PART ONE

Biosafety in Principle and in Practice

"It is a maxim universally agreed upon in agriculture, that nothing must be done too late; and again, that everything must be done at its proper season; while there is a third precept which reminds us that opportunities lost can never be regained."

• Pliny the Elder (A.D. c. 23—A.D. 79), *Natural History* •

1 Introduction

Rationale and Objectives

Biotechnology is a complex topic that embodies difficult technical, social, and economic issues played out against a backdrop of human hunger, economic marginalization, and environmental degradation. Adoption of crops and agricultural products improved through modern biotechnology has proceeded slowly in developing countries, where the context for their use tends to be an uncertain mixture of welcome and resistance. From the start, the development and deployment of genetically modified organisms (GMOs) and genetically modified (GM) products has been cast as a proposition with high stakes. Proponents promise solutions to intractable problems in agricultural production and human dietary needs, and opponents warn of unsafe food and environmental disaster.

Where inadequate and irregular supplies of food limit standards of living, those who see genetic engineering technology as holding great promise for improving lives anxiously await the arrival of GM seeds for local farmers. At the same time, those who see modern biotechnology as an icon for corporate exploitation of the defenseless and the possible cause of environmental degradation, if not destruction, label GMOs and the products made from them as the seeds of inequity and ruin. Our view is that biotechnology is a powerful and valuable tool that provides both new strategies to address long-standing problems and new considerations regarding its safe and appropriate use. This workbook is written with the basic assumption that when and where biotechnology is embraced, knowledge and education will allow it to be used safely.

Considerable international, regional, and national effort has been expended to pave the way for this new technology's benefits to reach farmers and consumers. Assistance programs use a variety of approaches to support developing countries to draft national biosafety regulations and build capacity to establish and operate national biosafety systems. Seminars and consultations are held to highlight the need for appropriate government policies. Educational conferences and workshops raise government leaders' awareness of the potential benefits as well as environmental and food safety concerns associated with biotechnology. Technical training for conducting biosafety reviews builds capacity in this critical area of biosafety implementation. All of these efforts are

directed towards a common goal: to support developing countries in taking responsible decisions regarding the introduction of GMOs into the environment and the marketplace.

The lack of biosafety capacity in developing countries is a major constraint to the transfer of this technology, as public and private sector research organizations await a clear regulatory environment through which to bring their products to the grower and consumer.

Successful regulatory implementation requires the capacity to conduct safety assessments to ascertain whether a proposed use of a particular GMO presents an unacceptable risk to the environment or human health. Such biosafety reviews are conducted to provide a scientific basis for decisions regarding:

- Requests from companies seeking to import and sell GM seed or planting material
- Applications to field test transgenic materials developed locally or by donor-funded programs and/or multinational companies
- Approval for importation of GMOs as commodities or for research and testing purposes
- Requests for authorization to produce or grow GMOs on a large scale or for commercial purposes

In some countries the development of GMOs in contained facilities (laboratories) and the movement of GMOs between facilities are also regulated.

The task necessitates training for members of national and institutional biosafety review committees, who typically have little or no experience with biosafety issues or evaluations. In this workbook we address the technical aspects of biosafety review. We provide extensive background information as well as guided, hands-on practice in applying risk-assessment and risk-management procedures using a case study approach. In practice, such training will strengthen the quality of biosafety committee recommendations and decisions. Specific objectives of this workbook are to:

1. Provide a structured framework for a technical training program aimed at biosafety reviewers
2. Build the competence and confidence necessary for reviewers to conduct science-based reviews leading to appropriate decisions
3. Provide instructional materials to support ongoing training conducted by local organizations

The focus of this workbook is on genetically engineered agricultural crop plants. However, most of the material is relevant to GM ornamental and tree species, with some applicability to GM microorganisms.

Audience

This workbook is designed to complement technical biosafety-assessment training courses in developing countries. We provide a background for the practical application of biosafety review procedures using a case study approach.

Our intended audience for such training includes members of national biosafety committees, biotechnology regulatory officials, and scientists working in the public and private sectors. Independent of a training course, the workbook itself may be a useful resource for national decision-making bodies, government regulators in related areas, and those charged with monitoring approved field-test releases. In addition, the workbook can serve as a resource for university and postgraduate students who have an interest in the responsible use of biotechnology for developing improved agricultural crops, trees, ornamental plants, and products derived from them.

Organization

This workbook is organized in three parts. Part One: Biosafety in Principle and Practice comprises background and instructional material organized in six sections. Following the purpose and rationale for creating the book, the intended audience, and the organization of the book, section two presents the context for biosafety assessments, the resources necessary for conducting them, and the process that supports regulatory decision making. Section three covers risk assessment and the environmental and health issues associated with products of agricultural biotechnology. Section four presents risk-management principles and applications. Monitoring is discussed in section five and risk communication, the art and skill of sharing information among interested parties, is covered in section six.

Part Two is the "working" part of the workbook — a collection of case study exercises that entail use of risk-assessment, risk-management, and risk-communication procedures by training course participants. The cases are based on applications submitted to national biosafety review committees; we have modified them to be suitable as classroom exercises. This edition contains two applications for greenhouse research, two for field testing, one for commercial release (placing on the market), and one for GM commodity import. During a training course, students will gain practical experience by evaluating applications under the guidance of experienced instructors.

Part Three contains supplemental information relevant to the text and case studies. Appendix I is a Glossary of Terms. Appendix 2 is an Annotated List of Internet Sites providing additional information. Appendix 3 is a list of Sources and Suggested Reading.

We are preparing a separate instructor's manual to facilitate subsequent training sessions conducted by local instructors. The instructor's version will include supplemental information, materials on additional topics that may be of interest, notes, supplements and guidance questions for case studies, pages to be made into transparencies, and the like.

2 Context for Biosafety Review and Decision Making

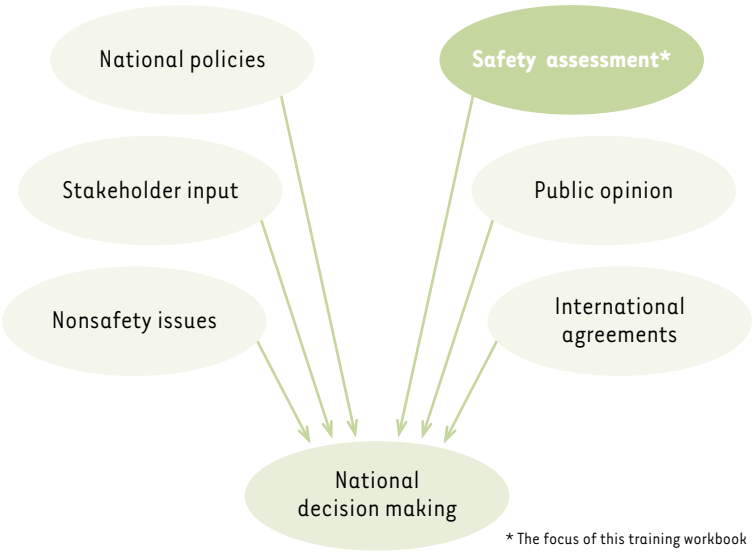
Biosafety review — the scientific evaluation of a GMO's potential effects on the environment and human and animal health — is often seen as the single factor that determines whether or not a GMO or product is approved for testing or use. However, safety assessments are conducted within a larger context for decision making that includes national policies for agriculture, biotechnology, and biosafety (or lack thereof), international agreements, stakeholder interests, and public attitudes (see Figure 1).

Factors Affecting Decision Making

Countries individually decide whether to develop, deploy, or use genetically modified organisms and the products made from them. Such decisions take into account national policies for agricultural research and development and the potential role of biotechnology in meeting national goals and objectives in food production, food security, trade, and related areas. Decisions regarding the use of this technology and its products are based, in part, on a determination that they do not pose an unacceptable risk to the environment or to human health.

With the pending entry into force of the Cartagena Protocol on Biosafety to the Convention on Biological Diversity (the Cartagena Protocol)[1] — a legally binding international protocol for the safe transfer, handling, and use of living modified organisms — such biosafety assessments soon will become part of international trade agreements. Other factors not related to environmental or health safety are typically considered in national decisions regarding the use of GM crops, organisms, and the products derived from them. Among these are social and economic considerations, requirements under national law and international agreements, stakeholder input, ethical issues, and impacts on trade. These nonsafety factors, significant in terms of public acceptance, are rightfully considered in decision making by competent authorities. However, this workbook is focused more on the technical aspects of scientific biosafety review; we do not attempt to address nonsafety factors fully here.

Figure 1. Factors governing decisions about the release and use of GMOs. Factors in decisions about the release of a GMO are based in part on safety assessment and necessarily include other considerations as well. Nonsafety issues such as effects on society, economic consequences, and effects on trade are also keys in decision making. Typically, decision making incorporates, whether formally or informally, stakeholder input, public concerns and opinions, existing policies in agriculture, the environment, and food safety and responsibilities under international agreements.



National Policy

A strong national policy environment for agriculture, new technologies, resource conservation, and related areas will foster the adoption of appropriate GM technologies. Coherent policies promote development of an implementable regulatory system for biosafety and guide its coordination with related regulatory mechanisms (e.g., phytosanitary requirements, seed registration, etc.). They provide a basis for accommodating the differing interests of ministries of agriculture, health, science and technology, environment, or others involved. Weak or absent national policy, in contrast, may serve as an impediment to technology transfer and adoption.

Around the world, national policies on genetic modification differ significantly in their objectives. Some countries design policy to protect the environment and human health against uncertain or unidentified risks, allowing use of the technology only to the extent that its impacts are known or can reliably be predicted. Others frame policy to encourage the introduction of technologies that will benefit the country and its people, striving to identify and manage actual or potential risks, to the extent possible given current knowledge, and to balance these against the status quo.

Policy decisions regarding the relative roles played by the various ministries involved shape biosafety implementation. The statutory nature of biosafety regulations, whether issued as law, by ministerial decree, or as advisory guidelines, will dictate the nature and extent of enforcement measures and the means for addressing noncompliance. Existing regulatory agencies, such as those for plant quarantine and seed registration, may

have statutory authorities that apply to GMOs and that need, therefore, to be coordinated with biosafety regulation.

International Agreements

At least three international agreements — the Cartegena Protocol on Biosafety, Codex Alimentarius, and the International Plant Protection Convention — pertain to biotechnology development and trade. This fact indicates that a wide and complex scope of regulatory issues are associated with the use of the technology.

Cartagena Protocol on Biosafety

The Cartagena Protocol on Biosafety (CPB) is a legally binding international agreement negotiated under the auspices of the 1992 Convention on Biological Diversity. Its primary aim is to protect biodiversity by ensuring the safe and responsible "development, handling, use, transfer and release of any Living Modified Organism." The protocol addresses transboundary movement of living GMOs; it also applies to the use or trade of products derived from GMOs, such as grain processed into meal or flour, cotton fiber or seedcake, vegetable oils, or any processed food. Under the terms of the

The Precautionary Principle as Stated in International Documents

"Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation."

— Rio Declaration on Environment and Development ("Earth Summit"), 1992, Principle 15

"Lack of scientific certainty due to insufficient relevant scientific information and knowledge regarding the extent of potential adverse effects of a living modified organism on the conservation and sustainable use of biological diversity in the Party of import, taking also into account risks to human health, shall not prevent that Party from taking a decision, as appropriate, with regard to the import of the living modified organism . . . in order to avoid or minimize such potential adverse effects."

— Cartagena Protocol on Biosafety, 2000, Articles 10.6 and 11.8

"In cases where relevant scientific evidence is insufficient, a Member may provisionally adopt . . . measures on the basis of available pertinent information . . . (I)n such circumstances, Members will seek to obtain the additional information necessary for a more objective assessment of risk and review . . . the measure accordingly within a reasonable period of time."

— World Trade Organization 1993 Agreement on Application of Sanitary and Phytosanitary Measures, Article 5.7

CPB, exporting member countries must obtain an advance informed agreement for GMO importation before shipment. Such agreement is conditioned on the recipient country's performance of both an environmental risk assessment and food-safety assessment. The CPB includes guidelines for assessing environmental impact and provides for a central clearinghouse of information on GMO production, export, and biosafety data.

Countries that sign the protocol assume certain responsibilities with respect to the use of living GMOs. They are obliged to designate a focal point for liaison with the CPB secretariat and one or more competent authorities to carry out the assessment provisions of the protocol. These include development and implementation of regulations to manage the safe use of living GMOs. In practical terms, this entails a review and modification of existing legislation or drafting of new legislation, infrastructure development, and strengthening of biosafety review capacity within the government and scientific communities.

Codex Alimentarius

The Codex Alimentarius Commission is an international working group that sets standards for food safety, quality, and labeling. It functions under the Food and Agricultural Organization (FAO) in Rome. The Codex *Ad Hoc* Intergovernmental Task Force on Foods Derived from Biotechnology was formed to develop standards, guidelines, or recommendations, as appropriate, for foods derived from biotechnology or traits introduced into foods by biotechnology. The final report is due at the twenty-fifth session of the commission in 2003.

In the interim, work on international guidelines for the labeling of GM foods is progressing; a draft was made available in 2002. Signatories to the Codex will be required to bring their national labeling legislation into line with the new Codex labeling guidelines when these enter into force.

International Plant Protection Convention

The International Plant Protection Convention (IPPC) is a multilateral treaty deposited with the director-general of the FAO and administered through the IPPC Secretariat located in FAO's Plant Protection Service. The purpose of the IPPC is to secure common and effective action to prevent the spread and introduction of pests of plants and plant products and to promote measures for their control. The convention provides a framework and forum for international cooperation, harmonization, and technical exchange in collaboration with regional and national plant protection organizations. The IPPC plays a role in trade because it is recognized by the World Trade Organization in the Agreement on the Application of Sanitary and Phytosanitary Measures (the WTO-SPS Agreement) as the source for international standards for the phytosanitary measures affecting trade. It therefore will affect the export and import of biotechnology products.

Stakeholder Involvement

Stakeholders in biosafety decision making are those interested in or affected by decisions regarding the use of GMOs. In addition to scientists and research directors, the term encompasses farmers and farm organizations, environmental groups, local landowners, consumer organizations, industry and trade organizations, seed suppliers, national and local authorities, and the like. Stakeholders and decision makers share the common goal of using biotechnology and GM products in such a way as to derive benefits that sufficiently outweigh potential detriments. The same can be said for the

use of any technology, whether it is automobiles, vaccines, or electricity.

Stakeholder input is critical in drafting biosafety regulations and laws that are realistic and implementable and that take into account the most current credible information. Stakeholders can provide critical input into setting research priorities that focus on primary constraints in agriculture and food supply for which biotechnology is the most appropriate approach. They are also in a position to promote compliance with regulatory requirements and implementation of management plans (e.g., farmers charged with field surveillance).

Public Input

The general public cannot have confidence in official statements that assert "this GM crop is safe to grow and safe to eat" if they feel deliberately excluded from the decision making. Needless to say, opponents of biotechnology are aware of this, too, and easily raise suspicion and fears by claiming that the public has no voice in decisions regarding the use of GM technology. Furthermore, perceptions that biosafety reviews are inadequate, that deliberations are conducted behind closed doors, and that private sector interests are strongly influential seriously undermine the credibility of biosafety reviewers and competent authorities.

With few exceptions, *technical* biosafety reviews are primarily scientific evaluations conducted by a small group of specialists and, usually, government officials. Final decisions about consumers' use of GMOs, however, must necessarily consider both safety and nonsafety (e.g., socioeconomic, trade, equity) issues. It is at this point that public input should become a factor in decision making.

Public participation in biosafety decision making, specifically addressed in Article 23 of the Cartagena Protocol, typically is achieved through mechanisms to solicit public comment on proposed activities and pending decisions on GMO market releases and deliver it to decision makers. National biosafety officials may use normal government communications channels to announce such events and call for public comment. In a few cases, even proposed field tests are open for public comment. Regulatory officials may place notifications and contact information in local newspapers and on radio programs or conduct local informational meetings. Public meetings are especially useful in that they allow diverse points of view to be heard. The discussions sensitize scientists and regulators to public concerns and at the same time provide an opportunity for the public to obtain accurate information. (See section six, "Communicating about Risk and Biosafety.") A few countries (e.g., the Philippines and the United Kingdom) have instituted direct public involvement in biosafety assessment of GMOs by including representatives of the general public on their national biosafety committees. These committee members may or may not have a technical background.

Terms of Reference for Biosafety Committees

Groups best work together when members have a common understanding of the group's purpose, scope of subject matter, and mode of operation. Ideally, such information for national biosafety committees is specified in formal or informal terms of reference. Although few committees in developing countries have written terms of reference (and many in developed countries lack them as well), they can be instrumental in setting up a functional and effective biosafety committee and serve to coordinate its operations within the larger national regulatory framework.

Terms of reference (principles of operation) are often the first level of guidance for a biosafety committee. They may be articulated within national regulations, guidelines, rules for implementation, or as a separate document. They may address a range of topics, several of which are listed in the box below. Usually, terms of reference establish how the committee is to function, the boundaries of activity in which it may be involved, and the expectations for its deliberations and output. The choice of topics to include and the language used to describe them will reflect the regulatory framework and the perspectives of those drafting the terms. In practice, the list would be longer, perhaps including such additional topics as document management and record keeping, committee procedures, handling of confidential business information, review procedures, member confidentiality, use of external

Terms of Reference for Biosafety Committees: Topics and Samples

The terms provided for each topic are examples of how each topic could be addressed; many other approaches are possible.

PURPOSE

A. The National Biosafety Committee (NBC) is constituted to conduct scientific reviews of applications to import, field test, produce, and/or place on the market genetically modified organisms (GMOs).
B. The NBC is the competent authority for determining the acceptability of a GMO intended for local consumption as food, feed or fiber, export or trade, production of industrial or pharmaceutical products, or any other applications, on the basis of a scientific evaluation of risks, benefits, and comparison of these with those of their conventional counterparts.
C. The Biosafety Advisory Group serves in an expert capacity to evaluate the potential risks of GMOs to human health and the environment and make recommendations to the Ministry of the Environment regarding their use and distribution.

AUTHORITY

A. The NBC is constituted under authority of the Minister of Agriculture as assigned in the Agricultural Products Use Act of 1999.
B. In accordance with Environmental Protection Directive 86-041, as amended on 3 June 1991, the Council for the Environment will establish, maintain, and provide support to an NBC.

APPOINTMENT

A. Members of the NBC will be appointed by the Deputy Minister of the Environment upon recommendation by the Secretary of the National Council of Environmental Affairs.
B. The Director of Agricultural Development and Trade will receive nominations for membership annually. After formal screening, selected individuals will be invited to sit on the committee for a term of 5 years.
C. Members are appointed by the Deputy Director of Agricultural Research and Development. In addition, the President may at any time appoint an additional member or members of his/her own choosing.

MEMBERSHIP

A. The committee is composed of scientists having expertise in relevant scientific disciplines, including molecular biol-

or *ad hoc* advisors, and dealing with conflicts of interest. Each country or committee must formulate its own terms of reference according to its biosafety objectives, regulatory infrastructure, human resources, and similar contributing factors.

Note that some of the sample terms of reference are overly restrictive. An example is "Scope of Review: The committee's primary responsibility is to conduct a safety assessment of applications to field test or commercialize GMOs. Risks are to be identified, their magnitude estimated, and their potential negative consequences described." The wording confines reviewers to look only at risk. No balancing consideration is to be given to potential benefits or positive consequences.

In other cases, the terms are very broad. An example is "Membership: The committee is composed of scientists having expertise in relevant science, plant breeding, genetics, plant pathology, agronomy, weed science, ecology, and others.

B. Members include the Deputy Minister of Agriculture, Director of the National Council for Science and Technology, the Minister's science advisor, representatives of the Ministries of Environment, Health, Production and Trade, and scientists having expertise in disciplines.

SCOPE OF REVIEW

A. Biosafety reviews will focus on scientific issues related to environmental impacts of the proposed activity. Analyses will be based on scientific data provided by the applicant or by outside sources.
B. The NBC evaluation will focus on the potential risks and potential benefits of a particular GMO in light of the known risks and benefits of the nonmodified conventional variety.
C. The committee's primary responsibility is to conduct a risk assessment of applications to field test or commercialize GMOs. Risks are to be identified, their magnitude estimated, and their potential consequences described.
D. The Biosafety Advisory Board Review will, in the course of its assessment, consider the necessity for developing the GM variety, its relevance to national needs and priorities, and comparative advantages/disadvantages over non-GM varieties.
E. The NBC will not comment on the proposed experimental design or choice of scientific methods except where concerns are raised that safety could be compromised.
F. Nonsafety concerns (e.g., socioeconomic impact) will be referred to an auxiliary body established for that purpose or to the decision-making authority for independent evaluation.

POSTREVIEW RESPONSIBILITIES

A. The committee will be responsible for establishing a follow-up monitoring program for compliance with regulatory decisions and any constraints therein. This may be accomplished through submission by the applicant of annual reports or a final report, site visits by NBC member(s) or their representative(s), or as otherwise deemed sufficient by the committee.
B. After completion of each review, the committee or an appointed spokesperson will be available to the Deputy Minister of Agriculture to respond to follow-up questions or additional analyses as deemed necessary.

entific disciplines, including molecular biology, plant breeding, genetics, plant pathology, agronomy, weed science, ecology, and others." This term leaves open who makes the appointments, by what process, the number of members, and their length of service. Both strong and weak examples are given as a way to stimulate discussions of the merits, drawbacks, and, most importantly, the implications of each.

Additional terms of reference may address topics such as committee procedures, use of external or *ad hoc* advisors, record keeping, handling of confidential business information, and dealing with conflicts of interest.

Use of Prior Reviews

Applications for field tests or market releases in developing countries in many cases involve GMOs previously approved by national biosafety committees elsewhere in the world. The findings of these committees are a valuable resource because they can direct subsequent reviewers to specific areas of concern and indicate how these concerns might be addressed. Sharing documentation from prior reviews helps build familiarity with specific GM products, gives insight into management procedures, provides direction on additional information that may be needed for the current review or at later stages in the development process, and raises the confidence with which decisions are made.

The validity of conclusions from risk assessments conducted in other countries is limited, however, by the extent to which there are significant differences in environmental, ecological, and agronomic conditions. Existing biosafety data should be acceptable but are not necessarily sufficient for reviews conducted elsewhere, particularly in countries that are centers of origin or centers of diversity for certain crop species. Local experts will need to evaluate the available data. They may request that additional data pertaining to local conditions be provided before approval can be given or that additional safety data be collected during the field-testing phase of a GM product with commercial potential. Regional environmental similarities and crop preferences may allow neighboring countries to share biosafety data and collaborate on environmental risk assessments for the region. This approach offers advantages in sharing biosafety costs and expertise within the region and reduces duplication of effort, yet leaves decision making to national authorities.

To facilitate access to previous biosafety review data, the Secretariat for the Cartagena Protocol on Biosafety will provide a clearing house[2] for biosafety data that can be accessed by national scientific review and decision-making committees. This database will house information that addresses concerns about specific GM products in specific environments and methods to manage and monitor them. Parties to the protocol will be required to submit their biosafety information to the clearing house.

Decision Documents

Biosafety decisions typically are recorded in some form of decision document. The documents present key findings of the biosafety review committee and of other parties providing information and advice that collectively form the basis for a final decision to use, or not, a particular GMO in a specified way.

Decision documents prepared by biosafety committees serve to communicate their science-based findings to regulators, applicants, stakeholders, and interested parties. Such reports will:

- Summarize the application
- Note any information missing from the original application and steps taken to provide it to the committee's satisfaction
- Summarize the review process, discussions, and findings of the committee
- Detail the committee's recommendations in regard to their mandate
- Add additional comments (outside the immediate mandate of the committee and the scope of the present application) that regulators or the applicant may wish to consider in subsequent applications
- Outline the conditions under which an approved activity is to proceed, including required risk-management measures, reporting procedures in case of unexpected events, and record keeping

In contrast to the relatively simple safety assessments of field-test applications, requests for large-scale or commercial GMO production and/or marketing are subject to much more extensive review that includes factors such as long-term environmental effects, food-safety assessment, and nonsafety considerations. Accordingly, in addition to the findings and recommendations of the review committee, decision documents pertaining to commercial releases may incorporate:

- Findings and recommendations of the national food-safety committee
- Opinions given by *ad hoc* scientific experts as requested by the review committee (e.g., ecological studies)
- Findings of outside review teams charged with evaluating the social, economic, and trade impacts of the GMO
- A summary of input from the public
- Any combination of these depending on the structure of the advisory groups and their mandates

Decision documents serve to advise regulators and government officials and inform the public of how a decision was reached. As such, the language should be nontechnical — key words should be defined and all jargon eliminated. For transparency and accountability, documents should be signed by the review committee or competent authority.

Resource Requirements

Scientifically sound safety assessments and measures for handling GM crops, trees, and ornamental species and their products safely require human, financial, and information resources as well as an adequate infrastructure. Below we detail some of the specific resource needs.

Personnel

Scientists

Sound biosafety reviews require the expertise of scientists knowledgeable about the organisms, the introduced traits, and the environment into which specific GMOs will be released. The scope of disciplines relevant to biotechnology and biosafety is extensive. Some countries, such as the Philippines and China, have a large pool of qualified life scientists and thus are capable of securing the necessary expertise. Many others lack sufficient scientific capacity and will find it difficult, if not impossible, to assemble a properly constituted national biosafety committee.

Circumventions (not necessarily solutions) to this widespread problem include:

- Using experts drawn from neighboring countries
- Using international experts, consultants, or advisors
- Accepting biosafety assessment conclusions

reached by national review committees in other countries
- Establishing a regional biosafety system that pools resources to evaluate proposed field-test releases having regional relevance

In addition to basic scientific expertise, biosafety reviewers need skills in risk-assessment and risk-management procedures (see sections three and four). Those who will serve as inspectors and monitors of field-test releases need to understand the why, where, when, and how of field or facility inspection and monitoring (see section five).

Training programs can help build technical capacity; however, it takes time to build the competence and confidence of biosafety officials. Training should be an ongoing activity; attendance at one course, such as one based on this workbook, is not equivalent to being "knowledgeable and trained." For that, accumulated practice and hands-on experience are needed.

Managers

In the course of implementing biosafety, management responsibilities are commonly placed on people who have little or no prior experience in this area. New managers will need skills in:

- Priority setting
- Resource acquisition and allocation
- Coordination with multiple agencies
- Meeting management
- Communications across many sectors
- Information access and management
- Handling of confidential or proprietary information

Government Officials / Decision Makers

Political support, or its absence, is key to determining whether a functional biosafety system can be established and put into operation, or whether the effort falls short despite strong support at the institutional level and among scientists. Thus it is vitally important that ministry officials and their science advisors are well informed about the role of biotechnology in agricultural development and the role of the biosafety system in bringing beneficial products to all citizens.

Officials who have formal responsibility for biosafety and who make decisions on proposed field-test releases are, in essence, the gatekeepers who determine what biotechnology products, if any, will be allowed, and when. Those more directly involved in biosafety operations are potential allies in helping secure necessary financial resources. Those having regulatory authority set the pace for actual testing and commercial use. The cooperation and support of these people may, in fact, be the most important resource of all. Efforts to engage them and keep them as informed as possible are likely to be well worthwhile.

Scientific Expertise Used in Reviewing South Africa's First 150 Field-Test Applications

Molecular biology	Agronomy	Human health
Plant pathology	Pesticide usage	Biochemistry
Microbiology	Nutrition	Plant genetics
Plant taxonomy	Soil biology	Biocontrol
Fermentation	Ecology	Food safety
Pollination biology	Plant physiology	Weather
Veterinary science	Entomology	Law

Information and Access

Scientific biosafety review teams require a significant amount of information and data on which to base their recommendations. The greater the degree of confidence sought, or the lower the tolerance for an erroneous finding, the more information needed. Much of the necessary information may be supplied with the application. However, a predetermined set of questions may not elicit all that is necessary and sufficient to complete an informed risk assessment. Where gaps exist, or if supporting or confirming information is needed, review teams need access to other sources.

Sources

Information to support safety assessments and recommendations is available from a wide range of sources and in a variety formats: peer-reviewed scientific publications, experts in relevant professional fields (e.g., breeders, agronomists, seed suppliers), conference proceedings, review articles, and even colleagues working in local institutions. Decision documents from other national biosafety committees are a particularly rich source of information on identified risks and management options for particular GM crops and products.

The scientific literature is full of useful information, but persistence is often required to locate the right material. Biosafety-related information may be found in books and journals concerning:

- Basic knowledge of crop biology and agronomic practices
- Ecological relationships in agricultural systems including the crop, its pests and pathogens, and environmental conditions
- Major biotic and abiotic constraints to crop productivity
- Peer-reviewed experimental risk-assessment data and analyses
- Review articles on biosafety issues and current expert opinions on associated risks and risk-management procedures
- Regulations and guidelines from other countries
- Reports and documents from international organizations

To address the need for support in biosafety implementation, the Cartagena Protocol calls for an international biosafety clearing house to coordinate and disseminate information to member countries. The clearing house will be restricted to information about the deliberate transboundary movement of living modified organisms. Until it is set up, a number of research, educational, government, private sector, and civic organizations have attempted to make certain information more readily accessible. Appendix 2 is an annotated list of Internet sites providing useful information about agricultural biotechnology, basics of genetic engineering, benefits and potential risks, national regulations, the Cartagena Protocol, field tests and commercial products, and related topics.

Acquiring information

Information can be accessed through many channels. Books, journal subscriptions, participation in conferences and symposia, and personal networking have long been the mainstays of information transfer. These sources remain extremely valuable and should continue to receive institutional support. However, the world is in the midst of a rapid transition from paper-based to electronic forms of information. The Internet has overtaken other resources in terms of sheer volume of material. Internet-based and electronic information is much more difficult to

obtain in countries where e-mail and Internet connections are unavailable, unreliable, or laborious. Accordingly, countries seeking to implement biosafety systems must give high priority to strengthening the communications infrastructure to provide adequate access to electronic information.

Misinformation

The Internet is without doubt the world's richest source of information; with a little skill in search methodology, information seekers can find practically any information they want. However, because the Internet is open to all and there is no mechanism for moderating its use or policing its content, the quality of information found there is highly variable, to say the least. There is no requirement for accuracy, honesty, or accountability. The situation is compounded by the widely held view that any information that is published is "true." Web site owners can post, move, alter, or remove content at will; original sources can be hidden or absent. This state of affairs brings a new responsibility to biosafety reviewers and decision makers: They must double check the accuracy of information from unknown or unaccredited Web sites before using or disseminating it. In this age of information overload, the ability to critically evaluate the quality of information and be appropriately selective is a skill of increasing importance.

Needed Resources

The expenses of obtaining information, maintaining libraries or data bases, and sorting and disseminating information are unavoidable. Funding must be secured for the necessary infrastructure (computers and communications equipment, reliable links for telephone, fax, e-mail, and Internet connections) and technical support. Information costs associated with conducting biosafety reviews may escalate in time as well as money if required data are unavailable and the only way to get them is through additional research. Striving to improve accuracy in biosafety reviews – by increasing the amount of information obtained or the robustness of the analysis performed – increases the cost of the enterprise and decreases the relative value of additional information. At some point, the value of additional information may not be sufficient to justify its cost. Decisions will need to be made about how much is enough and how available information will be used to best meet national biosafety needs.

Feedback Mechanisms

Field trials of GM varieties are carried out to collect data of commercial and biosafety importance. Feedback, in the form of data and information derived from prior GMO releases, helps support subsequent biosafety committee deliberations, particularly in the early phase of biosafety implementation. Feedback mechanisms can also provide information that may help improve procedures for future field tests. Extensive plantings of commercial GM crops provide unique conditions that may also result in new data. Requiring applicants to continue to collect specific data after market release enables ongoing monitoring of the crop's impact on the environment.

Many countries obtain feedback by requiring a report to be submitted at the end of a trial period. Taking the time to specify the data required in each field test report ensures that the relevant data are collected. Data collection after approval for commercial use can be requested as a condition of the authorization to commercialize.

Financial Support

Biosafety systems impose financial costs for implementation and for compliance.

Implementation Costs

Costs of establishing and operating a biosafety system include:

- Education of policy makers and stakeholders
- Development of regulations
- Development and distribution of procedural information
- Training for reviewers
- Administrative expenses of the biosafety review committee
- Salary and support for paid staff
- Pre-release site visits (if required)
- Inspections during and upon termination of the field-test release
- Follow-up monitoring
- Training for inspectors
- Documentation and record keeping

In some countries, applicants are charged fees to cover these costs. While this approach may be suitable for applicants from the private sector, where such costs are viewed as a normal part of doing business, applicants from national research institutes, universities, and other public sector organizations may find the costs prohibitive.

Compliance Costs

Compliance costs are those incurred by the GMO developer in meeting regulatory requirements. Included are expenses for:

- Generating data needed for the application
- Implementation of risk-management measures
- Post-release monitoring prescribed as a condition of approval
- Reporting and documentation

For GMOs that have undergone prior review in another country, requiring a complete replication of the data, particularly food-safety data, is a costly process difficult to justify. The financial outlay for collecting a new set of data may preclude some applicants from testing GM products.

3 Risk Assessment

Risk assessment is inherently the most critical component of biosafety implementation. Those who make determinations of the relative safety of a biotechnology product and its use will be well served to master an understanding of the approaches that have been used for assessment of environmental risk and the reality of what an assessment may or may not do. With some grasp of the basics, better choices of personnel, education, and training needs may be brought to the formation of biosafety committees and their implementation of regulations or laws.

To fully understand the concepts of risk assessment, it is necessary to have some comprehension of what it is and, as importantly, what it is not. A number of definitions have been offered. Each assumes a basis in or reliance on scientific information. In the broader view, risk assessment is a means for dealing with uncertainties and incomplete data in order that decisions may be made in full consideration of potential consequences. It is influenced by policy choices, individual experience, and public reaction.

Methodology for Biotechnology Risk Assessment

A generally accepted methodology for biotechnology risk assessment has been outlined in several easily accessible documents including the *UNEP International Technical Guidelines for Safety in Biotechnology*[3], the Cartagena Protocol[4], and EC Directive 2001/18/EEC[5]. Each of these include the following steps that, together, identify potential impacts and assess the risks:

1. Identify potential adverse effects on human health and/or the environment
2. Estimate the likelihood of these adverse effects being realized
3. Evaluate the consequences should the identified effects be realized (the risk)
4. Consider appropriate risk-management strategies
5. Estimate the overall potential environmental impact, including a consideration of potential impacts that may be beneficial to human health or the environment

At any point, more data may be needed to arrive at a final recommendation about whether the

Definitions of Risk Assessment

". . . the attempt to quantify the degree of hazard that might result from human activities . . . an exercise that combines available data on . . . potency in causing adverse . . . effects with information about likely . . . exposure, and through the use of plausible assumptions, it generates an estimate of risk."

—William D. Ruckelshaus, 1985

". . . the scientific activity of evaluating the potential effects of an entity and its application in order to ascertain the likelihood that an adverse effect may occur, and to characterize the nature of that effect."

—Paraphrase from National Research Council, 1983

". . . the process of obtaining quantitative or qualitative measures of risk levels, including estimates of possible health and other consequences."

—V. T. Covello and J. R. Fiksel, 1985

". . . an analytical tool that facilitates the organisation of large amounts of diverse data with the goal of estimating the potential risk posed by a process (or event) of interest."

—H. S. Strauss, 1991

". . . the measures to estimate what harm might be caused, how likely it would be to occur and the scale of the estimated damage."

—United Nations Environment Programme (UNEP), 1996

activity can proceed with an acceptable level of safety. Thus the process may be "put on hold" until the needed information is provided.

Organizing the Scientific Information

The very large and ever increasing amount of scientific information available warrants consideration of structured approaches to risk assessment. Indeed, risk assessment requires a different way for scientists to organize and evaluate information. They are asked to evaluate a product's safety as opposed to its potential contribution to scientific knowledge.

In this brief discussion we highlight some of the important aspects of the thinking that has gone into developing such structured approaches. Although these appear disparate in nature, they are consistent with the goal of defining and quantifying potential risks or supporting the notion of "no foreseeable risk." In reality, no single approach is best; the one used typically is the approach most suitable to the needs of the present circumstances. Reviewers will find themselves using different approaches to different applications, or even to different sections of one application.

Over the years, many approaches to biosafety analysis have been used by regulatory scientists or proposed in the literature.

Trait Analysis Approach

In trait analysis, the assessor categorically evaluates attributes of (1) the parental organisms, (2) the genetic construct, (3) the modified organism, and (4) the environment in which the organism is to be released for testing. The analysis uses pertinent criteria and an indication of levels of concern dependent upon the attributes. For example, an organism with a short survival time would be of less concern than one with a long survival time.

Approaches to Risk Assessment

APPROACH	FOCUS	COMMENTS
TRAIT ANALYSIS	Characteristics of the modified organism including the transferred gene(s), the parental organisms, and the receiving environment	Works well when releases are small in scale, but becomes increasingly difficult and less certain as spatial and temporal scale increases
FAMILIARITY	Comparison of modified organism to similar organism(s) that is (are) well known and of GM traits to similar traits derived through classical genetic methods	Based on the assumption that "small" genetic changes (one to four genes) will result in no significant change in a well-known organism (e.g., crop plant) and that phenotypic expression is the same regardless of how the modification was obtained
FORMULAIC	Possible adverse effects (e.g., to the environment or human health) and the probability for their occurrence	Useful for organizing scientific information into two categories; facilitates consideration of risk-management options
INTUITIVE REASONING	What is known or available to an individual or group of assessors based on education, experience, and reason	May rely too much on what seems important as opposed to what should be considered (becomes less of a concern with training and experience)

Similarly, an organism with a narrow geographic range would be of less concern than one with a wide or unknown range.

Familiarity Approach

This popular line of approach advances the concept of relative risk assessment. The determination of level of concern is based not only on the genetic characteristics of the organism, its phenotype, and the environment into which it will be released, but also on a comparison of the GM organism to the corresponding well-known non-GM organism, and the GM trait derived from classical genetic techniques. In other words, how "familiar" scientists are with a particular organism and trait helps them to determine the appropriate level of concern. The essence of the argument is that because most crop plants are genetically modified in increments, the amount of new genetic material is a very small percentage of the plant's genome, and, regardless of how the trait was derived (through classical breeding or by modern molecular techniques), it will phenotypically be the same. For example, by comparing GM plants with the parental plants that, based on past introductions, have a safe history, it is possible

to arrive at a reasonable assessment of how the modified plants will behave in the environment.

Formulaic Approach

Some regulatory agencies have modified the basic risk-assessment approach used for chemicals to use with biotechnology products. In essence, categorical considerations of hazard (H) ascribable to a chemical and the chemical's potential exposure (E) to individuals or groups of individuals are determined. In combination, they determine a level of risk (R). This is commonly described algorithmically as $R = H \times E$. The important insight this equation offers is its inherent organizational nature. The analysis may be subdivided into manageable parts. Using estimates of a potential impact (hazard) and the proximity of a material to the potentially affected component of the environment (exposure), an estimate of the level of risk is obtained. Both hazard and exposure are necessary for risk to be present. That is, presence of a hazard without exposure, or exposure to something that is not hazardous, poses no risk. Other considerations such as dose response (a measure of the level of potential impact) and risk characterization (severity of concern and level of uncertainty) complete the process. More recent thinking about this paradigm has led to minor alterations in the basic formula to recognize and account for the nature of organisms as opposed to chemicals. These alterations include the addition of terms for survivability (fitness), mutation, and reproduction.

Intuitive Reasoning

Assessors tend strongly to rely on their intuition when evaluating applications to release GMOs. Of course they are educated and have considerable expertise, usually in a specific discipline, but because they will have to make decisions with incomplete information, they tend to base decisions on what "feels right." Unlike the previous approaches, the intuitive approach has no structure per se on which to develop an assessment; individual assessors have differing intuitions. Because some measure of consistency is lacking, risk assessors using only this approach may find it more difficult to communicate with other assessors and decision makers.

Despite the inherent level of uncertainty involved in a risk-assessment process and the fact that, at present, assessors are addressing events with a low probability of occurring, using a systematic approach to risk assessment is a worthwhile exercise. When used appropriately, the approaches described above will help to organize scientific information, facilitate communication, and minimize paralysis in decision making.

Practical Considerations

Risk Assessment is Subjective

Although risk assessment ideally should be objective and unbiased, the process is necessarily affected by the unavoidable biases and limitations of individual reviewers – their education, work experience, social values, and cultural background. External factors such as policy decisions at local, regional, or national levels, and public perceptions and attitudes likewise color the context for biosafety committee deliberations. These factors will affect reviewers' comprehension, analysis, and judgment.

Objective biosafety assessments should be based on the best science available. (As we discussed earlier, *decision making* on the use of GMOs also takes into account various nonsafety factors

such as economic impact, dietary and nutritional needs, religious and social values, and the like.) In reality, however, other influences will creep into the assessment process. For example, national policy determinations on the institutional home of biosafety and type of regulatory instrument employed (e.g., regulations under the ministry of environment vs. biosafety legislation in the ministry of agriculture) will shape assessment objectives and the configuration of review panels. Figure 1 (page 8) suggests a balanced influence of these factors on risk assessment, but this is rarely obtained in practice. It is much more likely that one or two of these factors will dominate the decisions that will be made.

This is certainly so when dealing with biological materials and their potential interactions in the environment. The number of possible permutations and combinations will easily challenge the most talented assessor. Whether risk assessment methodology is considered a "scientific activity" or an "analytical tool," understanding and using it may be the only acceptable means for making determinations for the safe development and use of biotechnology products.

Imperfect Knowledge

Findings based on scientific data are often limited by incomplete or missing information. It is not uncommon for biosafety committees to raise questions for which experimental data are lacking. Their deliberations must accommodate this inherent limitation of risk assessment. Otherwise, a circular argument results: if all questions must be answered before approving a field test, and if the answers can be found only by conducting field tests, then no approvals can be granted. Part of the solution to this difficulty is to actively seek all available information (beyond that provided in the application), weigh the history of use and collective experience of experts, and use this to recommend appropriate management controls (see section four, "Risk Management") as a condition for approval.

Scale-up

The risk assessor needs to be aware of the spatial and temporal scale of GMO introductions. Questions may change as the size of the area being planted changes. For example, some questions pertaining to commercial-scale release cannot be answered by data from small-scale field tests (e.g., probability of gene transfer). Low-probability events are more likely to occur when large numbers of plants are cultivated. Differences in scale may have profound effects on the ability to provide meaningful monitoring when called for, or to devise reasonable and affordable methods to monitor specific events of concern (see section five, "Monitoring"). Fortunately, the normal progression of genetically modified crop plants allows for the accumulation of useful information as the GM product progresses from the laboratory to the market.

Benefits of Iterative Processing

The iterative – regularly repeated – nature of risk assessment is fundamental to good assessment practice (Figure 2, page 28). The question-and-answer "conversations" inform applicants of regulatory concerns so that they may provide additional information, satisfy unintended omissions, and clarify language. Information gaps that become evident through the process draw attention to biosafety-related topics that need to be researched.

Reviewers interact primarily with applicants during the review process. Contacts with the scientific community, decision makers, and the public may be likely as well. By conducting several rounds

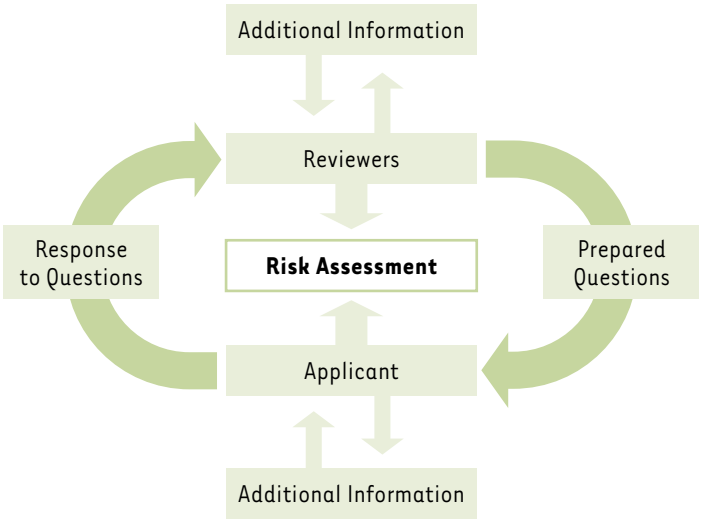


Figure 2. The iterative nature of risk assessment. Risk assessment proceeds by cycles of questions and answers between the applicant and biosafety reviewers. Through this interactive process, initial and emerging information needs can be addressed so that the biosafety committee can formulate a set of recommendations regarding the proposed activity.

of questions and answers with the applicant, reviewers have an opportunity to ask new questions based on points raised by outside contacts, thus bringing wider input to the risk-assessment process.

Use of Expert Committees

Although not always required, expert committees offer an invaluable adjunct to risk assessors. They not only expand the pool of expertise brought to bear on specific issues, but also provide stimulating debate around the limitations of scientific data to arrive at conclusions and the uncertainties that must be considered. These advisory groups have been used successfully for many years.

Already limited in the supply of national experts, developing countries with active biotechnology research programs may be particularly hard pressed to find independent reviewers/assessors without a conflict of interest. This gap may be partially filled through regional cooperation or the use of expertise from the larger international community. The costs of assembling such experts must be taken into consideration. Alternatively, making experience and information available in written form may help to fill the void. In a practical sense, however, providing useful, relevant information is not a trivial task and, in fact, may be limited.

Scientific Issues for Environmental Risk Assessment

Concerns about the impact that GMOs may have on the environment center around their potential to displace or "genetically contaminate" native species and their potential to cause deleterious effects on other organisms. Either consequence could disturb existing ecological relationships or in some unintended way change the living (biotic) or nonliving (abiotic) components of the surrounding ecosystem. Of primary concern is the potential threat to the biodiversity of organisms living in and around a commercial release site.

The negative environmental impacts associated with agricultural biotechnology products can be generally grouped into four areas: weediness, gene flow, pest or pathogen effects, and toxicity to other organisms. Food-safety evaluations address a very different set of potential concerns and typically are handled through a different government agency. (A brief treatment of the subject may be found in "Human Health and Food Safety" on page 33.) Because of the differences between field tests and commercial releases in terms of scale, physical control, management options, and other parameters, risk issues are viewed somewhat differently for the two types of release.

Weediness

The concept of weediness—with its numerous characteristics contributing to complex and variable phenotypes—is difficult to define. Weediness is not an inherent property of certain plant species, but rather is a judgment based on the time and circumstances in which the plant is growing in light of human preferences at that time and place. Thus the simplistic definition of a weed is "a plant in a place where you don't want it." In cultivated fields, a GM crop may become an agricultural pest (weed) by showing up as a "volunteer" in subsequent planting seasons. If engineered for tolerance to a particular herbicide, the "weeds" would be more difficult to control, requiring application of a different herbicide or use of alternative weed control measures. True weediness, however, results from the action of many, many genes. Most crop varieties have been domesticated sufficiently to be nearly incapable of surviving outside of managed agricultural fields; it is unlikely that any single gene transfer would enable them to become pernicious weeds.

Some single-gene traits introduced by genetic engineering may confer a weed-like characteristic that enhances fitness. For example, if a crop's ability to grow in areas outside a cultivated field is held in check by a single limiting factor such as a fungal disease, engineering resistance to the fungus may give the crop an increased ability to spread into adjacent areas. Thus the GM crop, no longer susceptible to the limiting factor, may gain a selective advantage in the local environment by exhibiting the weed-like behavior of invasiveness. Therefore, it may threaten to displace native species. This presents an environmental concern if (and only if) the crop has sufficient genetic capacity to become established and persist in those new unmanaged areas.

Of greater concern is the potential for less domesticated self-seeding crops (alfalfa) and commercial tree varieties (pine, poplar, eucalyptus) to become problems. These plants already have a capacity to survive on their own; transgenes could enhance their fitness in the wild. Pine trees, for example, engineered for resistance to seed-feeding insects might gain a significant advantage through decreased seed destruction, potentially allowing them to out compete other indigenous species. If that happened, forest communities could be disrupted.

Gene Flow

The possibility that genes introduced by genetic engineering may "escape" (be transferred via pollen) to wild or weedy related species growing nearby is often cited as one of the major risks of GMOs. Gene flow between crops and the wild species from which they were derived, however, is a well-documented natural phenomenon. Over the course of evolution, familiar crop species – wheat, potatoes, corn, canola, and numerous others – were modified from their original form because of hybridization with related species or weedy or culti-

vated strains growing nearby. Through this long-established mechanism for gene transfer, any gene in a cultivated crop or plant, irrespective of how it got there, can be transferred to its wild or semi-domesticated relatives.

The real concern is *not* that such outcrossing will occur—because we know that it does—but rather that negative consequences may result from it. In some cases, serious weeds are relatives to crops (Johnson grass to sorghum, wild mustards to canola, red rice to rice). If a wild plant's fitness is enhanced by a transgene that gave it protection from naturally occurring pests or diseases, would the plant become a worse pest (the "superweed" scenario), or would it shift the ecological balance in a natural plant community? Wild relatives of crops suffer from disease and insect attack, but few studies address whether resistance to pests in wild plants would result in significant ecological problems. Weeds often evolve resistance to disease by natural evolutionary processes. However, in some cases, gene transfer from crops could speed up this process considerably.

Wild races are especially important weeds in direct-seeded rice fields, which are becoming more common in Asia. It has been shown that genes often are naturally transferred between domestic rice and weedy wild races. In commercial fields planted to a genetically engineered herbicide-tolerant (HT) rice cultivar, weedy wild rice could be controlled by applying the herbicide, *until* the wild rice acquired the HT gene from the cultivar. At that point, the herbicide would become useless. In this case, the wild rice would not become a worse weed as a result of acquiring the HT gene. It would simply be more difficult to control and would nullify the benefit of the engineering effort. Weeds can evolve resistance to some herbicides without gene transfer, but the process takes much longer. For example, herbicides such as glyphosate (Round-Up™) from Monsanto are difficult for plants to resist with their normally inherited genes. Nonetheless, in Australia decades of intensive use of glyphosate have led to the emergence of resistance in some weed populations.

Two other gene flow concerns deserve mention. First, nontransgenic crop plants may be pollinated by a GM variety growing in an adjacent field. If the GMO is engineered to produce a protein harmful to certain organisms, the protein may be present in the seed and progeny of the non-GMO plants. Conceivably, the gene transfer may escape the notice of those growing the non-GM variety and other organisms may unknowingly be exposed to the harmful protein. Second, gene transfer to diverse organisms (microbes, animals) is not impossible, but the probability of such an event is exceedingly low. It is not normally a major factor in biosafety reviews.

Pest or Pathogen Effects

A GMO may worsen an existing pest or pathogen problem in a variety of ways. Currently the most common genetic engineering approach to increase plant resistance to insect pests is the "Bt strategy." This is based on the discovery that strains of a soil-dwelling bacterium, *Bacillus thuringiensis* (Bt), produce a class of proteins selectively toxic to many insect species that attack crops. Farmers and gardeners have used microbial sprays of Bt for many years to control insect pests as part of integrated pest-management programs. Bt insect control proteins have been engineered into major commodity crops and a growing list of vegetable, fruit, and tree species. The potential consequences of extensive and long-term use of Bt crops are one of the most widely discussed environmental issues associated with transgenic crops. The concern is that as insect pest populations increas-

ingly are exposed to high levels of Bt proteins over long periods, emergence of resistant individuals within the pest population will be accelerated. This concern with pest resistance to transgenic pesticides is the same as that with resistance to chemical pesticides as a result of overexposure. Many experts agree that the question of pest resistance to Bt is not "if" but "when." This is particularly important in organic farming where chemical alternatives are not acceptable.

The *de novo* generation of new viruses from virus-resistant (VR) engineered crops has also been raised as a potential risk. To date, the most widely used biotechnology approach to controlling plant virus diseases has been the use of genes derived from the plant viruses themselves. For a number of important virus pathogens, expression of the viral coat protein gene in the host plant inhibits replication of that virus. In addition to being the structural component of virus particles, coat proteins also play a role in determining the host range of the virus and serve other functions as well. For some virus groups, other viral genes have been used successfully to limit disease.

The presence of viral sequences in major crop plants may increase the likelihood of creating novel viruses through molecular recombination between the transgenes and the genomes of other viruses that infect the plant. Such exchange of genetic information encoding coat proteins genes, for instance, could lead to the production of a new recombinant virus that has a unique coat protein that alters its host range. Similarly, recombination between other transgenes and infecting viruses could yield new virus strains with novel characteristics. Multiple plant viruses simultaneously infect many crops, and there is strong molecular evidence that virus evolution has proceeded rapidly through the exchange of large blocks of genetic information via recombination. Ongoing studies are examining the frequency of recombination events in naturally infected plants compared with transgenic VR plants.

Toxicity

There are some concerns regarding the safety of new proteins expressed in transgenic plants. Even low-level expression of a new transgene potentially may have an unintended, deleterious effect on other organisms including birds, insects, browsing animals, and soil organisms in the local environment. This is particularly the case when the protein has no prior history of being found in plants, or is not found at the levels expected in the GMO.

Proteins intended to control specifically targeted pests may be harmful to nontarget species. In terms of plant-produced insecticides, the only insecticidal compounds that currently are commercialized are the toxin proteins naturally produced by Bt. These proteins are highly specific in their toxic effects. One group of these proteins affects only certain species of caterpillars whereas others affect only a restricted set of beetles. None of these proteins has been shown to have a significant disruptive effect on predators of pest species or beneficial insects.

The toxicity issue (and any potential risk issue) can sometimes be inflated to alarming proportions. A report that pollen from Bt corn killed larvae of the monarch butterfly was taken to mean that Bt crops were harmful, prompting extensive negative press coverage. Numerous studies seeking to verify and clarify the reported findings all found that, under field conditions, monarch populations were not harmed. This episode may serve to underscore to biosafety reviewers the importance of carefully examining the quality and credibility of data relevant to biosafety decision making.

Risk-Assessment Research

Biosafety reviewers often face uncertainty when certain data needed for a complete evaluation are missing. Risk-assessment research is designed to provide information and generate data that fill in knowledge gaps and expand basic understanding of crop biology, agricultural ecosystems, and the ecological interactions of crop plants and their environment.

High-priority topics for risk-assessment research are often identified in the course of biosafety reviews. They may take the form of questions such as:

- What characteristics of the crop limit its ability to become established, persist, or spread in the environment where it grows?
- How will the genetic modification change this?
- In cases where crops and their wild relatives are known to hybridize naturally:
  - Are there genetic mechanisms that favor or hinder gene introgression?
  - What is the relative fitness of hybrid progeny?
  - Will they have ecological characteristics that are more problematic than either parent?
- Where the engineered trait confers pest resistance:
  - What are the potential secondary effects? (e.g., changes in local/field-level ecology)
  - What new problems may develop as a result? (e.g., emergence of alternative pests as a consequence of changes in pesticide applications)
- Where the engineered trait confers virus resistance:
  - What viruses other than the target virus infect the crop?
  - What is the incidence of multiple virus infection?
  - What are the similarities and differences in the replication mechanisms of infecting viruses?
- Regarding the new gene product:
  - What parts of the engineered plant will contain the new protein?
  - What nontarget species will be exposed to it?
  - What is its toxicity to those species?
  - What is their expected level of exposure?
  - What are the likely biological effects of exposure?

These questions, and others like them, reflect sharpened awareness of (1) the ecological complexities of cultivated fields and adjacent areas; (2) the potential for long-term effects whose nature and probability can only be guessed; and (3) the knowledge gaps that hamper science-based decision making. These same types of questions, modified to fit a particular interaction among crop, introduced trait, location, and scale and expanded to cover any other applicable environmental or ecological considerations, constitute the basis of risk assessment for a proposed GMO field test or commercial use. It must be emphasized, however, that *lack of complete knowledge should not prevent biosafety decision making. An element of uncertainty will always be present.*

Human Health and Food Safety

The primary human health concern with foods produced from transgenic crops is that new proteins expressed in the GM plant may be hazardous – they may be toxic or cause an allergic reaction. Other hazards may include reduced levels of certain nutrients, or elevated levels of certain antinutrients. Genes themselves are made of DNA and are present in all foods. DNA ingestion is not associated with any negative health effects.

In general, health ministries are responsible for the safety of foods including those derived through biotechnology. Biosafety risk assessors review data on the nature and expression of newly inserted genes, detailed characterization of new proteins, changes in composition or nutritional qualities of food, intended new uses of the product, and a comparison of the new food with conventional counterparts.

Countries that are signatories to Codex Alimentarius, the international commission that sets food safety standards, usually have reactive rather than proactive food-safety regulations in place – that is, regulatory supervision begins only when products are commercialized. Codex requires that any new food that varies from its conventional counterpart in composition, nutrition, or intended use must be labeled as such. Thus, according to Codex rules, foods produced using oil from GM canola having a modified fatty acid profile are routinely labeled. Note that labeling is required because of the altered composition of the oil, not because it came from a GM crop.

Assessing Food Safety

Many plants routinely used for food contain toxins (e.g., beans contain lectins, potatoes contain alkaloids). Any method of crop improvement (by traditional breeding practices or through biotechnology), can possibly introduce unknown changes in food composition. New varieties that contain an increased amount of toxic compounds may be hazardous. This is one reason why countries with crop variety registration procedures usually look at certain aspects of food safety before registration of new, conventionally derived varieties.

The first step in a food-safety review is testing of the new protein expressed from the inserted gene. If the protein is not already present in other foods with a proven history of safety to humans, it is thoroughly tested to ensure its safety. Even if the newly expressed protein is well known, studies are conducted with the GM material to confirm its safety and to assess whether any unexpected effects occur in the plant.

Genetic engineering need not make a food inherently different from its conventional counterpart. The technology itself is unlikely to increase the food's probability of containing an allergen. Concern about food allergies, however, is frequently cited as a major consumer issue with GM foods. Fortunately, much is known about foods that trigger allergic reactions—for example, 90% of all food allergies in the United States are caused by a very small number of foods: cow's milk, eggs, fish and shellfish, tree nuts, wheat, peanuts, and legumes.

The amino acid sequence of the new protein is compared to that of known allergens. A very high dose of the expressed protein is fed to laboratory animals to assess toxicity, and immunological tests are conducted to ensure that the newly expressed protein is not an allergen. Digestibility studies are carried out with the purified protein and with the whole food. These tests determine whether the new protein is rapidly digested like other dietary proteins (a trait generally indicating nonallergenicity). If digestion breakdown products result, they are identified and checked for safety.

(Initially there was some concern that virus proteins expressed in virus-resistant GM crops might trigger allergic reactions if included in food. This concern has largely been abandoned since many foods are infected with one or more plant viruses, and viral proteins have been consumed thousands of years without deleterious effects.)

Even genes from sources not known to be allergenic are subjected to detailed allergenicity screens. The level of the new protein in the GM plant and the amount present in parts consumed as food

are assessed to estimate how much would be consumed in a normal diet. Studies on whole foods indicate whether the inserted genes or new protein might have an unexpected effect on the normal composition and qualities of the food. Tests are performed to determine whether nutrients, vitamins, and minerals in the new plant occur at the same level as in the conventionally bred plant. Other studies examine whether antinutrients (substances that interfere with nutrient absorption), natural toxicants, or known allergens occur at levels comparable to those in the conventional plant. In some cases, baseline data on conventional foods against which comparisons with GM foods can be made are lacking.

When foods derived from transgenic crops and their conventional counterparts are demonstrated to be essentially the same, the GM food is said to be "as safe as" or "substantially equivalent to" the conventional product. Any significant change in nutrition, composition, or intended use prevents the claim of substantial equivalence. While the first generation of transgenic crops largely fulfils the substantial equivalence requirements, subsequent generations will include many types of food GMOs specifically designed to be nutritionally enhanced and therefore different. For these, substantial equivalence will not be an appropriate measure of safety.

Collection of Food Safety Data

Gathering food- and feed-safety data is an expensive process. For this reason, developers collect data according to the stage of product development. During the laboratory research stage, if the inserted gene(s) comes from a source known to contain allergens and the GMO under development is intended for the food or feed industry, it is prudent for developers to check the introduced proteins for allergenicity or toxicity. Preliminary food-safety checks usually involve comparisons of the cloned gene with the DNA and amino acid sequences of known allergens and toxins and, if indicated, the protein may be subject to clinical testing. If the protein is found to be potentially allergenic or to have unacceptable toxic properties, further development of the GMO may voluntarily be halted. Otherwise, good laboratory practice simply requires that experimental GMOs be neither eaten nor allowed to enter any food chain.

As GM lines advance to greenhouse trials, good reason seldom exists to require collection or submission of food- and feed-safety data for approval from the biosafety committee, except when it is difficult to exclude the possibility that the GMO will enter the food chain. Greenhouse studies are used primarily to test for efficacy of the introduced trait and to identify individual lines that will be further tested in field trials. For lines showing promise, however, developers may use greenhouse trials to begin collecting data that later will support a commercial-use application. Greenhouse experimentation can provide the material needed for initial testing of, for example, levels of the foreign protein found in various tissues and at various stages of growth.

Field trials give the first clear indication of how GMOs perform in the environment. At this point, it is usually prudent to make a preliminary assessment of food and feed safety. If data on the GMO's potential toxicity and allergenicity are not complete, regulators typically will require that field trials be conducted at sites not accessible to the general public and that measures be taken to insure against accidental release of GM material into local food chains. Means to control access to the trial site, including access by unauthorized people, animals that may feed on the GMO, and other organisms likely present in the field test area are carefully evaluated by risk-assessment reviewers.

Once individual lines ("events") have been

chosen for commercialization, collection of relevant food-safety data begins in earnest. Material from field trials is gathered and used in comparative assessments against the non-GM variety. Food- and feed-safety reviews generally focus on the products of the foreign genes and the characteristics of the whole food. Investigations consider:

- Toxicity to humans, other animals, birds, fish, insects, and soil microbes[6]
- Pathogenicity
- Allergenicity
- Nutritional and compositional changes
- Digestibility and digestion products
- Stability of gene products and the genes in the food source
- The fate of genes and gene products in food processing
- Any other area that food technologists believe is important to evaluating the safety of the new food for humans and animals

To date, all proteins introduced into transgenic crops currently approved for human consumption have been shown to be nontoxic and nonallergenic.

Marker Genes

As part of the genetic modification process, "marker" genes are usually linked to the gene of interest to make it easier to determine whether the treated cells or tissues are in fact genetically modified. There is some concern that the use of antibiotic-resistance genes as markers in transgenic crops might cause or increase resistance to antibiotics in microorganisms that cause disease in humans and animals. In other words, could use of these genes increase the problem of drug-resistant "super bugs"? Antibiotic resistance is a serious public health issue. However, scientists widely agree that the root cause of the problem is the overuse or misuse of antibiotics in clinical treatments and animal production. As such, the possibility that use of antibiotic-resistance marker genes in crops could pose a public health concern has been largely discounted.[7] Nevertheless, food developers have started to pursue alternative types of marker genes, and in time it is likely that antibiotic-resistance genes will no longer be used. New marker genes and their products will be subject to the same rigorous biosafety assessment.

These assessments allow regulators to conclude whether a biotechnology product attains a common safety standard expressed as "reasonable certainty that no harm will result from intended uses under the anticipated conditions of consumption." If the GM crop or inserted DNA does not cause a change in any of the numerous parameters examined, regulators are able to conclude with confidence that the food is safe for consumption.

4 Risk Management

Risk management in the context of agricultural biotechnology is the use or application of procedures and means to reduce the negative consequences of a risk to an acceptable level. Attention generally is focused on limiting risk by proper handling and use of various preventive measures. In fact, opportunities to manage potential or identified risks can be found throughout the process of developing and testing genetically engineered organisms.

Risk Management in the Laboratory and Greenhouse

GMO Design

When planning a genetic engineering project, scientists work out the molecular details of the GMO they intend to produce. These details include identification of DNA sequences encoding the desired trait, choice of marker genes, and nature of regulatory sequences that will direct expression of the transgene. Choices are also made regarding minimization of extraneous DNA, options for targeting the site of insertion, as well as the method of transformation.

Transformation methods for inserting new genes into plants are relatively inefficient; only a very small proportion of treated cells actually take up the new DNA. Marker genes are included in the segment of inserted DNA in order to distinguish cells that contain the new genes from those that do not. Some marker genes encode enzymes that lead to the production of a pigment or fluorescent light, allowing easy identification of GM cells. Other marker genes encode proteins that inactivate antibiotic compounds; when treated cells are grown in the presence of the antibiotic, only those that took up the new DNA are able to survive. In the past, the gene encoding neomycin phosphotransferase II (*nptII*, the so-called "kanamycin gene") was the preferred marker because it provided a cheap and effective way to grow selectively only the GM cells.

Concern arose that GM plants containing antibiotic-resistance genes would, if consumed as food, present a risk to individuals taking the antibiotic as a therapeutic agent. Despite numerous detailed studies that unanimously concluded the risk was immeasurably low, and despite approval by the food safety regulatory agencies in numerous countries, public opinion remains

opposed to the presence of antibiotic-resistance marker genes in foods. In response, developers of GMOs to be used as food are moving away from these genes. Ongoing efforts are under way to identify other types of genes useful as markers and to develop methods for removing marker genes before GM products get to the market. It is worth noting that even though the protein encoded by the *nptII* gene presents negligible biosafety risk, GMO designers are well advised to consider such concerns.

Molecular biologists have identified a number of promoters able to turn on gene expression in specific tissues. In plants, these tissue-specific promoters restrict transgene expression to roots, leaves, or other selected tissues where the new protein is desired. For example, a leaf-specific promoter, directing toxin production in the leaves but not roots, stems, or flowers, could control a gene encoding a toxin active against a leaf-attacking pest. In transgenic animals, a tissue-specific promoter has been used to direct transgene expression in mammary glands so that the new protein is secreted in milk.

Inducible promoters can switch transgene expression on and off during the life of the plant. For example, certain promoters respond to a chemical signal; simply spraying the transgenic plant or plant part with that chemical can activate them. Water stress, temperature, mechanical damage, light, or various other types of stimuli activate other inducible promoters. The next generation of GMOs is expected to make use of these more sophisticated gene regulatory sequences that can contribute to reducing potential risks.

Cells transformed by *Agrobacterium*-mediated DNA transfer methods usually contain, in addition to the desired gene or genes, extra pieces of DNA that come from the *Agrobacterium* vector. Although vector-derived sequences rarely cause any problem, one view holds that the safest approach to designing GMOs is to avoid including any extraneous DNA sequences. An alternative approach, direct gene transfer via a "gene gun" or electroporation, avoids the potential for inserting unnecessary vector DNA because no vector is used. Other transformation methods make it possible to insert transgenes into chloroplast DNA. The value of this approach is that pollen grains of most, but not all, plant species do not contain chloroplasts; therefore, concern about the spread of transgenes via pollen (gene flow) is essentially eliminated.

Although these methods of advance risk management are easy to implement, they must be integrated into the research plan before the first candidate GMOs are produced. If applied, they simplify later risk assessment by avoiding certain features known to raise questions of risk.

Containment

As a GMO under development progresses through the laboratory to the growth room and into the greenhouse, the basic biosafety requirement is to limit spread of the engineered organism and its genetic material. *Containment* is a term for the use of physical barriers to restrict spread within a structure or enclosed space. Laboratory facilities and greenhouses afford this relatively high level of control.

Laboratory containment

Physical containment of transgenic plants and plant cells within laboratories, tissue culture facilities, and growth cabinets is maintained by good laboratory practice. Plants can be monitored relatively easily under such conditions, although care must be taken to ensure that seeds produced under lab or growth cabinet conditions are carefully collected for disposal or subsequent use. Labeling

plants or pots will help avoid accidental mixing of transgenic and nontransgenic plants. Materials to be disposed of need to be treated in a way that prevents their survival or growth outside the contained facility. This may be achieved by autoclaving, steam sterilization, treatment with a household bleach solution, or proper composting.

Greenhouse containment

Greenhouses are designed to keep insects and animals out and plant and plant parts in. Construction details and procedures for handling GMOs will vary depending on the types and degrees of biosafety concern associated with the experimental materials to be housed within. In many cases, conventional greenhouses can be made suitable for GMOs by simple refurbishing and minor structural upgrades. For higher levels of containment, facilities may have to meet such specifications as controlled and filtered airflow, systems to control and disinfect water leaving the facility, autoclaves for on-site sterilization of plant material and equipment, disinfecting the facility after experiments, strict limits on whom is allowed to enter, and staff and worker training. Consideration also must be given to safe transport of GMOs into and out of the facility and methods to monitor for accidental escape during and after the experiment.

Greenhouses cannot prevent pollen from escaping; even newly built, top-quality greenhouses will not contain microscopically small grains of pollen. Pollen containment requires specialized equipment, materials, and expensive construction details that may be beyond the means of most public institutions. An easy and commonly used solution to this problem is to place small bags over the male flowers before the pollen is shed; collected pollen may then be used for hand-pollination as needed, or disposed of. More effective containment is achieved by building within the greenhouse a small sealed room fitted with special air filters that block pollen escape. For more detailed information, refer to *A Practical Guide to Containment: Greenhouse Research with Transgenic Plants and Microbes*.[8]

Risk Management in the Field

Environmental risk is a function of the combined characteristics of the organism, the nature of the genetic modification, and the site (local ecosystem) where the GMO is to be released. Each characteristic affords opportunities to manage potential risks. Not all GMOs pose an environmental risk; of those that may cause harmful effects, not all pose the same level of risk. Accordingly, biosafety reviewers strive to tailor risk-management procedures to the nature and magnitude of an identified risk. Some of these strategies are discussed in the following sections.

Confinement

Confinement, or measures to keep experimental organisms within a zone having designated borders or limits, is the most common method for preventing or minimizing the unintentional spread of a GMO or its genetic material.

Physical strategies for confinement

Physical means to confine GM plants and plant parts include geographical or spatial isolation or use of structures such as fences, screens, mesh, and the like to keep animals out and prevent "unauthorized harvest." In order to be considered an environmental risk, transgenic pollen must be able to fertilize plants of a sexually compatible

Isolation Distances (in meters) from Contaminating Sources for Selected Crops

Crop	Foundation	Registered	Certified
Corn (inbred)[a]	200	——	——
Corn (hybrid)	——	——	200
Cotton (hybrid) [b]	0	0	0
Millet (selfed)[c]	400	400	200
Millet (crossed)[d]	0	0	0
Mung beans [d]	0	0	0
Onion	1,600	800	400
Peanuts [d]	0	0	0
Pepper	200	100	30
Potato (male fertile)	400	400	400
Potato (male sterile)	0	0	0
Rapeseed (selfed)	400	——	100
Rapeseed (crossed)	200	——	100
Rice	3	3	3
Sorghum (hybrid)	300	300	200
Sorghum (hybrid)	——	——	200
Soybeans [d]	0	0	0
Sunflower [e]	800	800	800
Tomato	200	100	10
Watermelon[f]	800	800	400

SOURCE: Modified from "Genetic and Crop Standards" of the AOSCA: *http://www.aosca.org/*

a. No isolation is required for the production of hand-pollinated seed.
b. Isolation distance between upland and Egyptian types must be at least 400, 400, and 200 meters for Foundation, Registered, and Certified classes, respectively.
c. Distance adequate to prevent mechanical mixture is necessary.
d. Isolation between millets of different genera must be 2 meters.
e. An isolation distance of 1,600 meters is required between oil and nonoil sunflower types and between either type and other volunteers or wild types.
f. The minimum distance may be reduced by 50 percent if natural or artificial barriers adequately protect the field.

species growing in the vicinity. Crop breeders are an excellent source of information about the presence and distribution of cross-fertile wild or weedy relatives of cultivated species. *Genetic and Crop Standards*, an annual publication of the Association of Official Seed Certifying Agencies (AOSCA[9]), describes the isolation distances required to avoid genetic contamination by pollen dispersal in the production of certified seed. (The terms *foundation, registered*, and *certified* refer to classes of certified seed produced and handled under procedures established by the certifying agency according to each class for maintaining genetic purity and identity. In simple terms, they are the first-, second-, and third-generation progeny of breeder seed, respectively.) The accompanying table shows isolation distances for the three certified seed classes of selected crops.

Where available land is insufficient for spatial isolation, one or more of the following procedures can reduce or prevent GMO or transgene spread via pollen or seed:

- Plant border rows of the non-GM variety around the test plot to "trap" pollen from the GMO.
- Bag flowering structures to screen out pollinating insects and/or prevent pollen spread by insect vectors, wind, or mechanical transfer.
- Cover female flowers after pollination to prevent loss or dissemination of GM seed.
- In cases where research objectives do not require seed production for analysis or subsequent planting, remove flower heads before pollen and seed production.
- Harvest plant material of experimental interest before sexual maturity.
- Locate test plots surrounded by roads or buildings.

Biological strategies for confinement

Biological processes can provide highly effective means of preventing unintended transmission of genetic material. Reproductive isolation, a common method of biological confinement, can be achieved in a variety of ways:

- Grow GM plants in an area where sexually compatible wild or weedy species are not found.
- Remove all plants of sexually compatible wild or weedy species found within the known effective pollinating distance of the GM crop.
- Cover or bag flowers to screen out insect pollinators or prevent wind pollination.
- Prevent production of viable pollen by using genetic male sterility, applying a gametocyte, or removing all reproductive structures at an early stage of development.
- Recover tubers, rhizomes, storage roots, and all tissues capable of developing into mature plants under natural conditions.
- Exploit differences in flowering time so that GM pollen is not shed at the time when sexually compatible plants nearby are receptive.
- Engineer genes into chloroplast DNA instead of chromosomal DNA, since pollen from most species does not contain chloroplasts. This technology is still in its infancy, may not be effective for all genes, and would not be effective in plants in which chloroplasts are transferred by pollen.
- Engineer transgenic plants to produce sterile seed. This technology was developed as a "technology protection" system to secure intellectual property rights for the improved seed (the so-called Terminator gene). It is highly effective for risk- management purposes, but has raised ethical questions regarding seed saving and the role of multinational corporations in controlling seed and therefore food supplies in developing countries.

Other strategies for confinement

For small-scale field tests, environmental conditions can be manipulated to limit reproduction, survival, or dissemination of GMOs outside the experimental area. For example, temperature, water supply, humidity, and photoperiod can be controlled naturally by suitable placement of the test site, or artificially by using irrigation, lights, misters, and the like. In some parts of the world, trials can be conducted in which climatic conditions preclude flowering or survival outside the experimental area.

Chemicals can be used to limit survival and reproduction of GMOs outside the trial area. Herbicides, fungicides, insecticides, disinfectants, or other materials toxic to the test organism can be applied, but effects of the chemical on other organisms or the immediate vicinity must be taken into account. At the end of an experiment, the whole experimental area, if necessary, can be treated chemically or sterilized. Lastly, decreasing the number of test organisms or the land area used in an experiment may reduce the possibility of unintended dissemination.

In sum, organisms that engender little or no risk to the environment may require no or minimal confinement. GMOs with a very high potential for causing serious adverse effects *in some cases* may not be safely grown outside of containment. Most agricultural GMOs will be found safe for small-scale (field-test) release when specific risk-management procedures are part of the experimental design.

Other Standard Risk-Management Procedures

Termination and Follow-up Procedures

Measures are usually implemented at the end of laboratory, greenhouse, and field trials to ensure that the GMOs are effectively removed from the experimental area. The required measures are determined by the type of organisms, their natural means of spread, and the environment in which testing was

carried out. As such, the requirements for cleanup must be determined on a case-by-case basis.

For microorganisms, some form of disinfecting may be necessary. For plants, harvesting seed and ploughing in or burning residual plant material are usually effective where vegetative reproduction does not occur. This is followed by a fallow period during which volunteer plants arising from escaped seed or from vegetative reproductive structures are monitored and destroyed before the onset of flowering. The extent of the fallow period is dependent on the climate and crop. Cold winters are effective seed and tuber destroyers for many crops. Harvested seed and plant material must be documented and stored, or disposed of, according to the requirements of the regulators. This, too, is crop dependent.

Record Keeping and Reporting

Careful records of GMO experiments need to be kept. They provide documentation of the genetic modifications and verification data, observed phenotype, unexpected observations, and the like. This information is necessary for both preparing and evaluating an application for field-test release, as well as for documenting performance in the field. Records of all measures taken to comply with any conditions or risk-management measures imposed by the biosafety review committee may be useful for later reference. Regulators need accurate records to ensure compliance with risk-management conditions and redress in the case of accidental release. The biosafety review committee determines what information the applicant must record and the times at which the information must be submitted. These record-keeping parameters are then outlined in the approval document. Having collected efficacy data, applicants can easily neglect to forward risk-management records to regulators. Making the receipt of trial records a condition for review of subsequent applications is one way of ensuring that even the mundane risk-management records of uneventful trials are lodged as requested.

Risk-Management Realities

Some environmental risks can be reduced to an acceptable level by careful management. When biosafety reviewers determine that a proposed field test poses such a risk, they typically recommend that adjustments be made in the field-test release plan to address specific points of concern. For example, monitoring plans could be adjusted to be more comprehensive or provide different focus; contingency plans could be called for when early termination of the field-test release was seen as a distinct possibility; removal of an antibiotic-resistance marker gene before release could eliminate a concern that threatened to make approval unlikely; specific labeling could be created and attached to seed containers to reduce concerns about inadvertent mixing of GMO and non-GMO seed.

Such adjustments modify the risk potential of the proposed release and are a factor in the review committee's decision. Consequently, it is incumbent upon both risk assessors and applicants to be aware of management options that could be applied to a given field-test plan, taking into consideration not only science-based issues but also the policies of the regulatory authority and what measures are possible – scientifically and economically. Details of the risk-management requirements usually are appended to authorization documents issued for the field-test release.

In essentially every country, the costs of risk management are borne by the applicant. It is important, therefore, to ensure that risk-manage-

ment requirements are in fact necessary and not just "nice to have." The cost of implementing risk management and the difficulty in meeting some specified conditions may lead applicants to postpone or cancel trials. This is especially true of publicly funded research in developing countries. Often biosafety frameworks are established in developing countries to prevent exploitation by outside interests and with the budgets of multinational companies in mind. This strategy can backfire when locally developed technology is ready for testing and public institutes are unable to afford the sometimes excessive requirements of over-cautious national frameworks.

An example is the indefinitely postponed marketing of fungal resistant strawberries developed in South Africa in the 1990s. Because the strawberries had performed extremely well in field trials, the national agricultural research institute planned to release them for commercial production. However, it has been unable to fund the food-safety tests required for commercial production. All three new genes in these transgenic plants are common in regular foods, and eight public juries believe the crop should be approved if labeled. However, the biosafety regulations require extensive toxicity, allergenicity, and nutrient testing before submission of a commercial application. As of late 2002, the status of the fungal resistant strawberries remains unchanged. The strawberries are maintained in tissue culture, but no additional work is being done with them. The public research institute can only wait until the genes have been approved in other crops and then request to use this safety data for their application. Interestingly, when presented with this case, most public juries are keen to eat the strawberries themselves to provide food-safety data.

5 Monitoring

Monitoring in biotechnology has different meanings and interpretations depending on individual perspectives or circumstances. In one sense, monitoring is the measuring and comparison of new plant varieties for relative performance and is a normal component of all stages of research and development. However, with the emergence of modern biotechnology, speculation about potential harm from GMOs introduced into the environment has shifted the focus of monitoring to following the fate of these organisms and the transgenes they carry and to be vigilant for unanticipated consequences.

Biosafety Monitoring . . .

- May contribute knowledge and experience in the use of organisms with novel traits
- Ranges from simple observation to extensive research studies
- Can be the responsibility of the "user" or an independent authority, organization, or body
- Can be used to verify assumptions made in a risk assessment
- Should be used to evaluate whether risk-management measures used are appropriate and effective.

—United Nations Environment Programme (UNEP), 1996

Background

Historically, monitoring programs in association with field-test releases of genetically modified organisms have been called for, explicitly or implicitly, as part of the regulatory agenda or as part of risk-management schemes. For example, in European Commission Directive 2001/18/EC[10] for releases of genetically modified organisms, Annex VII clearly describes the objective and general principles expected to be followed when developing a monitoring plan.

Voluntary compliance with monitoring programs (i.e., people did what they said they would do or what they were required to do) in the early days of field testing was encouraged by the notion that applications that incorporated monitoring into the experimental plan would be considered more favorably. Now, compliance with monitoring requirements is commonly ensured through reporting and follow-up field visits by regulatory authorities.

The Monitoring Paradox

"On one hand, new problems cannot be predicted and on the other hand if we can predict problems, they are not new. Wide-ranging, open-ended monitoring is probably the way to detect new or unique effects of genetic engineering. Yet such monitoring is expensive in time and money. It is also inefficient: surely most studies will find nothing at great expense even if a previously unknown problem eventually turns up. *It is helpful to decision makers and those who will be charged with the design and implementation of monitoring to know explicitly what should be monitored, the reason behind the concern(s), how monitoring should be carried out, and finally the purpose for data collected*" (emphasis added).

—K. Keeler, 1994

Monitoring Categories

EXPERIMENTATION

- Gather basic scientific information
- Test pre-release assumptions
- Improve experimental design

TRACKING

- Product development/marketing
- Regulatory compliance
- Incremental dissemination/dispersal

SURVEILLANCE

- Identified events
- Unanticipated impacts

When the first field tests of GMOs took place, it was not clear what should be monitored, why, or for how long. Monitoring objectives and methodologies were conceived and implemented with no precedent to follow and often resulted in unusable data or no data at all. Subsequently, methods and sampling designs have been refocused through experimentation to accommodate the large-scale releases of GM crops. For example, the issue of monitoring for the development of insect resistance to pesticides was raised as early as 1994 but did not become a major focus of risk-management programs until the commercialization of Bt crops. It is important to note, however, that the utility of monitoring programs is not restricted to answering biosafety concerns or indicating information gaps or the need for new assessments. Monitoring may also indicate a need for a different approach to regulatory or management decisions.

Biosafety Monitoring

Biosafety considerations are important in determining the need for monitoring, identifying appropriate target(s), and justifying the reasons for establishing specified levels of monitoring. Whether a GM crop or its DNA poses a safety concern if it should "move" into adjacent fields or to related plant species is an important environmental issue that raises the question of the extent to which transgene movement can or should be monitored. Furthermore, it necessitates the availability of efficient, accurate, and reliable methods of identifying transgenic material present in unintended locations.

Current methods include use of visual or selectable markers (e.g., β-glucuronidase, antibiotic resistance) or molecular analysis (e.g., PCR, Southern hybridization). Often the decision about

what to monitor has depended as much on what is possible to monitor as on the identified concern. However, it is not possible to know what to monitor without knowing what potential problem might arise—the monitoring paradox.

Scales of Monitoring

Monitoring programs fall into three categories—experimentation, tracking, and surveillance. The categories correspond, respectively, to the progressive scale-up in field-test, pre-, and post-marketing stages of product development.

Each successive stage brings different monitoring objectives and the need to consider larger geographic sampling areas and longer term observation regimes. Further, care must be taken in extrapolating experimental field-test monitoring results to commercial applications. For example, significant variations in gene flow measurements have been associated with increasing population size. The increasing temporal and spatial scales of monitoring programs is paralleled by an increasing difficulty to control and implement them (Figure 3). Similarly, the magnitude of potential adverse effect and the degree of uncertainty in the monitored parameter is mirrored by a need to increase the intensity of the monitoring program (Figure 4).

Experimentation

When field testing of genetically modified microorganisms first began in the United States, assumptions regarding monitoring needs led to ill-conceived and expensive protocols. Perhaps because little experience and no experimental evidence were available to draw upon, unproven methods were often chosen. During the course of field testing, it was discovered that these monitoring procedures were inadequate (i.e., inappropriately timed, provided poorly discriminated detection, or

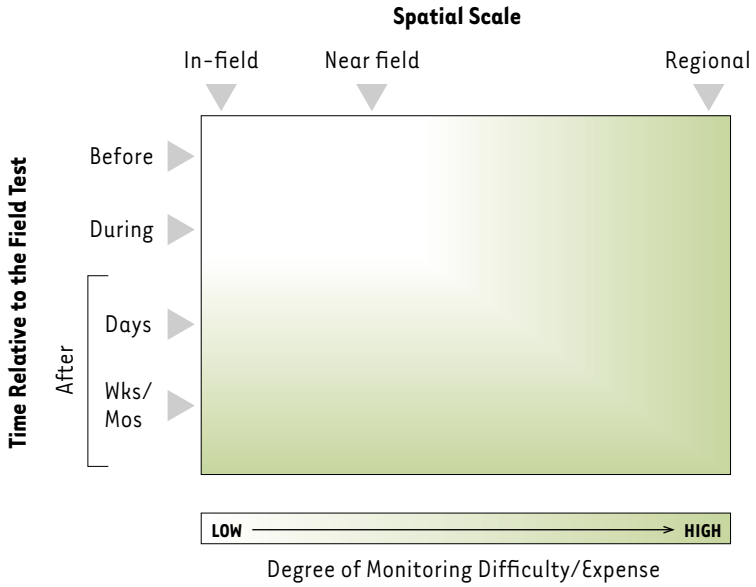


Figure 3. Influences on the difficulty of monitoring. Spatial and temporal considerations influence the degree of monitoring difficulty and expense. Monitoring conducted early and near the test plot or large-scale field is relatively simple and cheap compared with later or longer term plans carried out over a larger area.

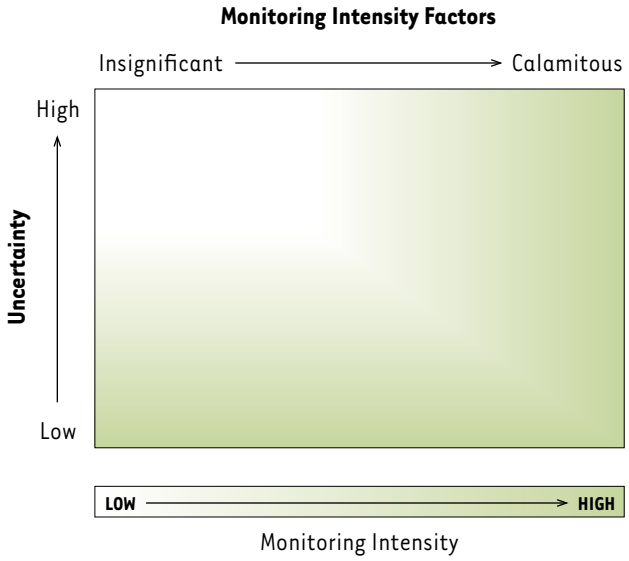


Figure 4. Factors contributing to the intensity of monitoring. The degree of uncertainty and magnitude of potential adverse effects determine the intensity of a monitoring plan.

naively conceived). The result was expensive monitoring schemes that produced little or no usable data. Research and field-testing experience led to the unfortunate conclusion that these early monitoring procedures would not answer the questions of concern. Experimenters and biosafety authorities must be aware that they will not always know the best monitoring approach at the outset. This argues for having a biosafety review process that balances concerns with the reality of scientific capability.

Tracking

Tracking refers to monitoring the movement and dispersal of organisms and their genes over time. If crop plants do not survive well beyond cultivated fields, tracking is not necessary. But if cultivated plots of crop plants have close relatives growing nearby, outcrossing of the engineered genes may be a concern. It is commonly recognized by breeders and agronomists that natural mechanisms for such outcrossing do exist. However, it is only in certain cases that a biosafety concern is raised (see "Scientific Issues for Environmental Risk Assessment," page 28).

Expanding the geographic range or duration of "sampling" beyond small-scale field tests poses significant difficulties for a comprehensive monitoring program. Assumptions about the best monitoring design and methodologies must be made on the basis of incomplete or insufficient information, despite what is often characterized as long-term experience with specific organisms and a full understanding of their growth characteristics. Episodic events at disparate intervals may produce very large differences in monitoring data. For example, the dispersal distance for oilseed rape pollen from commercial fields was measured at more than 150 meters as opposed to less than 10 meters from experimental plots. For events that have a very low probability of occurring, spatial and temporal expansion of monitoring protocols may be necessary to see gene flow when it happens.

Surveillance

Surveillance, the ongoing post-release observation of the organism to monitor its survival and dispersal or its environmental impact, is a form of monitoring appropriate when predetermined sampling regimes are impractical. However, devising a meaningful surveillance program presents difficulties when the environmental effects of a GMO release are only speculative. Furthermore, the large distances (e.g., kilometers) and long time intervals (e.g., years) associated with monitoring, for example, wind-driven pollen or seed dispersal may pres-

ent technical difficulties in the design of sampling regimes. Large-scale surveillance may demand large numbers of people or large numbers of sampling sites and is likely to challenge even the most ample budget. Unfortunately, these factors may influence responsible investigators to suggest monitoring schemes based more on the availability of resources than on the collection of scientifically valid data that addresses a biosafety question.

When the United States Environmental Protection Agency granted a permit for the sale of insect-resistant Bt cotton, the agency required implementation of surveillance programs to monitor for the occurrence of increased insect pest resistance to the endotoxin of *Bacillus thuringiensis*. Upon evaluating the methods employed initially, the agency subsequently called for the use of more sensitive methods to increase the probability of early detection should resistance to Bt emerge in the pest population.[11]

Practical Planning

Monitoring procedures may vary from qualitative to quantitative, from simple to complex. We present a representative basic approach to designing a monitoring plan in Figure 5. The first step in

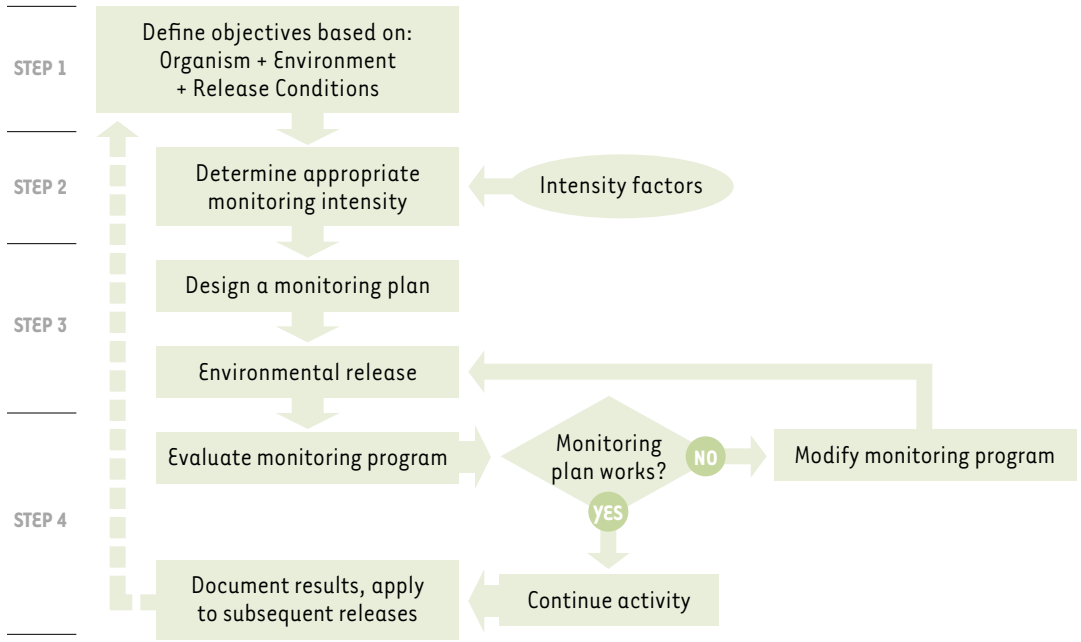


Figure 5. A basic approach to designing a monitoring program. The flow diagram depicts the process of designing and conducting a monitoring program.

Pitfalls of Monitoring

- Too much or too little effort given
- Unclear what to look for
- Doesn't go on "long enough"
- No appropriate mitigation available

—K. Keeler, 1994

planning a design is to define clearly the objectives of the monitoring plan, taking into consideration available knowledge of the organism to be released, the environment, conditions of the release (e.g., limited geographic area *vs.* open-market sales), potential risks as determined in a risk assessment, and regulatory requirements. The objectives of the monitoring plan determine the measurement endpoints. Integration of this information provides the basis for development of a specific monitoring plan.

The second step in a monitoring plan is to determine the appropriate level of intensity. Monitoring intensity is determined by the degree of uncertainty and the potential severity or probability of unwanted environmental impacts. The third step is to design the monitoring plan so that it includes specific sampling regimes and testing procedures. Step four is to evaluate the effectiveness of the plan after it is implemented. Thus it is important that monitoring plans be dynamic so that modifications can be made in response to changing conditions or unanticipated problems that might develop during the course of the program.

Biosafety assessors have an obligation to anticipate and avoid potential pitfalls in any monitoring design.

Ideally, a diverse collection of professionals will be involved in decisions about planning a monitoring program. These may include scientists conducting the research and development work, industry representatives concerned about financial soundness, legislators tracking constituency concerns, and regulators who claim jurisdiction. When working across professional boundaries, a risk assessor must learn to get results from diverse groups, which often requires finding a way to ask the question correctly and ensure that the right (trained) people are involved in the monitoring efforts. Cooperation (dialogue) among those involved is best begun even before applications are made and continued through data acquisition and analysis. The intent is not only to establish clear objectives, but also to ensure precise communication.

The risk assessor helps to ensure that adequate attention is paid to monitoring design and implementation. He or she needs to understand the monitoring objective and have some assurance that it is obtainable by implementing the monitoring design. If monitoring is intended as an environmental early-warning mechanism, there must be sufficient sensitivity to ensure the "alarm" is sounded in time to actually do something. A strategy must be in place for remediating an unwanted or unacceptable environmental impact, or, put more directly, there needs to be a plan describing what will be done should a crop be found going astray. It is equally important to distinguish between what is "nice to know" from what is "necessary to know." Monitoring programs not justified on the basis of risk simply waste resources, including the time of scientists and regulatory officials who will be obligated to review the irrelevant data collected.

6 Communicating about Risk and Biosafety

Introduction

As we stated at the beginning, biotechnology is a complex topic; it is a proposition with high stakes and has passionate proponents and opponents. Risk-assessment and risk-management procedures intended to identify and minimize potential negative effects on human health and the environment are key elements in making technical decisions to use, or not use, a product of biotechnology. However, just as a three-legged stool will not stand with only two legs, the public will not accept biotechnology as a tool for crop improvement until the third element – risk communication – becomes an integral part of biosafety procedures.

One of the most damaging lessons to emerge from the development of GM crops comes from early efforts to gain public acceptance of GMOs. When biotechnology products were first being field tested in the United States and Europe, public communications were seriously mishandled. Simplistic messages that oversold the technology (e.g., "biotechnology will put an end to world hunger"), dismissed people's concerns (e.g., "biotechnology is just an extension of what humans have been doing to improve crops for thousands of years"), or glossed over uncertainty (e.g., "I just don't think outcrossing will cause any problems") succeeded only in alienating an uneasy public. The private sector in particular transmitted an attitude of arrogance and deception that continues to undermine its credibility today, more than twenty years later.

Objectives of Risk Communication

Communication, not science, is the heart of risk communication. Regardless of subject matter and level of risk – whether reporting an outbreak of a devastating animal disease, announcing a GM crop field test, or talking to people living near a chemical spill – risk communication seeks to:

- Better educate the public about risks, risk assessment, and risk management
- Better inform the public about specific risks and about actions taken to alleviate them
- Improve communicators' understanding of public values and concerns
- Provide a mechanism for the public to voice concerns

"Danger is real, but risk is socially constructed."

—P. Slovic, 1987

- Increase mutual trust and credibility
- Reduce conflicts or controversies
- Promote transparency in the regulatory process

Part of the difficulty in communicating about biotechnology and biosafety is overcoming negative perceptions that already may be ingrained in public opinion. Common perceptions include:

- Companies put profit ahead of safety.
- Government regulators are either politically motivated, technically unqualified, or lack legitimate authority.
- Companies are untruthful in discussing risks and will lie if it serves their purposes.
- Scientists working in the private sector are unscrupulous or have been "bought."
- Developing countries are used as a dumping ground for products not approved elsewhere.
- The public is forced to assume the risk but gets none of the benefit.

It is important to note that some such perceptions do in fact arise from experience. Too often, however, public opinion about biotechnology is based on misperceptions of risk fueled by insufficient or inaccurate information. More fully informed opinions can arise only when people have a better and more realistic understanding of how biotechnology will affect their immediate lives and the environment in which they live. Risk communication is thus an important first step towards public dialogue concerning the development and use of GMOs. The following sections provide some of the basic rules for risk communication and offer practical guidance in communicating effectively.[12]

Principles of Risk Communication

Experience in communicating with the public about difficult topics such as toxic waste sites, immunization programs, and contaminated food incidents has provided some vitally important though sometimes painful lessons. These lessons can be distilled into basic principles of risk communication that have broad application to all areas of science and technology. Used wisely, they can help shape more meaningful and informative public communications.

Accept and involve the public as a legitimate partner

Contrary to proponents' initial expectations, the public has not enthusiastically embraced agricultural biotechnology. In retrospect, it is not hard to see how this came about. In the beginning, most scientists and, to a greater extent, company executives assumed that the wonders of biotechnology were self-evident and that the benefits were almost unlimited. They were slow to recognize that the public was becoming increasingly alienated by decision makers who ignored the need for public input into how the technology could or should be used, and they tended to underestimate or dismiss the public's concerns about safety.

More recently, policy makers, regulatory authorities, and GMO developers have started to change their way of thinking. They now see that providing a means for public involvement in decision making and paying attention to public concerns before they become adversarial issues are the first and perhaps most important steps in building

public confidence in the safety of GMOs and acceptance of GM products.

How and to what extent this can be achieved will vary from one country to another. In the Philippines, representatives of nongovernmental organizations (NGOs) and public interest groups are members of the National Committee for Biosafety. By law, local communities where field tests are to be conducted must be notified in advance and given the opportunity to voice their position regarding the proposed tests. If public opposition is strong for whatever reason, the test may not be approved. At the other end of the spectrum, particularly in countries having nonparticipatory forms of government, there are no mechanisms for public input and it is not considered in official decision making.

Somewhere in the middle are countries, Argentina for example, where research scientists and national biosafety committee members engage in numerous formal and informal dialogues with environmental NGOs and consumer groups. In the United States, a public notice that an application for commercial production has been received by the Department of Agriculture's regulatory agency is published in the daily Federal Register. The announcement briefly describes the GMO, informs readers where to get full information about the proposal, and invites public comment within a specified timeframe (usually sixty or ninety days). During the subsequent biosafety review and in the ensuing decision document, all comments submitted by the interested parties are specifically addressed and responses given. In many countries, government regulators, biosafety officials, and scientists routinely appear in public discussion forums and, from time to time, organize informational meetings intended for general audiences.

Provide information through credible sources

People tend to pay attention to information coming from sources they trust. To a public hearing inconsistent and conflicting information about controversial issues, who the messenger is may be as important as the message. The "public" is not a homogeneous entity but rather a collection of numerous groups whose priorities and concerns are highly variable. To whom do different constituent groups turn for information? Who is viewed as a credible spokesperson? In some countries, government authorities may enjoy the public's full confidence. In others, authorities may not be well respected and may even be viewed with suspicion. Health care professionals and religious leaders often receive high marks for public trust. Industry representatives, particularly those from large multinational companies, are very often seen as being among the least trustworthy sources. Among differing cultures, farmers, scientists, extension officers, teachers, and community leaders may have greater or lesser credibility with the public at large. Information campaigns are likely to have greater impact when trusted sources are identified at the start and enlisted to deliver information to the target audiences.

Be honest, frank, and open

No single person has all the answers. Communicators build trust and credibility with their audience by acknowledging when questions go beyond their knowledge and offering to find the information and provide it later. Perceptions are extremely important; if the communicator appears honest and sincere, what he or she says is perceived as honest and sincere.

Because culture and personal values are ingrained within us, it is very difficult for any one

individual to be totally without bias. Having more than one communicator on hand, preparing remarks in advance, and having speakers and listeners cross-check to make sure what is being said and what is being heard are the same can lessen the impact of personal bias.

Be proactive

Uninformed consumers are more receptive to inaccurate, biased, or inflammatory messages than those who have some knowledge about GMOs. A balanced and realistic information strategy needs to be implemented *before* misinformation from other sources takes root in public opinion. Having to react hastily to antibiotechnology actions and rush to repair the damage is often too little, too late.

Risk Communication in Practice

Provide clear and accurate information. In communicating about biotechnology to a nontechnical audience, information needs to be translated into everyday language. Explanations using ordinary words can help the public gain more realistic ideas about the technology – what it is, what benefits it offers, what concerns it raises – and how it is being used. For instance, the subject of DNA can be introduced with an analogy to videotape: both are linear and carry information that must be decoded. Genetic engineering can be viewed as similar to editing videotape. Like videotape, DNA can be cut and spliced back together; it can be copied; segments can be removed, duplicated, or moved to another position; segments from different sources can be combined into one; pieces can be put in reverse orientation, and so on.

Through experience, a number of useful observations have emerged. Among these are:

- There is no one-size-fits-all talk suitable for all audiences. Knowing who the audience is and what their concerns are allows speakers to deliver information focused on subjects most important to them.
- In talking about benefits and risks, good communicators strive to present balanced, credible information that seeks to inform, not convince, the audience.
- Legitimate concerns posed by certain combinations of crop-trait-location deserve to be acknowledged and, where possible, applicable risk-management strategies can be described.
- A balanced discussion of potential risks includes consideration of the risks of not using the technology, choosing instead to continue current practices.
- Statements presented as fact will have more credibility when supported by documentation that can be verified.
- Good communicators are wary of the tendency to speak authoritatively about a subject on which actual knowledge lies somewhere between experimentally proven fact and personal belief. (Presenting speculation as fact and drawing major conclusions from irrelevant, out-of-context, or untrue "facts" are transgressions commonly committed by groups opposed to the use of biotechnology.)
- No one knows everything. It is only sensible to acknowledge that for some questions, the answers are not known.

Listen to your audience

People attending any kind of discussion forum generally want to either learn more about the subject, express their opinion, or both. Effective communicators make it a point to find out what their audience wants to know and are prepared to pro-

vide that information. They give people an opportunity to speak without being judged and pay attention to what is said. Experts in conflict management stress that making the effort to hear someone's concerns and showing that they have been heard and understood are critical to ensuring that an issue is resolved.

Biotechnology can stir up strong feelings in many people, even though they themselves may not be able to pinpoint the root cause. When commenting on a given subject, they may start out calmly but become increasingly angry or accusatory as they address more and more issues. In these difficult situations, it is worth remembering that the speaker is not really looking for immediate solutions, but needs to feel that his/her concerns are being heard.

Understand our human nature

Many of the public's concerns about using GMOs seem to derive from a lack of data that would "prove" safety or at least absence of risk. The implication is that if sufficient scientific information became available, public concerns would likely subside. Although there may be some truth to this simple explanation, attitudes about biotechnology are significantly complicated by ordinary human attitudes and perceptions including the following.

Fear of the unknown

No one can predict what long-term effects might arise from growing GMOs and eating GM foods. Past cases of unanticipated or delayed harmful consequences arising from new technologies and products touted as safe (e.g., use of broad-spectrum synthetic pesticides, introduction of exotic species, or ground-water contamination by agrochemicals) have made consumers much more cautious.

Resistance to change

Change takes energy and causes discomfort until people become familiar with the new situation. Traditional farming methods are seen as an icon for a simpler, purer kind of existence.

Inaccurate perceptions of risk

Studies measuring human perceptions of the relative riskiness of certain activities or behaviors (medical x-rays, cigarette smoking, riding in a car, use of pesticides, and the like) reveal wide discrepancies between those perceptions and statistical data.

Unrealistic expectations

Where uncertainty exists, many people want, and some demand, a guarantee of zero risk or absolute "proof" of safety. Both are impossible.

Recognize that the debate is not about science alone

Biotechnology has several unique features that raise powerful concerns not associated with conventional agriculture: its capacity to manipulate the very nature of living things in unprecedented ways; its use of patents and other means of intellectual property protection that severely limit access to its products; its identification with large multinational companies that are seen as the nemesis of small farmers, particularly in developing countries; and its added costs for regulatory compliance and patent protection that make it unaffordable to poor farmers. Addressing only the

scientific issues will have limited impact on public acceptance because, unlike conventional research methods, biotechnology triggers deep-rooted social, economic, and ethical concerns.

Trust

Government agencies lose credibility when the public learns, belatedly, they were misled about the seriousness of a hazard or not fully informed about a hazardous incident. A prime example is the mishandling by government officials in the United Kingdom of the outbreak of "mad cow" disease, first by denying the disease was present and then by grossly underplaying the extent of its spread and the number of people affected. The public, having found government authorities to be untrustworthy in the past, now is disinclined to believe their assurances of safety with respect to biotechnology. Within the private sector, many of the leading biotechnology companies are considered highly untrustworthy because of their record of mishandled public relations that oversold the benefits, denied any sort of risk, and dismissed consumer concerns as irrelevant.

Control

The ongoing consolidation of the agribusiness sector, marked by a trail of industry mergers and acquisitions that have created megamultinational corporations and caused the disappearance of many smaller seed companies, leads many people to feel that important decisions and choices are being taken away from them. Consumers feel they are losing control over what they eat. In major GMO-producing countries such as the United States and Argentina, standard commodity-handling procedures result in a mixing of GMO and non-GMO varieties of corn and soybeans. As a result, a high percentage of processed foods made with corn or soy ingredients have some GMO content. Consumers insisting that GMO-containing foods be labeled are reacting to their loss of control over the choice to buy or not buy foods derived through biotechnology.

From farmers' point of view, companies are exercising increasing control over their choice of what to plant and how to manage their farms. Unlike commercially sold or publicly held conventional varieties, GM varieties carry patents that restrict farmers' ability to save seed for replanting or to sell or trade it with other farmers. Some transgenic crops engineered with a Bt gene for insect protection are subject to planting restrictions that require the farmer to grow a specified percentage of non-Bt seed at the same time. These developments reduce farmers' options and tend to make them increasingly dependent on the seed companies.

Equity

Biotechnology raises fundamental questions about the equitable distribution of its benefits. Private-sector companies seeking profits are propelling advances in crop quality and productivity, whereas public sector research to improve the status of resource-poor farmers lags far behind. Almost all commercialized GMOs to date are crops and varieties that are economically important in developed countries but poorly adapted or unsuitable for use by farmers in developing countries. Access to improved seed is not uniform; small-scale and subsistence-level farmers in developing countries cannot afford the associated costs.

Simple fairness holds that in any undertaking having an element of uncertainty, those who accrue the benefits should bear the risks. This has not been the case for biotechnology and GM products. Many people feel that they, not the companies, are being

asked to assume the potential risks of negative environmental and health impacts from products that have no direct benefit for them. Although the situation is likely to change as more consumer-oriented products reach the market, the perception of inequity has impeded public acceptance.

Morality and Ethics

The power of biotechnology to manipulate the genetic makeup of a plant or animal in ways that do not appear to occur "naturally" may conflict with some people's religious beliefs and innate sense of right and wrong. Some see the ability to cross species barriers as tampering with things with which humans ought not to interfere, a form of playing God. Further, the public's low level of scientific understanding to some extent leads to a perception of biotechnology in which genetically engineered crops lie within a continuum of research that leads inevitably to the cloning of human beings.

Identify and train communicators

Good communications skills are the hallmark of effective spokespersons. They are comfortable meeting and talking with the public and the press. They are able to convey complex ideas in simple yet accurate words. They have good listening skills and pay attention to what others are saying. Good communicators distinguish between what is known as fact and what is believed but speculative. They are able to respond point by point to a wide range of questions, criticisms, inaccuracies, and accusations without resorting to heated or antagonistic words. They are able to calmly point out false, misleading, or unsupported statements and correct them with an even-handed response that can be substantiated. They avoid being distracted by comments or questions not relevant to the topic at hand. They show a sense of humor, admit fallibility, and claim their own role as consumer, concerned citizen, and part of the public.

These skills can be learned. The field of risk communication has produced a substantial literature on the principles and methods of responding to public concerns that is adaptable to many subject areas. Institutions including regulatory agencies can seek to identify those who would make effective spokespersons and support their skills development through risk-communication training.

Meet the needs of the media

Media's main purpose is to sell newspapers and attract viewers and listeners. Media act as filters of information by being selective about what is published or broadcast. To help keep a story alive, media present different views on controversial issues as being equally valid or as having equivalent support in the larger community. When the subject is biotechnology, too often articles with sensationalized headlines, frightening misstatements of fact, wild extrapolations, and baseless pronouncements win out over sober reporting that distinguishes clearly between what is known by science, what is reasonable speculation, and what cannot be supported by any evidence.

Regardless of whether the reporting is accurate, biased or erroneous, the media are the public's primary source of information about biotechnology. Reporters are unlikely to be knowledgeable about GMOs and may know little about science. Accordingly, media education is important in promoting informed discussions on the merits and concerns associated with biotechnology.

Communicators, especially official spokespersons who regularly speak to the media, are well advised to keep messages brief, clear, and to-the-point. Repeating the most important statements in

exactly the same words helps reporters remember them correctly and may provide a useful quote.

Experts in risk communication advise spokespersons never to assume that reporters or media representatives are neutral, independent, sympathetic to you, objective, or altruistic. Nor should spokespersons assume that reporters are devious or dishonest. All parties benefit when members of the biotechnology community cultivate cooperative relationships with reporters and editors. They can do this by making themselves readily available for interviews, accommodating media deadlines, and being prepared to provide names of other resource people knowledgeable about biotechnology, GMOs, environmental issues, food safety, regulations, and related areas.

Notes

1. "Cartagena Protocol on Biosafety to the Convention on Biological Diversity." 2000. Adopted at the Convention on Biological Diversity, January 29, 2000, Montreal, Canada. *http://www.biodiv.org/biosafety*
2. *http://www.biodiv.org/biosafety*
3. United Nations Environment Programme (UNEP). 1996. *UNEP International Technical Guidelines for Safety in Biotechnology*. Nairobi, Kenya: UNEP.
4. "Cartagena Protocol on Biosafety to the Convention on Biological Diversity."
5. "Directive 2001/18/EC of the European Parliament and of the Council (on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/20/EEC." *http://biosafety.ihe.be/GB/Dir.Eur.GB/Del.Rel./2001_18/2001_18_TC.html*
6. Mocrobes are exposed to root exudates and plant debris remaining in the field after the end of the growing season.
7. Australia New Zealand Food Authority (ANZFA). 2000. "GM Foods and the Consumer." ANZFA Occasional Paper Series No. 1. *http://www.anzfa.gov.au*
8. Traynor, P., Adair, D., and Irwin, R. 2001. *A Practical Guide to Containment: Greenhouse Research with Transgenic Plants and Microbes*. Blacksburg, Virginia: Information Systems for Biotechnology.
9. *http://www.aosca.org*
10. "Directive 2001/18/EC of the European Parliament and of the Council."
11. U.S. Environmental Protection Agency, Office of Pesticide Programs, Biopesticides and Pollution Prevention Division. 2001. "*Bacillus thuringiensis* (*Bt*) Plant-Incorporated Protectants." Biopesticides Registration Action Document, October 15, 2001. *http://www.epa.gov/oppbppd1/biopesticides/otherdocs/bt_brad2/4 irm.pdf*
12. Some of the material is based on the work of Peter Sandman, a leading consultant in risk communication, and Vince Covello, Center for Risk Communication, New York.