LACC, on the other hand, are not yet wealthy or well fed. This suggests they would have much more to gain from agricultural biotechnology for the following reasons:

- Poor farmers in the LACC currently lose a large share of their crop production (probably more than 30 percent) to diseases and pests. Biotechnology makes possible the development of plants resistant to pathogens and pests.

- Low average crop yields are in part caused by biotic stresses (such as salt or drought) on plants. This constraint may be overcome by engineering plants better adapted to such stresses.

- The use of crops protected against insects and disease offers potential agricultural, economic, and environmental benefits to the LACC farmers.

The countries of the region require appropriate infrastructures that will permit them to acquire, absorb, develop, and efficiently manage biotechnologies. The creation of enabling conditions must be addressed to obtain the potential benefits of these new technologies and to minimize any possible adverse effects on the environment, on human health or on the agricultural production systems.

The adoption and expansion of biotechnology in the LACC have increased in recent years. One indicator used to measure the progress in the agricultural biotechnology sector is the number of field tests of transgenic crops, which has been estimated to be near 870 in the region since 1997. Nevertheless, with very few exceptions, transgenic crops tested in agricultural ecosystems of the LACC have been those developed in the northern industrialized countries.

If we take into account that the cultivated area for the majority of conventional crops is greater in the developing countries than the cultivated area in the industrialized countries (14.5 times greater in rice, 3 times greater in cotton, 2 times greater in corn, and almost the totality of cassava and sweet potato), we can assume that the demand for transgenic cultivars will increase in developing countries.

The LACC must take advantage of these technologies if they want to move forward in agricultural development. However, the region must also make an objective, technical evaluation of possible risks for human health, the environment, and agricultural and cattle production that could result from the introduction of these technologies—especially when introduced into the tropical ecosystems. Every country in the region should analyze the necessity for having systems in place to identify and monitor potential adverse effects from crops protected against herbicides, deseases, and insects, through modified modern biotechnology or conventional breeding practices.

Although some countries in the LACC have biosafety regulations, the majority do not. What is even more critical is that many do not have the sort of multiply trained and interdisciplinary personnel needed to carry out risk analyses and risk management within a methodological framework, as stipulated by contemporary international regulations. Because of this limitation, the potential advantages of engineered crops may not be obtained to guarantee necessary biosafety requirements to protect the environment, human health, agricultural production, and the equitable distribution of the benefits for the welfare of the region's inhabitants.

It is clear that the LACC must continue to develop and perfect existing regulatory instruments on a par with related international agreements to prevent or minimize possible risks derived from the use and handling of transgenic products. For this to occur, competent national institutions must also develop institutional capacities to manage and evaluate field trials. Only then will countries in the region be able to take full advantage of transgenic crops capable of enhancing agricultural production and improving food security.

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Field Application of LMOs: Developing Country Perspective

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Abstract

About 87 million people are added annually to this world (Kendall et al. 1997). A majority of these people reside in developing countries. Biotechnological interventions like living modified organism (LMO) technology offer tools for increased food production and can be of great benefit to the developing world facing the challenge of feeding the growing population.

Although the potential of LMO technology is accurately perceived, the benefits of this technology remain limited largely to the developed nations. Most developing countries remain deprived of the benefits of LMO technology and have witnessed limited field applications on a commercial basis. Efforts are needed to take the technology closer to the developing parts of the world. This can be successfully done by a holistic approach that keeps in view the social, economic, and ecological considerations of individual countries.

This paper points out some unique considerations and perspectives of the developing world and focuses on the need for "tailoring" the technology implementation strategy according to those unique considerations.

Introduction

It is estimated that the global food demand will double by the year 2050. This increasing demand with decreasing natural resources like arable land and water conveys the challenge of producing more food in a sustainable manner. Although the global population increases annually at a rate of 1.5 percent, the amount of cultivable land is expected to decrease to 0.15 hectare per capita by the year 2050 (Engelman and LeRoy 1995). In view of globalization and the concept of our "common future," the challenge is global and is a concern for each one of us.

The need to produce more food in a sustainable agricultural system makes way for innovation in traditional agricultural practices. Incorporation of biotechnological methods like genetic engineering and its products like the LMOs can serve as one of the important tools, contributing to global food security. According to a report (Kendall et al. 1997) by a panel of experts commissioned by the World Bank, "it is likely that efforts to improve the rice yield in Asia through biotechnology will result in a production increase of 10 to 25 percent over the next 10 years." This estimation has been proven realistic in many field trials of LMOs in which the yield increase has been significant.

Incorporation of LMOs in the existing agricultural system promises encouraging beneficial consequences for the future of agriculture. The technology is of greater importance in developing nations where the population growth is higher and the challenge of food security is more intense. Biotechnological tools like LMOs, combined with some conventional breeding practices, offer effective means to meet the future demand of food production. Integration of biotechnology into the agriculture system has the potential to offer an increase in food yield in view of the economic and environmental considerations.

Although a very small portion of the globe has received the benefit of LMO technology, in most parts of the world, especially the developing nations, it remains a concept far from commercial application. Introduction and incorporation of LMOs call for innovative strategies. The strategies will have to be based on the unique considerations pertinent to a particular country. These considerations include social, ecological, and economic ones.

This paper will focus on the perspectives of developing countries on the following:

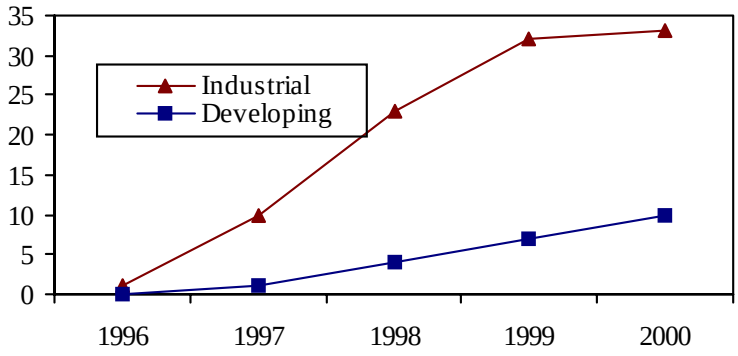
- Current status of application
- Traits of priority
- Future research trends.

I will try to give the developing countries point of view on these topics cited while comparing them with the industrialized nations' perspectives. The comparisons are made to differentiate the unique considerations of developing and developed parts of the world.

Current Status of Application

During the 5-year period between 1996 and 2000, the global area of transgenic crops increased by more than 25-fold from 1.7 million hectares in 1996 to 44.2 million hectares in 2000 (James 2000). Although the growth of technology adoption has been very rapid, it has been concentrated mainly in the industrialized nations. Figure 1 indicates the rapid yet uneven growth of transgenic technology adoption.

Figure1. Global Area ofTransgenic Crops, 1996 to 2000: Industrial and Developing Countries (million hectares)



Source: Clive James, 2000.

In view of the potential contribution of LMO technology towards food security and its economic benefits, it is of greater importance to the developing nations. According to a United Nations estimate, by the year 2050, 90 percent of the world's population will reside in Asia, Africa, and Latin America (http://www.unfpa.org). This clearly emphasizes the need for technologies like LMOs that may contribute to an increase in food production in the less developed nations. Although presently 85 percent of the transgenic crops are grown in industrialized nations, most developing nations remain deprived of this technology.

The uneven growth of LMO adoption needs serious consideration. In a global context, the benefits of this technology need to be extended to most developing nations that await the field application of their first transgenic crop.

Traits of Priority

Table 1 shows the relative frequency of traits in transgenic field trials conducted in 1999 and 2000. Most of these activities have been concentrated on the area of crop protection, including traits like herbicide tolerance, fungal resistance, viral and insect resistance, and so forth. The traits incorporated in the crops and with the priorities chosen are by and large the industrialized countries' priorities and considerations. Seventy-four percent of transgenic crops grown today are for herbicide tolerance trait. This trait is of greater importance for industrialized nations in which minimum human involvement is desired in order to cut the cost of labor in agriculture is one of the important considerations.

Table 1. Global area of transgenic crops in 1999 and 2000: by trait

	(Million hectares)			
Trait	1999	%	2000	%
Herbicide tolerance	28.1	71	32.7	74
Insect resistance (**Bt**)	8.9	22	8.3	19
Bt–Herbicide tolerance	2.9	7	3.2	7
Virus resistance/Other	<0.1	<1	<0.1	<1
Global Totals	39.9	100	44.2	100

Source: Clive James 2000.

Although crop protection traits are also important in the developing nations, the ranking of priorities for agriculture in developing countries may be different from that of developed nations. For developing nations that host more than 80 percent of the world's population, an increase in yield still remains a number one priority. This is especially true when 815 million citizens of the developing world are suffering from malnutrition.

The traits of high priority for a developing country are those that contribute towards increased food production. Although heading towards economic growth by way of ensuring food security, the developing nations also face the challenge of generating employment for their population that is growing at an alarming rate. Providing employment for the people, and thus making them capable of buying food, is also an important aspect of food security achievement. Therefore, unlike industrialized nations, where a trait like herbicide tolerance leads to a jobless economic growth (by minimum human involvement), the developing nations require job-led economic growth.

The traits of priority for the developing world should be considered with respect to their impacts on socioeconomic structure. The traits that will give maximum outcome in terms of quantity and quality of food and that use natural resources in a sustainable manner should attain highest priority in developing countries. The social considerations are also important when the introduction of technology will have to be focused on the needs of the people. Some examples of traits of high priority for the developing world are discussed in the sections that follow.

Traits with Improved Nutritional Value

About 30 percent of the people in the world suffer from iron deficiency and more than 40 million from vitamin A deficiency. A majority of these deficient people reside in less developed nations. Incorporation of a gene for ferritin, an iron-rich soybean storage protein, into the rice plant is a very good example of "need driven" biotechnology produce. This kind of iron-enriched rice can be one of the most socially and economically viable answers to minimizing iron deficiency in developing parts of the world.

Research work carried out by Ingo Potrykus and his team on development of vitamin A enriched rice can be used as an important tool to alleviate the serious health hazards caused by vitamin A deficiency in the developing world (Potrykus 1999). The development of vitamin

A enriched rice has the potential to save 250,000 children annually from becoming blind in the rice-eating Southeast Asian countries.

Improved nutritional qualities in the locally grown crops, like rice, can be a very effective tool for combating widespread nutritional deficiency in developing nations at a cost much lower then dietary supplement drugs.

Preventing Post Harvest Loss

Countries like India lose about 28 percent of their total food produce in postharvest losses. This is primarily due to lack of infrastructure like transport systems, storage facilities and so forth. Lack of proper storage mechanisms not only results in quantitative losses but also accounts for considerable deterioration in the nutritive quality of food.

Traits for increasing shelf life can contribute greatly to preventing food waste and making it accessible to food deficient people. These traits can help the harvest withstand the effects of poor storage and transport facilities in countries in which modern tools of quick transportation and environmentally controlled storage facilities are a luxury.

Traits for Resistance Against Abiotic Stress

Extreme climatic conditions are one of the major factors limiting world food production capacity, especially in the developing nations. It is difficult to find "stress free" areas in which crops may approach their potential yield. Abiotic stresses are considered to be the main source (71 percent) of yield reduction (Boyer 1982). Incorporating traits for stress resistance and tolerance can be an economically and environmentally viable approach to bridging the gap between actual and potential crop yield in marginal areas. Development of crops suitable to grow in conditions of abiotic stress can make a significant contribution toward utilizing the arable land to its maximum potential and thereby increasing crop productivity.

The foregoing traits combined with traits for pest resistance, increased fertilizer efficiency, and edible vaccine production are of prime importance to the developing nations and offer economically and environmentally suitable, sustainable solutions.

Future Research Trends

Future research that aims to incorporate newer traits in crops should consider the needs of both the developed and the less developed parts of the world. The current debate about and limited acceptance of, LMOs in many parts of the world are largely a consequence of the lack of communication between scientists and the consumers of technology, including the farmer. Understanding and effective communication between the two would help in clarifying many misconceptions about the technology. The study of public perception of biotechnology and the development of a stronger to-land link needs to be considered as one important research direction for the future.

Ironically there is a global communications network that makes the latest findings of science available almost immediately to research workers around the globe. What is urgently required is a similar communications network at the service of farmers and consumers of technology. Serious efforts are needed towards setting up a "global" mechanism in which the involvement of international agencies can play a significant role. International agencies like Consultative Group on International Agricultural Research (CGIAR) and Food and Agriculture Organization (FAO) involved with agricultural development work can take a lead in educating farmers about revolutionary technology like LMOs. Consortia of agencies should be formed under the umbrella of international agencies with local government, industries, scientific organizations and educational media as its members in developing countries. The consortia can take up the challenge of educating the farmers. The consortia can also become a tool for communication between various research efforts, media, farmers, and policymakers. This role is similar to the one played by international agencies like the World Health Organization (WHO), in health education during the past two decades. Agricultural education needs similar attention and can optimize the advantage of technology in leading the less-developed world towards food security.

At the present time in countries like India there is a lack of educational mechanisms for farmers. This is one of the greatest reasons for relatively slow acceptance of concept technologies like LMOs. Traditionally, in the absence of efficient government-initiated education mechanisms, agro-industries have played an important role in the farmer's education. The industry's efforts (quite understandably) have been biased towards prototing a particular product rather then a technology. This identifies the need for unbiased agencies to get involved with educational efforts and to facilitate public understanding of the variety of applications and issues associated with agricultural biotechnology. Such education must be based on an in-depth assessment of public awareness and attitudes about biotechnology. Existing research is not addressing the need to design and implement effective educational programs (Hoban 1992).

Conclusion

There is an increasing amount of compelling evidence that LMOs can deliver important economic and social benefits in addressing the global need for sustainable food security. The promise of the technology can only be fulfilled when the benefits of the technology will be extended evenly to all parts of the world. Because LMO adoption is now primarily concentrated in the industrialized nations, serious efforts towards taking the technology to the developing world are needed. That this important technology does not remain limited to the more advanced nations but gets incorporated into the agricultural systems of the less developed world should be seen as a global necessity.

Today, 85 percent of the land area covered under transgenic crops is in industrialized nations. Consequently, the crop and traits being incorporated are based on the priorities of the developed world. The developing nation's priorities may differ from those of industrialized nations—especially because most developing nations host a very large number of food deficient people. Producing a greater quantity of food with limited natural resources remains a prime priority of food-deficient nations, but this may not be the case in industrialized nations. The traits and crops of importance should be considered from the standpoint of these unique considerations of developing nations and expected priority differences.

The technology transfer from laboratories to land should be done holistically on the basis of the individual country's socioeconomic and ecological needs. This kind of approach will contribute towards extending the benefits of LMO technology more evenly to all parts of the world. Educating the farmer and the consumer about the benefits of the technology will help in promoting it in such a way that we do not have to "push" the technology but instead the people will "pull" the technology because it is seen as advantageous and profitable.

Acknowledgments

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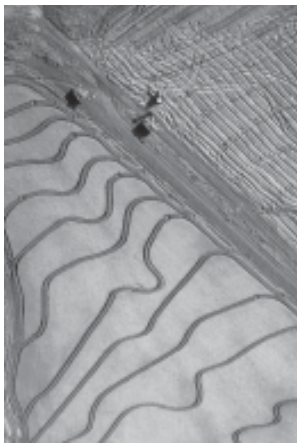
Life Cycle Assessment (LCA) of the Cultivation of Transgenic Crops as a Tool for a Comprehensive Assessment of Potential Environmental Effects



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Abstract

In a study commissioned by the Austrian Federal Environment Agency comparative life-cycle assessment was tested for the first time as a method to evaluate the short-term and long-term environmental effects of conventionally bred and transgenic crops in a given, specific agricultural system.

The methodology developed was based on life-cycle assessment in accordance with ISO 14040 ff. A scenario-based approach was chosen. To increase the usefulness of the life-cycle assessment, a risk assessment was added to the impact assessment. Insect-resistant maize (BT-176, Novartis) and herbicide-tolerant rapeseed (BASTA-tolerant, AgrEvo) were chosen as model plants.

Inventory analysis was performed using a set of data specific to Austrian agriculture and so-called generic data on energy, transport, and commodities. The quantitative impact assessment for a selection of broadly accepted impact categories was enlarged by adding a qualitative risk analysis on the human and ecotoxicological impacts of genetically modified organisms and those pesticides that can be replaced by the use of such organisms.

Introduction

The application of genetic engineering in plant breeding has triggered a discussion on the potential benefits and risks of using transgenic plants in agriculture. Comparative life-cycle assessment (LCA) may be a method to assess the short-term and long-term environmental effects of conventionally bred and transgenic crops in a given agricultural system.

Therefore, the Austrian Federal Environment Agency in Vienna commissioned a team of scientists from C.A.U. GmbH, Öko-Institut e.V. and ÖVAF (Österrichische Vereinigung für Agrarwissenschaftliche Forschung) to perform a study (Klöpffer et al. 1999) titled "Life-Cycle Assessment of Genetically Modified Products as a basis for an Assessment of Potential Environmental Effects."

A comparative assessment of genetically modified plants and "naturally" bred plants by LCA cannot replace public discussion. But it can identify the most important measurable factors, quantify mass and energy flows, and compare the environmental impacts of different systems. Therefore, it can be a meaningful instrument for an extensive evaluation.

An LCA takes into account all the relevant energy and mass flows, including emissions and waste during the whole life cycle "from cradle to grave" of a product or service. It relates the numerical results obtained to "functional units"—a measure of product utility. The "functional unit" is laid down in the "goal definition" together with the system boundaries of the product systems under study and other information. The "cradle" in the case of replenishable raw materials and agricultural produce is usually taken to mean the seed. This "holistic" approach is what distinguishes LCA from other assessment methods that only consider partial aspects of environmental protection and are thus liable to misinterpret results. Furthermore, LCA is the only internationally standardized method of analyzing product-related environmental effects.

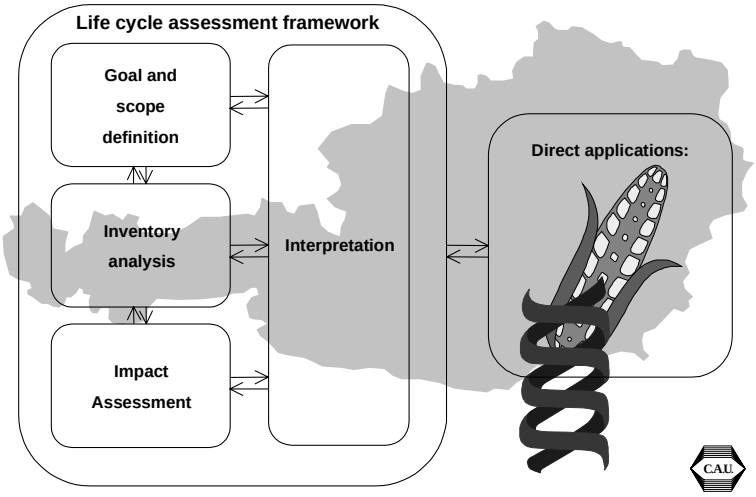
An LCA, as defined in ISO 14040 (ISO, 1997)(see figure 1), consists of four steps:

- Goal and scope definition
- Inventory analysis
- Impact assessment
- Interpretation.

Applications of the method are, among others,

- Product development and improvement
- Strategic planning
- Public policymaking
- Marketing.

Figure 1: Life cycle assessment as defined in ISO 14040 applied to the cultivation of trasgenic crops in Austria



Goal and Scope Definition

The main goal of the study was to adapt the LCA methodology to the special questions connected with the cultivation of genetically modified crop plants. Such an approach posed a methodological challenge. First, on a European scale there are few data available on the performance of transgenic plants under normal agricultural conditions. Second, the problem of how to integrate the currently undertaken risk assessment according to the European Union (EU) directives into the framework of the LCA has to be solved. In selecting the model plants for this study several aspects were considered as follows:

- Relevance among applications for release of genetically modified crops in the European Community
- Environmental relevance of the receiving plant
- Environmental relevance of the genetic modification
- Expected agricultural practice
- Economic potential.

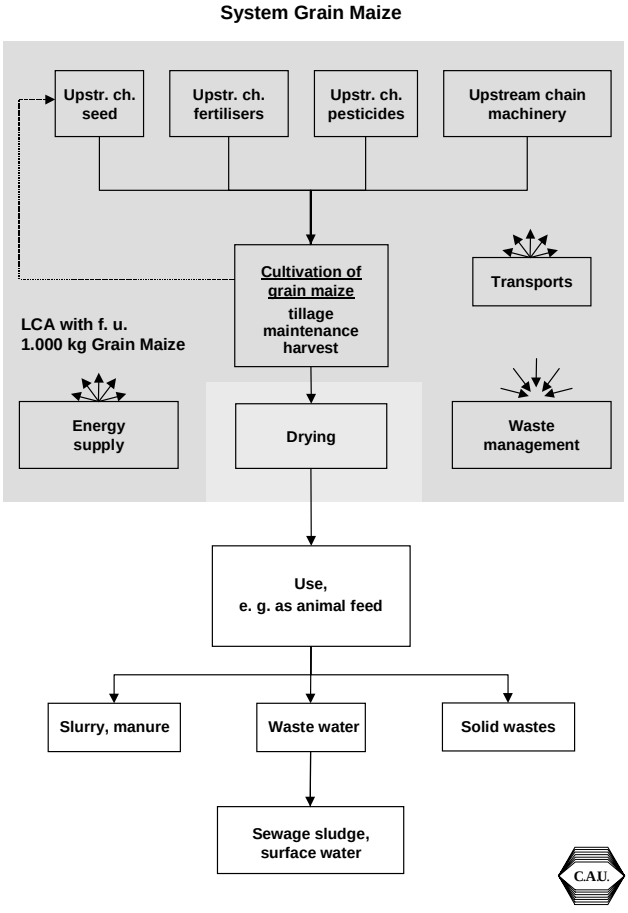
Grain maize and winter rape were chosen. They both represent crops with large areas under cultivation in Austria. The genetic modifications are the introduction of an insecticidal protein into grain maize by using the delta-endotoxin gene of *Bacillus thuringiensis* (Bt-176, Novartis, now Syngenta) and, in the case of winter rape a resistance gene against the herbicide Basta or Liberty (AgrEvo, now Aventis).

The two model plants were studied on the basis of three different cultivation methods appropriately adapted to reflect conditions in Austria:

- Conventional cropping
- Conventional cropping with genetically modified organisms (GMOs)
- Organic cropping.

Organic farming was included in the analysis to do justice to the importance that this method has attained in Austria. All quantitative results are referred to a functional unit, defined here as 1,000-kg grain maize (e.g., used as animal feed) and 1,000-L rapeseed oil (for food purposes), respectively. To illustrate the systems under study, Figure 2 gives an overview of the life cycle of grain maize.

Figure 2: Overview of the processes in the life cycle of grain maize; the lower part was not quantified in inventory analysis, but considered as target compartments in risk analysis.



The geographic system boundary in the context of agricultural production is the national border of the Austrian Republic. As with almost all life-cycle assessments with national system boundaries, the supply of fossil fuels and raw materials constitutes a transgression of

the present system boundary. The temporal system boundary primarily applies to the agricultural scenarios, which were developed with reference to the period from 1994 to 1996. Most available data were selected for their up-to-dateness; older data (before 1990) were only used in exceptional cases where newer ones were unavailable.

Inventory Analysis

Key features of inventory analysis in LCA are data collection about

- raw materials, energy, and land use;
- emissions to air, water, and soil;
- waste;

and include the quantification of inputs and outputs for all modules of the system under study.

Inventory analysis here was performed in accordance with ISO 14041 (ISO 1998) using a set of data specific to Austrian agriculture (supplemented with information from other EU member states and Switzerland (EC–DG VI 1997) and so-called generic data on energy, transport, and commonly used materials. Great effort was made to get representative data on Austrian cultivation of grain maize and winter rape. The specific agricultural data collected by ÖVAF derive from official statistics, official model calculations, advisory papers, responses to questionnaires, and expert talks with chambers of agriculture, the Federal Office and Research Centre for Agriculture, University for Agriculture Vienna, and Raiffeisen Ware Austria.

In the case of grain maize, four scenarios for conventional cultivation, three for the use of GMOs and one for an organic scenario were analyzed. On the basis of data reflecting typical Austrian growing conditions, these different scenarios gave attention to variable infestation by the European corn borer and resulting yield loss or to plant protection strategies (application of the insecticide Decis or straw flailing). The scenarios investigated are listed in table 1. The scenarios GM 6 and 7 represent a typical Austrian average with and without use of a genetically modified organism (GMO), and scenario 1 is a worst-case assumption. For winter rape, one conventional, two GMO, and one organic scenario were defined. The two GMO scenarios differ in the extent of Basta application. Weed control in the organic scenarios was mechanical.

Table 1: Overview of the scenarios for the two crops in the Austrian study

Scenario	Description
Grain maize	
GM-Sc. 1	conventional, 100% infestation of corn borer
GM-Sc. 2	as 1, but application of insecticide
GM-Sc. 3	conventional, no infestation
GM-Sc. 4	GMO, no infestation
GM-Sc. 5	GMO, 100% infestation
GM-Sc. 6	conventional, 25% infestation, insecticide use on 10% of area
GM-Sc. 7	conventional, 25% infestation, GMO on 10% of area
GM-Sc. 8	organic
Winterrape	
WR-Sc. 1	conventional
WR-Sc. 2	GMO, one Basta application
WR-Sc. 3	GMO, two Basta applications
WR-Sc. 4	organic

GMO-specific data provided by the company Novartis showed that it is reasonable to assume that the GMO scenarios only differ in plant protection from the conventional scenarios. Inventory analyses were performed for all the preceding scenarios.

The most widely used generic dataset employed originates from the "Eco-inventories of Energy Systems" developed at ETH Zürich (ESU–ETH 1996). Infrastructure was generally taken into account, for example, by balancing machinery production, maintenance, and farm buildings for accommodating the machinery. The generic datasets of ESU–ETH, which are largely used, also take infrastructure into account, and thus data compatibility was ensured.

Impact Assessment

Life-cycle impact assessment (LCIA) entails the following:

- Classification of interventions from the inventory like CO_2 emissions to an appropriate impact category like climate change.
- Characterization—modelling the potential environmental impact of interventions from inventory within an impact category (e.g., Global Warming Potential (GWP) of CO_2 = 1.
- Optional elements: normalization, sorting, grouping, weighting.

A quantitative impact assessment was conducted for a selection of impact categories, as described in table 2. The assessment was largely based on the method published by Klöpffer and Renner (1995) with modifications in the categories resource depletion and nutrification.

In the category of resource depletion, each resource is weighted with the reciprocal value of its static lifetime (Lindfors et al. 1995). The static lifetime of a resource is expressed in relation to that of crude oil, which serves as a standard.

Table 2: Selected Impact Categories for Impact Assessment in an LCA of genetically modified plants

Selection of Impact Categories

Impact Category	Relevant Exchanges in Inventory
Cumulative Energy Demand (CED)	Fuels
Resource Depletion	Raw Materials
Climate Changes (GWP)	CO_2, CH4, N2O
Acidification (AP)	SO2, NH3, NOx
Eutrophication NPA, (NPT)	N, P
Human Toxicity (HTP)	Heavy Metals, Pesticides, GMO
Ecotoxicity (AEP), (TEP)	Heavy Metals, Pesticides, GMO
Appropriation of Environmental Space	Land Use

Cumulative energy demand (CED) is defined in Verein Deutsche Ingenievre (VDI) Guideline 4600 (VDI 1997). It does not include manpower, metabolic energy (e.g., the energy content of food), and passively used solar energy. The CED is normally calculated on the basis of the net calorific value (NCV).

For characterization in the categories human toxicity and ecotoxicity (aquatic and terrestrial), the critical surface time method conceived by Jolliet and Crettaz (Jolliet and Crettaz 1997, Jolliet et al. 1998) was applied.

The impact category of "appropriation of environmental space" is intended to embrace impact potentials caused by land use pertaining to the spheres of nature conservation, species diversity, soil protection, erosion, and direct landscape consumption. It is meant in particular for possible damages that go beyond the toxic effects of emissions.

Risk Analysis

The risk analysis was done on the basis of the risk categories defined by the Organization for Economic Cooperation and Development (OECD) in 1993, EU Directive 94/15 EC (Commission of the EU 1994), and the "Framework Approach to Environmental Risk Assessment for the Release of Genetically Modified Organisms" jointly elaborated by the member States (Doc XI/0877/96—Rev. 4). According to these sources, the release of transgenic plants merits an examination of the following types of risks:

- Pathogenicity for other organisms
- Altered host ranges
- Potential for adverse health effects on human beings
- Questions of allergenicity and toxicity
- Population dynamic effects and effects on biogeochemical cycles
- Effects on target and nontarget organisms
- Pathogen–host interrelationships
- Predator–prey relationship
- Competition and displacement effects
- Interactions with the abiotic environment
- Possibilities of survival, establishment, and dispersal
- Introgressive tendencies and competitive advantages of transgenic plants
- Gene transfer to natural cross-breeding partners
- Horizontal transfer of recombinant genes to microorganisms
- Phenotypic and genetic stability
- Pleiotropic and position effects

Not all of these categories are applicable to the two selected transgenic plant groups (maize, rape).

Following Torgersen's suggestion (1996), this study analyzed alterations in agricultural practice with a view to identifying possible additional effects of transgenic maize and rape cultivation on the environment.

For the Bt-176 maize scenario the possibility of resistance development in the corn borer as the target pest and to resistance management strategies was also considered. Risk evaluation was undertaken to estimate the effects of Bt-176 maize cultivation and Basta-resistant rape on the environment, giving due consideration to possible damage to natural ecosystems as required under EU Directive 90/220/EEC. To have considered natural ecosystems alone, however, would have meant neglecting many other effects with environmental consequences. Following Torgersen's (1996, p. 41ff) demand, the present study therefore took a broader view in evaluating the possible effects of transgenic maize and rape cropping as practiced in their GMO scenarios. This was done by considering the potential effects on agricultural ecosystems, ruderal habitats, and small island populations. Furthermore, it discusses the environmental effects of the altered methods used in GMO cropping. Nevertheless, any prospective risk assessment is inevitably subject to multiple uncertainty factors. These problems of prospective risk assessments are attributable to

- the complexity of the matter;
- lack of knowledge on essential factors governing a system and their interactions;
- lack of unequivocal cause-and-effect relationships (which cannot be established in complex systems that are governed by very many parameters; if at all, they can only be identified retrospectively at a statistical level);
- the difficulty of transferring contained systems (e.g. a greenhouse) to open systems;
- the difficulty of transferring results from small areas to large ones.

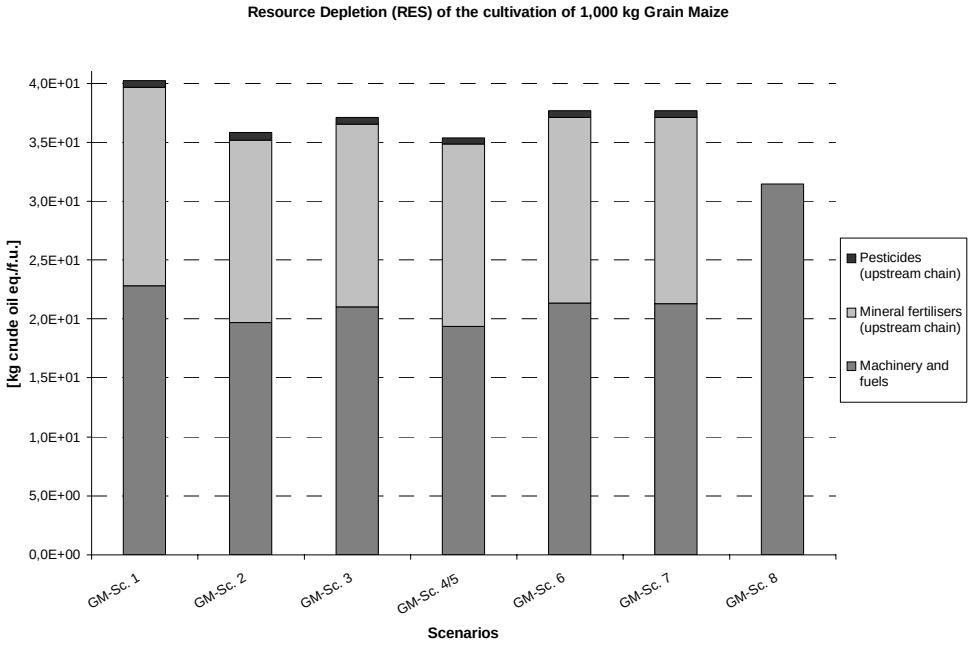
Prospective risk assessment becomes more convincing the more it can be backed up by demonstrable effects or data. A matrix was used to make a differentiated presentation of what are proven, or experimentally demonstrable phenomena, or both, on the one hand and, on the other, associated with the former, effects that are presumed or plausibly explainable or have been demonstrated in individual cases.

Results

Working from the inventory analyses, impact category results were calculated for the categories of cumulative energy demand (CED), resource depletion (RES), appropriation of environmental space, global warming potential (GWP), acidification potential (AP), eutrophication potential (aquatic NPA and terrestrial NPT), human toxicity potential (HTP), and ecotoxicity potential (aquatic AEP and terrestrial TEP). Save for the semiquantitative part aspects, risk analyses were performed on a qualitative basis, covering the issues of outcrossing, resistance development, uptake of transgenes by micro-organisms, resistance management, diminished effectiveness of biological plant protectants,and human and ecotoxicological impacts of those pesticides that can be replaced by the use of a GMO.

As an example for the results of quantitative impact assessment, the resource depletion (RES) for the eight-grain maize scenarios is shown in figure 3.

Figure 3: Resource depletion (RES) for the cultivation of grain maize including upstream chains (referred to the functional unit of 1,000 kg grain maize))



Interpretation

For interpretation of the quantitative impact assessment, the investigated systems have been compared within each impact category to identify significant differences that indicate advantages or disadvantages of one system with regard to environmental burdens. Significant here means differences of at least 20 percent.

Evaluation of the impact assessment shows that in most of the impact categories the result is determined, apart from the level of the yield, by the nitrogen fertilization. Whereas the data basis for the mineral fertilizers is satisfactory (apart from some data gaps in the process emissions), the uncertainty about heavy metal content in the case of the organic fertilizer has to be pointed out.

The upstream chain of the pesticides has only a minor influence on the results. Because herbicides dominate in the cultivation of maize and the scenarios 1 to 7 differ in the use of insecticides, there are only small differences in the categories on human toxicity and ecotoxicity.

In table 1 a list is presented for the grain maize scenarios. The conventional scenarios 1, 2, 3, and 6 are distinguished by corn borer infestation, yield, and measures of insecticide use or straw flailing. The GMO scenarios 4 and 5 correspond to the conventional scenarios 2 and 3, and the GMO scenario 7 corresponds to the conventional scenario 6. The scenario 6, which mirrors the average situation for the conventional cultivation of grain maize in Austria, is selected as the standard. In figures 4 and 5, the percentage deviation of the other scenarios from the standard scenario shown. Bars pointing to the left indicate smaller ecological burdens relative to the reference scenario; bars pointing towards the right indicate greater burdens.

The deviations of the scenarios 1 to 7 are mainly due to different yields. However, they have to be judged as not significant because the deviations are smaller than 10 percent for all impact categories. No ecological advantages for *Bt*-maize in Austria can be deduced from the results.

Figures 4 and 5 show examples for grain maize scenario 1, which represents worst-case assumptions and the Bt-grain maize scenario 4/5.

Figure 4: Comparison of impact category indicator results of grain maize scenario4/5 (GM-Sc. 4/5) relative to the Austrian standard scenario (GM-Sc. 6)

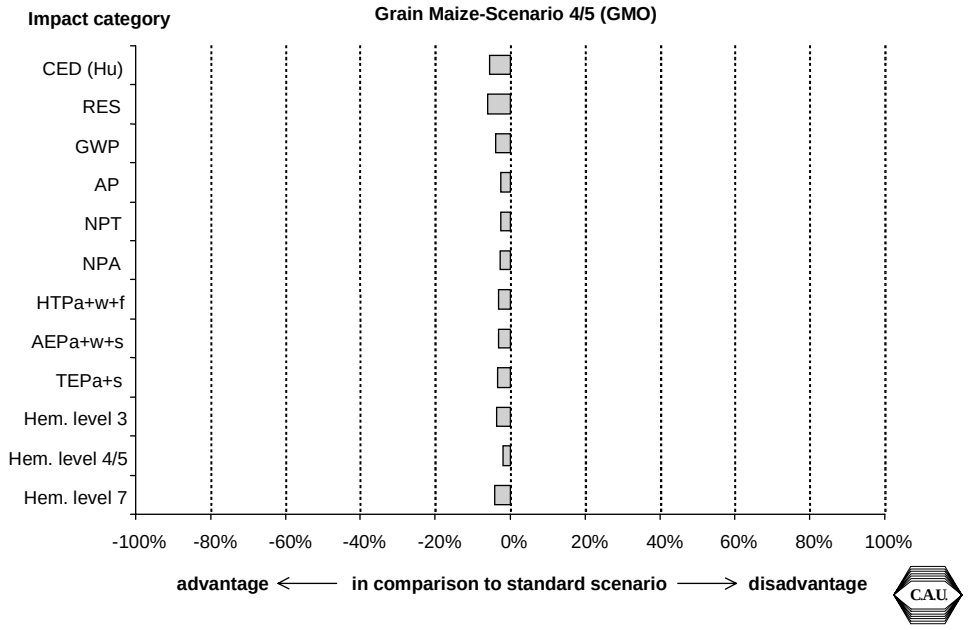
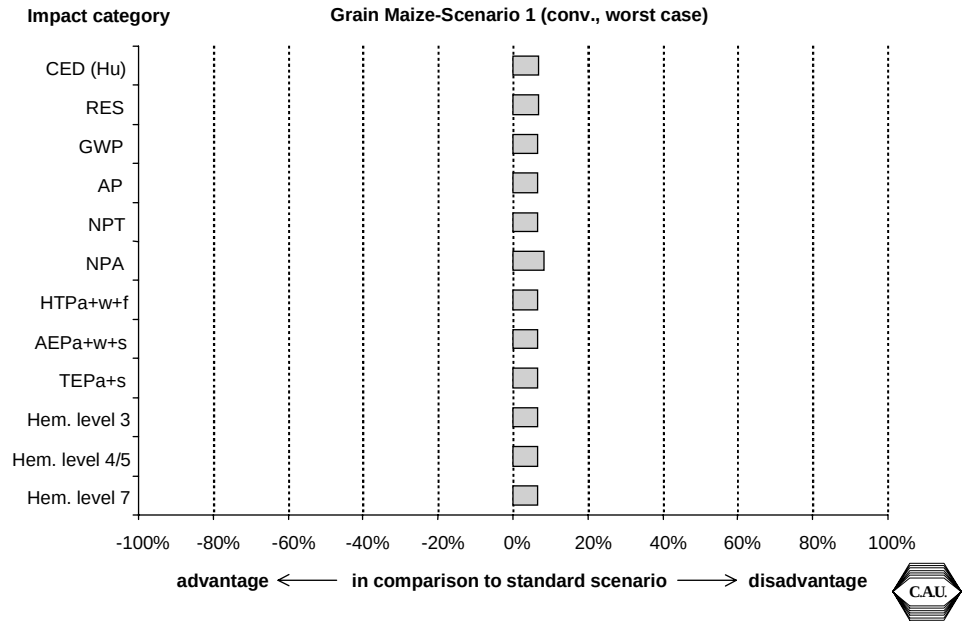


Figure 5: Comparison of impact category indicator results of grain maize scenario1 (GM-Sc. 1) relative to the Austrian standard scenario (GM-Sc. 6)



Discussion and Conclusions

The essential results of the present LCAs on the systems of grain maize and rape oil, considered for the cultivation methods conventional farming, conventional farming using GMO, and organic farming under Austrian conditions, respectively, were as follows:

- The chosen methodology (LCA according to ISO–EN 14040 [1997] supplemented by a risk analysis on the nonquantifiable impact categories) is suitable for arriving at a meaningful comparison of systems.
- The inventory analyses and impact assessments show that in terms of the quantifiable parameters the differences between GMO and conventional farming are small, whereas organic farming performs significantly better in some categories such as cumulative energy demand, acidification and eutrophication.
- In all systems studied, fertilizer use was found to contribute the greatest burden. Data on this point were particularly deficient in the case of organic farming.
- Verbal risk analysis on the basis of risk categories revealed a considerable degree of uncertainty regarding the ecological behaviour of GMOs. These must be taken seriously as risks associated with GMO release and commercialization as required by the precautionary principle.

As political action usually proceeds after a weighing of the potential benefit of a proposed measure with its associated risks, the question emerges whether the risks of GMO farming identified in the study are compensated by any ecological advantages. Under the agricultural and environmental conditions prevailing in Austria the examples studied show no significant advantages. On the basis of the study's recommendations a further approach to integrating the risk analysis of the use of transgenic crops in agriculture into the methodological framework of life-cycle impact assessment was made (Klöpffer et al. 2000, Renner et al. 2001). This was done by creating a new impact category called "effects of genetically modified crop plants." This impact category enables taking into account the risks of the deliberate release of genetically modified crop plants in the course of agricultural production and the comparison of different genetically modified crop plants. To calculate a factor for characterizing a specific genetically modified crop plant, a risk number is determined on the basis of the likelihood of each risk category's being realized. This depends on the likelihood of dissemination in a specific climate zone as well as on the number of transferred or modified genes. This risk number is combined with the number of the potentially affected safeguard subjects (natural environment, human health, manmade environment). The data are gained from the respective notification dossiers for the specific genetically modified plant.

Life-cycle assessment is now applied to the cultivation of transgenic maize in several European countries in a project subsidized by the European Commission (CAMPLES 2000-2002).

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- Austrian Association for Agricultural Research (ÖVAF), Vienna (Richard Dietrich)

Advisory Group

The project team was complemented by an advisory group that contributed substantially to the selection of systems, discussion of interim results, and data gathering. The advisory group included the following institutions

- University for Agriculture, Vienna (Institute for Organic Farming)
- Austrian Academy of Sciences (Institute for Technology Assessment)
- NOVARTIS International AG

Reviewer

According to ISO 14040 § 7.3 (ISO 1997) the publication of an LCA study report containing comparative assertions necessitates a critical review by external experts. The review was conducted by Dr. Gérard Gaillard, FAT, Tänikon, Switzerland, now Forschungsanstalt für Agraröleologie und Landbau (FAL), Reckenholz, Switzerland).

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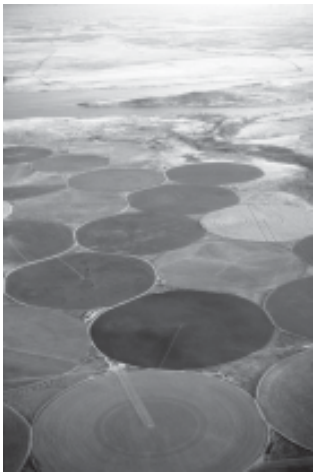
Living Modified Organisms and the Environment: Social and Economic Issues to Consider



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Abstract

The typical approach to risk analysis does not explicitly incorporate socioeconomic factors as a required step. A common argument against their incorporation is that socioeconomic considerations are more elusive and difficult to assess using sound science. Nevertheless, some of the possible effects of socioeconomic factors may be identified through adequate methodologies. Society´s traditional practices and cultural responses to perceived risks may alter the overall risk as well as the net benefits of a new technology and increase the associated cost of risk mitigation strategies. Therefore, risk analysis will be inaccurate unless assessors adequately consider relevant socioeconomic factors. Differences in socioeconomic conditions across regions in which new technological products are to be applied must be known, understood, and properly incorporated into existing methodologies for risk analysis. A wider multidisciplinary approach to evaluate these issues and facilitate communication among experts in different fields or agencies must be ensured.

Introduction

Traditionally, approaches and methodologies in risk analysis, which comprises risk assessment, management and communication, have largely ignored the socioeconomic factors, also known as the "fourth criterion" or the "peoples' factor" National Research Council 1994, Lalcy 2000 in Batie and Ervin 2001). The incorporation of socioeconomic aspects into risk analysis is necessary to understand how humans create, react to and redistribute risks and hazards and decide on the best courses of action. People react to risk, and the collective probability they associate with health or environmental consequences affect their choices.

In the face of uncertainty, consumers may decide not to purchase some products, or peasants may opt for using different plant varieties, adopt different technologies, change the plots of land that they cultivate, and so on, in an attempt to protect themselves against risks. As a result, the overall risk and the net benefits and costs will change. Even more important, not all people and societies will react the same

way, nor will they balance the costs and benefits of a new technology in the same manner. The only way to make these factors apparent is through their incorporation as part of risk analysis. Therefore, risk analysts must explicitly incorporate socioeconomic factors into their methodolgies to take into account the consequences and desirability of adopting a new technology in a specific context.

In the case of new biotechnologies resulting in the production of genetically modified organisms (GMOs), adequate risk analysis is particularly important given the uncertainties and potential risks surrounding their adoption. Incorporating socioeconomic considerations into the analysis is also necessary given the large range of socioeconomic as well as environmental conditions under which these technologies are intended to be introduced. This is imperative also because globalization among other factors is accelerating the diffusion of new technologies and the range of environments in which they operate.

This paper will attempt to show the relevance of socioeconomic factors in risk analysis for new biotechnologies, particularly for genetically modified crops, and to highlight some of the methodological implications. The first part of the paper deals with the nature of technological developments and risk. The second part focuses the analysis on biotechnologies and GMOs. The third section provides some specific examples of socioeconomic factors that affect the outcome of risk analysis and considerws their implications.

Technology Adoption and Risk Analysis in Perspective

Technological developments arise from the conjunction of human creativity and human needs in a race to outcompete natural forces. Human creativity is constantly producing new solution concepts that, if successful, will improve social welfare. These new solutions, however, often have unexpected outcomes or do not always fulfill their promises. Why? Two main factors behind failing technologies are either that (a) they were applied in contexts (both natural and socioeconomic) for which they were not designed, leading to poor performance of the technology, or (b) unexpected negative outcomes were detected once they were adopted even when applied in appropriate contexts, leading to costs not previously accounted for.

With regard to the importance of the context for technological applications, it has been recognized that variations in skills and capacities and in cultural differences related to labor practices as well as differences among property rights systems do imply variations in costs and levels of productivity across various alternative production technologies (Hodgson 1988). Therefore, the same technology cannot be expected to perform in the same way in different contexts, and this will affect its benefits and relative costs. These differences may also lead to variations in associated risks.

The second factor, unexpected outcomes, is related to the state of knowledge at the time of adoption, and the negative impact of this factor on society depends on its willingness to adopt the new technology despite risk and uncertainty. Although it would be better to have full certainty about outcomes befor making decisions, there is a limit to our capacity to

understand the natural world therefore, society´s attitude to uncertainty must be adequately considered. Limited knowledge of the implications of new technologies has led in the past to unexpected outcomes not considered at the time these technologies were introduced.

One example of unexpected outcomes was the introduction of pesticides like DDT during the so-called green revolution that were considered risk-free by scientists and manufacturers. As time passed, however, evidence of negative impacts arose that led to different decisions regarding adoption of these pesticides. New information on the safety and performance of new technologies allows for better decisions to be made. It should not be forgotten, however, that some of the negative impacts of technology may be irreversible or very significant. Hence, it is desirable to find means to reduce the knowledge gap before the adoption of new technologies. This not only involves knowing more about the technology–environment and technology–society interactions but also about the "type" of information nneded by society to make a decision about the adoption of the technology. It is important to bear in mind that this information may not be the same for different socioeconomic contexts.

As a result, we can conclude that there are three elements of risk analysis for which socioeconomic factors play a significant role:

1. The extent and nature of perceived risks;
2. The extent of costs and benefits; and
3. The information needed for an adequate balance between overall risks and net benefits.

When transferring technology to other national contexts, we have to analyze the social, institutional, and economic impacts of doing so to ensure that risks are bearable and manageable and are offset by the benefits of the technology *in terms of the society in the new context*, not from the point of view of the society that produced the innovation.

If socioeconomic factors are included in risk assessment, differences in socioeconomic conditions across the regions in which the new technological products are to be applied must be identified and understood so that these issues may be properly incorporated into risk analysis.

However, consideration of these factors has not been required in the typical risk assessments of new technologies. A common argument for not including socioeconomic considerations into risk assessment and management is that socioeconomic factors are more elusive and cannot be assessed in the same way as "hard" sciences. Nevertheless, (1) the impossibility of assessing socioeconomic factors in the same controlled way as some biological aspects does not in itself diminish their importance, and (2) developments in social and behavioral sciences in the past decades allow for a broader set of analytical tools and methodologies to address these issues.

Future discussions of risk analysis must take into account socioeconomic aspects and enable a fluent and effective dialog across disciplines to construct a common understanding of the implications of socioeconomic factors and to expand current risk analysis procedures and develop integrated assessment methodologies.

From the government perspective, an integrated risk assessment methodology is essential to ensure that regulation based on risk analysis achieves the socially desirable outcome. The regulatory framework is an instrument that potentially could alter the perceived costs, benefits, and the possibility of different outcomes of new technologies, and it is therefore important that the policymaking process be guided by adequate risk assessments. To the extent that policy decisions take into account results from risk assessments, including socioeconomic considerations, decisionmakers will be able to consider strategies to distribute costs and benefits of a risk or hazard equitably among social and economic groups in the implementation of the risk management strategies. Consequently, Crocker and Shofgren (1999) concluded that "risk management in this area should take both biological and social-economic aspects into account, in order not to be (at best) inaccurate or (at worst) ineffective." It must be recognised that public opinion and social perceptions are also important elements to be taken into consideration. In the face of choice under uncertainty, the decision about what level of overall risk is considered appropriate, given potential benefits, is inherently a social, not a scientific one (Lalcy 2000 cited in Batie and Ervin 2001).

New Technologies, New Risks: Biotechnologies

In the case of modern biotechnologies, like the new range of GMOs, adequate risk analysis incorporating socioeconomic considerations is particularly important given the profound potential changes, both socioeconomic and ecological, that may arise from the use of these technologies. Biodiversity loss is a general category of impacts, which covers damages to crops, wild relatives, nontarget organisms, and to wider ecosystem processes. For instance, herbicide-resistant organisms stimulate the use of herbicides, antibiotic-resistant species create health risks, and genetic engineering in general stimulates homogeneous monocultures that in turn promote erosion and quickly spread diseases (van den Bergh and Holley 2001). These ecologically related potential consequences are among the most serious risks since insurance against them is often impossible. Effects such as genetic erosion, extinction, or loss of ecosystem functions are irreversible and cannot be compensated in financial terms (Crocker and Shogren 1999). It is therefore important to review the risk analysis procedures for these organisms.

Risk Assessment for GMOs and Conventional Improved Varieties

A controversy continues over whether genetic engineering is different from ordinary or traditional techniques used during domestication of organisms through controlled breeding and selection. This is an important starting point because disagreement with this statement could lead to different conclusions with other implications. If there is no intrinsic difference, then there is no need to respond differently to transgenic plant introductions than to the new variety introductions derived from conventional techniques. There would still be a need to improve the way in which we analyze the risk associated with new varieties, but probably to a lesser extent.

We believe, however, that there are intrinsic differences between traditional breeding for domestication and genetic engineering (table 1). Therefore, we have to analyze whether this new technology presents any new hazards to human health or the environment and how socioeconomic aspects might influence the levels of risks associated with the use of GMOs that are different from those generated through traditional breeding. For each case we have to consider a different three-fold interaction: (1) the genetically modified organisms (GMO), (2) the modification or inserted genes, and (3) the environment in which the GMO will be released. Here we propose an extended perception of the environment that includes, besides the typical biological factors, particular cultural, social, and economic factors, including characteristic farming practices.

Table 1. Comparison among traditional breeding and genetic engineering

Traditional Breeding	**Genetic Engineering**
Limited by compatibility and phylogenetic relationships	Not limited by reporductive barriers
Leads to the interaction of groups of genes in the same evolutionary lineage	Often includes the interaction of genes and genetic sequences from very distant lineages
Produces new gene combinations that are possible	Produces new gene combinations that are not possible

Socioeconomic Considerations in Risk Analysis for GMO Technologies: Methodological and Conceptual Challenges

Socioeconomic considerations are pertinent to risk assessment and risk management activities in relation to biotechnological products, as has been already recognized for risk communication. The socioeconomic considerations of most importance to risk analysis include the evaluation of economic costs and benefits of different decisions, development and communication of decision criteria for the release of a GMO (e.g., cultural considerations) and the cost-effectiveness of risk management strategies.

Socioeconomic considerations also include the analysis of economic risks that, although preexisting in the production systems under consideration, may be exacerbated or reduced by the introduction of a new biotechnology. For instance, consider that the market for biotechnological inputs in the crop sector is highly concentrated, that is, with only a few major companies. The result of the wide diffusion of biotechnologies is linked to an increased dependence of farmers on a limited number of suppliers of inputs for crop production (European Commission 2001). This dependency adds economic uncertainty for producers and processors who no longer have the same degree of technical and economic influence over their suppliers. Although the effect is more of a market nature rather than an ecological one, it is nonetheless

important to consider as part of a more holistic approach in risk assessment changes in markets may have effects on ecological processes and vice versa.

Some biotechnological applications tend to be nonreversible. Their irreversibility has both economic and ecological–evolutionary implications. Economically, irreversibility associated with the practical impossibility of eliminating released GMOs that may have transferred their transgene constructions may lead to the foreclosure of options to use alternative technologies or the access to specific markets demanding GMO-free products. Ecological irreversibility

Table 2. Examples of the relevance of socio economic factors in risk asessment and management

Risk Analysis	SocioEconomic Factor	Potential Effect
Risk Assessment	Consumption patterns.	Risk effects related to allergenic reactions are related to conumption pattersn, which in turn are culturally determined. Different human populations may have different thresholders for allergenic reactions.
	Technology choice is a function of socio economic conditions.	Different technologies may affect levels of exposure or levels of risks, e.g. may increase gene flow (see next section).
	Traditional practices vs. biological mans to protect intellectual property.	If some grains from "terminator" cropers were to be imported and planted by farmers, they will inadvertedly have a reduced output, since the seeds won't germinate.
	Economic strategies to diversify risk.	Exposure factors may be different in multicropping systems.
	Liability rules (legislation) and economic capacity.	Capacity resist or recover from impacts of a hazard in the long as well as in the short term may vary across regions.
Risk management	Participation mechanicsm in the decision making process.	Imbalance of voices in decisionmaking process may lead to inefficient/undesirable outcomes.
	Social perception and values.	Attitudes towards risk may vary.
	Technological patterns and economic conditions.	Differentiated cost of risk mitigation strategies.
Risk communication	Literacy and educational levels.	Efficacy of lables may vary.
	Social perception and values.	Public acceptace of the methods.

involves changes in the genetic composition of species, domesticated crop varieties, wild relatives, and interacting species (van den Bergh and Holley 2001). Both sets of impacts need to be taken into consideration by assessing the foregone alternatives when choosing to release a GMO into the environment.

Table 2 includes some possible effects of new biotechnologies involving GMOs associated with socioeconomic factors. The list, far from being exhaustive, is an indicative one showing how socioeconomic factors are relevant for all three stages of risk analysis: assessment, management, and communication.

A Subtle but Profound Impact of Culture on Risk: Seed or Grain?

To provide one example of the influence that social traditions may have on risk assessment and risk management, consider the diTfference between seed and grain. Peasants throughout Mexico, but especially in the southern part, usually save some of their harvest to be used as seed for the next cycle. They can just as well use some of the saved seed for human consumption if needed in extreme situations. They may also exchange seeds on a seasonal basis in order to avoid inbreeding depression. These three simple elements of traditional cropping systems, however, would need to be changed if we are to accommodate the requirements imposed by modern agricultural practices and biotechnological developments: seeds coated with a seed-protecting pesticide, or carrying an herbicide resistance gene are no longer suitable for human consumption. Seeds with pesticide would be toxic and should not be consumed, while herbicide resistant seeds have to be planted given the "extra" value for the included biotechnological quality that would be lost if consumed. Also, intellectual property protection and biosafety measures imply that some of the grain produced can neither be freely replanted nor traded as seed. Hence, seed or grain, conceptually the same in traditional cropping systems, would have to be differentiated. Full transfer of the GMO technological package would therefore imply significant changes in the way that traditional cropping systems have been operating over hundreds or maybe thousands of years. Limiting seed exchange and interfering with the mechanisms for diversification of traditional varieties could have a strong impact on world food security and also impact rural communities. In addition to these considerations we must also consider that in many cultures the use of some crops has deep social and religious meanings that may be affected by changes in practices required by modern biotechnology. Partial transfer of the GMO technological package, namely the seed only, does not affect the practices themselves, but it does have more subtle impacts, such as the increase in the gene flow from GMOs to the landraces with uncertain consequences.

Should We Ask: are GMOs Desirable?

Biotechnological developments are therefore technology-pushed processes rather than processes induced by social demand. In other words, biotechnology is a 'technology in search of applications' (Batie and Ervin, 2001). Private companies engaged in technological developments do not necessarily direct their efforts to flow to the areas where they are needed or direct them in ways that maximize welfare in all contexts where technologies are to be introduced. Therefore, the evaluations of GMOs prior to release have a double task of not only considering the risks involved, but also the social desirability of the organisms given the social objectives that were not considered in its development. Evaluations must

consider the social context surrounding the release. This task is not trivial and the speed of biotechnological development may catch public regulatory bodies unprepared for unintended social consequences.

Hence, environmental regulators are currently not focusing on the process, but simply introducing end-of-pipe type of measures, i.e. once the technology is here, they have to see which measures are needed to mitigate the risks involved. A more efficient approach for regulators would be to induce changes in the processes themselves and direct research efforts to those fields that are more desirable, or to induce research efforts to generate relevant information for risk analysis from the design stage, including socio economic data. This typically calls for public intervention in correcting potential market failures associated with biotechnological developments and ensuring that the developments are directed towards the most socially beneficial goals and take social risks into consideration. Once again, socio economic assessments are meant to shed light into the extent and nature of the tradeoffs between benefits, costs and risks that societies are willing to consider, and how these are in turn influenced by society´s reaction to new technologies.

Conclusions

Clear and reliable methodologies need to be designed and implemented to incorporate socioeconomic considerations into risk assessment and risk management activities regarding GMOs.

It is important that the field tests carried out to determine the potential risks of GMOs do provide relevant information that can be extrapolated to the kind of socioeconomic and environmental contexts in which each GMO is likely to be released. As of today, field experiments with genetically modified crops in confined conditions do not provide sufficient information about ultimate ecosystem and socioeconomic impacts of using such crops in normal agricultural circumstances. This is an area that needs further consideration.
Another policy implication for risk assessment and management which is related to socioeconomic factors is the need for more public involvement in the decision process. This is linked to the issue of risk communication where of course, it needs to be recognised and respected that different societies and individuals may perceive risk differently. An adequate risk communication strategy must *enable* society to take decisions and transmit them to policy makers, and not pre-empt outcomes by assuming that society will necessarily assess risk the same way as the evaluators. Lalcy cautions that "[However,] any public participation requirements would have to be designed carefully to control excessive transaction costs and to balance powerful lobbying groups that espouse narrow views (Lalcy 2000, in Batie and Ervin 2001)."

The incorporation of socioeconomic factors into risk analysis also implies that risk analysis must have a wider multidisciplinary approach. The objectives of environmental risk analysis and human health risk analysis are different, and in most countries, different agencies or ministeries undertake them. Effective communication is required among them, and also among experts on socio economic issues included in the analysis.

Several aspects of harmonization are desirable: the information generated in one country

must be relevant for the countries in which the technology is to be released. Additional considerations that must be incorporated in order to consider context specific factors, both environmental and socioeconomic, must be explicit in the methodology. Similarly, the definitions related to these metholologies must ensure that socioeconomic factors are taken into account and that social rather than private costs and benefits are used when assessing the technologies. Failure to incorporate these elements will most likely create an obstacle for the development of common criteria and principles in national legislation. If regulatory harmonization is to be feasible, the definitions and methods for risk analysis must be broad enough to accommodate the diversity of socioeconomic and environmental contexts in which new biotechnologies are adopted. A critical review of these issues in the context of national regulatory frameworks is a step in the right direction.

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