Secretariat
of the Convention
on Biological
Diversity

BIOSAFETY TECHNICAL SERIES 02

Summary and Comparative Analysis of Nine National Approaches to Ecological Risk Assessment of Living Modified Organisms in the Context of the Cartagena Protocol on Biosafety, Annex III

Convention on Biological Diversity
UNEP
2011-2020 United Nations Decade on Biodiversity

CBD BIOSAFETY TECHNICAL SERIES 02

Summary and Comparative Analysis of Nine National Approaches to Ecological Risk Assessment of Living Modified Organisms in the Context of the Cartagena Protocol on Biosafety, Annex III

Authors
(in alphabetical order):

Shelby Flint, Thelma Heidel, Scott Loss, Jacob Osborne,
Kristina Prescott, David Smith

Secretariat of the Convention of Biological Diversity
Montreal

Secretariat of the Convention on Biological Diversity
United Nations Environment Programme
413 St. Jacques Street West, Suite 800
Montreal, Quebec, Canada H2Y 1N9
Phone: +1 (514) 288 2220
Fax: +1 (514) 288 6588
E-mail: secretariat@cbd.int
Website: www.cbd.int and bch.cbd.int

 Published 2012
Printed in Canada
ISBN: 92-9225-424-3

This issue of the Biosafety Technical Series has been produced with the financial assistance of the European Union. The views expressed herein can in no way be taken to reflect the official opinion of the European Union.

LOCAL CATALOGUE RECORD:
Secretariat of the Convention on Biological Diversity.

Summary and Comparative Analysis of Nine National Approaches to Ecological Risk Assessment of Living Modified Organisms in the Context of the Cartagena Protocol on Biosafety, Annex III / Secretariat of the Convention on Biological Diversity... (CBD Biosafety Technical Series; no. 02)
Summary: "The purpose of this report is to: 1) summarize the LMO ecological risk assessment approaches used by a representative set of LMO-producing countries in the context of the criteria of Annex III of theCartagena Protocol; and 2) conduct a multi-country comparison of ecological risk assessment approaches for each criterion of Annex III. A primary goal of this process was to summarize and compare countries that have experience with conducting LMO risk assessment, as well as countries from different geographical regions and indices of socio-economic development." — Provided by the authors.
ISBN 92-9225-424-3
1. Biodiversity 2. Biosafety 3. Genetically modified organisms – risk assessment 4. Environmental risk assessment 5. Biotechnology
I. Convention on Biological Diversity (1992). II. CBD biosafety technical series. II. United Nations.

Cover photos: Left: "Tree lined farm road through field landscape in summer" (©iStockphoto.com/AVTG); Centre-top: "Morocco, Fez, Donkey carrying a load of straw and a farmer working in a field" (Medioimages/Photodisc/Thinkstock); Centre-bottom: "Laboratory equipment on reflective surface with gavel" (©iStockphoto.com/-Oxford-); Right: "Woman looking at seedlings digital composite, close-up" (Jason Reed/Ryan McVay/Digital Vision/Thinkstock).

For further information please contact the Secretariat of the Convention on Biological Diversity.

ACKNOWLEDGMENTS

The authors would like to would like to thank Jennifer Kuzma and David Andow, the faculty mentors for this project for providing indispensable advice and expertise, thought-provoking discussion, and constructive criticism that was invaluable throughout the entire project. The authors also thank Manoela Pessoa de Miranda and Giovanni Ferraiolo for providing expertise, discussion, and peer review for earlier versions of the report as well as the Secretariat of the Convention on Biological Diversity for graciously hosting our visit during the initial stages of the project. The authors are deeply grateful to the contacts from the national authorities who reviewed portions of this work or provided additional information or documents that further clarified their respective country's frameworks, specifically Cheryl Corbett and Philip Macdonald (Canada Food Inspection Agency – Plant and Biotechnology Risk Assessment Unit), Ulrich Ehlers and Inge Kruczek (German Federal Office of Consumer Protection and Food Safety, Department for Gene Technology), Vidya Jagadish (Australia's Office of the Gene Technology Regulator), Nancy Schellhorn (Australia's Commonwealth Scientific and Industrial Research Organisation), and Hiroaki Ichiba (Japan Ministry of Foreign Affairs – International Cooperation Bureau). Oulimathe Paraiso and Adam Kokotovich reviewed earlier drafts of this report and their thoughtful comments greatly improved its quality and relevance. Funding for research travel was provided by the National Science Foundation IGERT (Integrative Graduate Education and Research Traineeship) Program for Introduced Species and Genotypes at the University of Minnesota (NSF DGE-0653827).

TABLE OF CONTENTS

Biosafety Technical Series No. 2: Summary and comparative analysis of nine national approaches to ecological risk assessment of living modified organisms in the context of the Cartagena Protocol on Biosafety, Annex III. 178 pp., http://bch.cbd.int/protocol/cpb_technicalseries/cpb-ts-02-en.pdf, Montreal: SCBD, 2012.

Chapter 1. Introduction

Human societies across the globe derive nutritional, economic, aesthetic and cultural value from biological diversity.[1] Much of that biological diversity is currently threatened by human activities, particularly through alteration of landscapes and ecosystems associated with agriculture, urban development and management of waterways.[2] A recent addition to this list is the growing scale of production of organisms that possess novel combinations of genetic material obtained through the use of recombinant DNA or direct injection of nucleic acids into cells or organelles (i.e. modern genetic engineering).[3] Organisms developed using these techniques have been classified as 'living modified organisms' (LMOs) to differentiate them from those developed using traditional methods such as mutagenesis and selective breeding. Each molecular modification is referred to as an 'event' or a 'transformation.'

I. History of LMOs

One of the first published accounts of the use of genetic engineering techniques was the modification of the bacterium *Escherichia coli*, which is commonly found in the gastrointestinal tract of many organisms, so that it produced the molecular precursors of human insulin.[4] This achievement ultimately permitted mass production of insulin for use in the treatment of diabetes. Modern genetic engineering techniques were also applied to agriculture. The first agricultural LMO to be sold commercially in the United States was a strain of tomato that was modified so that the fruit softened more slowly during ripening and thus had an extended shelf life.[5] In that case the transformation consisted of using a bacterium (*Agrobacterium tumefaciens*) to insert into the tomato genome an artificial gene construct that inhibited expression of polygalacturonase, an enzyme associated with the ripening process that contributes to tissue softening.[6] Technological and commercial breakthroughs such as these spurred global interest in and development of modern GE techniques, particularly in the agricultural sector.

1 Ehrlich, P. R. and A. H. Ehrlich. 1992. The value of biodiversity. 21 (3): 219-226.

2 Corvalan, C., S. Hales, and A. McMichael. 2005. Ecosystems and Human Well-being: Health Synthesis. A Report of the Millennium Ecosystem Assessment. World Health Organization, Geneva.

3 CBD. "Text of the Convention on Biological Diversity." Secretariat of the Convention on Biological Diversity. 2009. Accessed 24 Nov. 2009. http://www.cbd.int/convention/convention.shtml.

4 Goeddel, D. V., D. G. Kleid, F. Bolivar, H. Heyneker, D. G. Yansura, R. Crea, T. Hirose, A. Kraszewski, K. Itakura, and A. Riggs. 1979. Expression in *Escherichia coli* of chemically synthesized genes for human insulin. *Proceedings of the National Academy of Sciences*. 76(1): 106-110.

5 Kramer, M. G. and K. Redenbaugh. 1994. Commercialization of a tomato with an antisense polygalacturonase gene: The FLAVR SAVR™ tomato story. 79: 293-297.

6 Sheehy, R. E., M. Kramer and W. R. Hiatt. 1988. Reduction of polygalacturonase activity in tomato fruit by antisense RNA. *Proceedings of the National Academy of Sciences USA*. 85: 8805-8809.

Commercial production of agricultural LMOs, in terms of area planted, crops modified, traits used, and countries using the technology, has changed dramatically over time. Between 1996 and 2010, global production of agricultural LMOs increased from 1.7 million hectares to over 148 million hectares, and the number of countries in which LMOs are produced increased from six to 29.[7] The vast majority of this production was of soybean, maize, cotton, and canola (in that order), although modified forms of other crops, such as alfalfa and sugar beet, have also been developed and commercialized.[8] The main traits that are engineered into agricultural plants are those related to plant protection such as insect resistance and herbicide tolerance[7] although other features pertaining to plant health and nutritional value, such as virus resistance and altered amino acid composition, respectively, have also been developed.[7,8] In addition to single transformation events, many agricultural LMOs possess multiple engineered traits (i.e. are "stacked events"). For example, the LMO maize event 59122 possesses both herbicide tolerance and insect resistance.[7]

Prior to 2000, more than 80% of LMO production in terms of area occurred in developed nations, particularly the United States and Canada.[7] However, the share of global production of LMOs occurring in developing nations has increased steadily. One report estimated that developing nations accounted for approximately 48% of total LMO production in 2010 and that future growth is likely to be highest in developing countries.[7] In 2012, a privately-operated database of genetically modified agricultural products listed a total of over 140 distinct events based on the introduction of 15 traits into 22 crops.[8]

The past and predicted expansion of production of LMO crops have at once been lauded as a benefit for human kind and as a cause for concern regarding the potential negative impacts of the technology on both human health and the environment.

7 James C. 2010. Global status of commercialized biotech/GM Crops: 2010. ISAAA Briefs 42. ISAAA, Ithaca, NY.

8 CERA. "GM Crop Database." Center for Environmental Risk Assessment. 2012. Accessed 28 March 2012. http://cera-gmc.org/index.php?action=gm_crop_database.

II. Benefits and potential costs of agricultural LMOs

Proponents of genetic engineering technology in agricultural systems advocate for an increase in LMO cultivation on a global scale, citing benefits such as increased crop yield,[7, 9, 10] greater nutritional value and reduction of chemical pesticide and herbicide use compared to conventional crops.[7, 10, 11] However, others argue that the interactions of these modified organisms with the environment have been inadequately studied and that the research, development, and large-scale cultivation of these organisms should be approached cautiously.[12] Many ecological risks associated with the use of genetically modified crops have been identified, including gene flow to unmodified counterparts and related species (wild or cultivated), evolution of resistance by pests to herbicides (plants) or expressed toxins (insects), and causation of general harm to non-target species.[13] With the rising interest in agricultural LMOs worldwide, it became evident to policymakers that countries engaged in the import, export, and domestic development of LMOs should be equipped with a legislative framework for systematically evaluating the risks associated with the these products and determining which risks were manageable.

> The past and predicted expansion of production of LMO crops have at once been lauded as a benefit for human kind and as a cause for concern regarding the potential negative impacts of the technology on both human health and the environment.

9 Mara, M., P. Pardey, and J. Alston. 2002. The payoffs to transgenic field crops: an assessment of the evidence. *AgBioForum*. 5(2): 43-50.

10 Mara, M., P. Pardey, and J. Alston. 2002. The payoffs to transgenic field crops: an assessment of the evidence. *AgBioForum*. 5(2): 43-50.

11 Brookes, G. and P. Barfoot. 2008. Global impact of biotech crops: socio-economic and environmental effects, 1996-2006. *AgBioForum*. 11(1): 21-38.

12 Myhr, A. I. and T. Traavik. 2003. Genetically modified (GM) crops: precautionary science and conflicts of interest. *Journal of Agricultural and Environmental Ethics*. 16(3): 227-247.

13 Snow, A. A., D. A. Andow, P. Gepts, E. M. Hallerman, A. Power, J. M. Tiedje, and L. L. Wolfenbarger. 2005. Genetically engineered organisms and the environment: current status and recommendations. *Ecological Applications*. 15(2): 377-404.

III. International agreements pertaining to LMOs

Prompted by concerns about threats to global biological diversity, the United Nations convened a summit in Rio de Janeiro, Brazil in 1992. This meeting produced an international agreement, the Convention on Biological Diversity (CBD), in which three primary objectives for the international community were outlined: 1) conservation of biological diversity, 2) sustainable use of biological diversity resources, and 3) fair and equitable sharing of the benefits derived from biological diversity.[3] Another outcome from the Rio summit was the creation of a working group tasked with creating a draft protocol addressing the ecological risks associated with trans-boundary movement of LMOs. The result of this and subsequent efforts was the Cartagena Protocol on Biosafety. This document was approved by Parties to the CBD in January 2000 in Montréal, Canada, ratified by the required number of countries by May 2003, and entered into force on September 11th, 2003. An important element of the Cartagena Protocol on Biosafety is Annex III, which provides broad guidelines for how ecological risk assessment of LMOs should be conducted (see Appendix: CPB – Annex III). Member nations lacking an existing biosafety framework were then asked to draft their own biosafety framework. Funding and technical resources were available for countries requiring assistance.

IV. IGERT project

In 1998, the United States National Science Foundation (NSF) established the Integrative Graduate Education and Research Traineeship (IGERT) program with the goal of engaging Ph.D. students from a variety of fields in interdisciplinary research. The IGERT program in Risk Analysis for Introduced Species and Genotypes (ISG-IGERT), designed to provide Ph.D. students with training in ecological risk analysis (ERA), was instituted at the University of Minnesota-Twin Cities. In spring 2009, the ISG-IGERT sent out a request for proposals for research projects.

One of the proposals received was from the Secretariat of the Convention on Biological Diversity (SCBD) in Montréal, Canada for a comparative study on risk assessment approaches from different countries. The Biosafety Division of the CBD Secretariat is responsible for the coordination and administration of all functions pursuant to the Cartagena Protocol on Biosafety, including the operation of the Biosafety Clearing-House (BCH). The BCH provides a centralized location for the exchange of information pertaining to the regulation, research and development, and production of LMOs.

V. Goal and structure of report

The purpose of this report is to: 1) summarize the LMO ecological risk assessment approaches used by a representative set of LMO-producing countries in the context of the criteria of Annex III of the Cartagena Protocol, and 2) conduct a multi-country comparison of ecological risk assessment approaches for each criterion of Annex III. A primary goal of this process was to summarize and compare countries that have experience with conducting LMO risk assessment, as well as countries from different geographical regions and indices of socio-economic development. The following chapters detail the methodology used for the analysis (Chapter 2), each of 9 countries' risk assessment frameworks (Chapters 3-11), a cross-case comparison of the most striking features of the frameworks (Chapter 12) and broader conclusions on elements of international LMO risk assessments (Chapter 13).

We envisage that this report may become a useful tool in assisting countries to compare different approaches to risk assessment and make informed decisions regarding the screening and approval of LMOs. Ultimately, the agents and agencies tasked with developing LMO ecological risk assessment protocols will need to determine what risks to biological diversity and the environment they are willing to accept or capable of managing, and therefore what LMOs and LMO-derived products they are willing to bring into their territories.

Chapter 2. Methods

I. Framing the analysis

As stated above, the purpose of our analysis was to summarize and compare different national approaches to ecological risk analysis (ERA) for living modified organisms (LMOs). In the first phase of this project, we investigated the materials from a subset of countries available through the Secretariat of the Convention on Biological Diversity's (CBD) Biosafety Clearing-House (BCH), noting such features as the presence or absence of laws, regulations and guidance documents, the number of decision documents, and the language(s) in which documents were published (Table 2.1). After this preliminary investigation, we narrowed the scope to 18 candidate countries (Table 2.1) and further investigated their specific risk assessments as well as legal, regulatory, and guidance documents.

> the purpose of our analysis was to summarize and compare different national approaches to ecological risk analysis (ERA) for living modified organisms (LMOs).

We structured our analysis according to Annex III of the Cartagena Protocol on Biosafety (CPB) (see Appendix: CPB – Annex III) and framed our comparisons of risk assessment approaches within the categories found in Annex III (i.e. "General principles", "methodology", and "points to consider"). These categories were retained throughout the process, although we subsequently expanded our analysis to include additional information on the characteristics of frameworks and regulatory systems that did not readily fit within the Annex III framework. We grouped this information under different themes as detailed in our analysis.

II. Selection of countries

Starting with a list of 18 countries that submitted risk assessment records to the BCH (Table 2.1), we narrowed the list of countries to allow intensive analysis. We selected a subset of countries based on the following criteria: the amount of available information, an index of development, and the usage of living modified (LM) crops. We also sought a broad geographic representation including countries that had not ratified the CPB. Upon further examination, some countries had limited available information and these were eliminated from further consideration. We used a collective ranking process to choose our final suite of nine countries from the remaining candidates (Table 2.1). This suite represented six continents, all possible combinations of CBD and CPB party status (i.e. non-party, CBD party, CBD & CPB party), three development indices (i.e. medium, high, very high) and areas of LM crop cultivation ranging from fewer than 50,000 hectares (e.g., Germany) to 66.8 million hectares (U.S.) (Table 2.1).

III. Sources of information

The BCH, national clearing-houses, and competent national authorities

Our primary sources of information were the CBD's Biosafety Clearing-House (BCH), national biosafety clearing-houses, and the websites and personnel of the competent national authorities. The BCH is an online resource built and maintained by the Secretariat of the CBD for the purposes of facilitating the exchange of information on LMOs and assisting the Parties to the Cartagena Protocol in carrying out their obligations.[1] The BCH includes electronic copies of regulations pertaining to LMOs, decision documents, risk assessments, and contact information for the competent national authorities. In some cases, the BCH provides links to documents rather than the documents themselves; generally those links were to national regulatory agency sites. The documents submitted to or linked from the BCH were chosen as the primary basis for the analysis because they are officially approved by the pertinent country for public viewing.[2] When necessary, we accessed the websites of the relevant competent national authorities directly (i.e. those not linked to BCH) to obtain additional documentation and information.

> The documents submitted to or linked from the BCH were chosen as the primary basis for the analysis because they are officially approved by the pertinent country for public viewing.

In several cases, we contacted staff members of the competent national authorities, requesting clarification of specific points or additional materials (e.g., risk assessments were requested if none were otherwise available to us).

IV. Primary sources

> the sources included laws, regulations, decision documents, and risk assessment summaries

The primary sources of materials for the nine countries that we reviewed appear in Table 2.1. Generally, the sources included laws, regulations, decision documents, and risk assessment summaries. In some cases, guidance documents and detailed risk assessments were also available. The specific sources of information used for each country are indicated in the relevant country summary chapters.

1 The Biosafety Clearing-House. 2009. County Profiles. http://bch.cbd.int/about/(accessed 20 Nov. 2009).

2 Secretariat of the Convention on Biological Diversity. 2009. Cartagena Protocol on Biosafety Ratification List. http://www.cbd.int/doc/lists/cpb-ratifications.pdf (accessed 24 Nov. 2009).

TABLE 2.1: List of the eighteen countries considered for LMO ERA summary and comparison analysis. The final nine countries chosen for analysis are indicated with gray.

Nation	Number of Records as of Nov. 2009[1]				Document language(s)	CBD[i] & CPB[ii] party status[3]	2009 United Nations - Human Development Index[4]	Living modified crop(s)[5]	Area of cultivation (million hectares)[5]
	Total	Law(s), regulation(s) or guideline(s)	Country's decisions or any other communications	Risk assessment					
AFRICA									
Egypt	1	1			English	CBD & CPB	Medium	Maize	0.05-0.1
Kenya	1	1			English	CBD & CPB	Medium		<0.05
South Africa	16	3	13		English	CBD & CPB	Medium	Maize, Soybean, Cotton	2.2
AMERICAS									
Caribbean									
Cuba	24	11	13		Spanish, English	CBD & CPB	High		<0.05
Central America									
Mexico	63	11	24		Spanish, English	CBD & CPB	High	Cotton, Soybean	0.1
North America									
Canada	137	23	58	56	English	CBD	Very High	Canola, maize, soybean, sugarbeet	8.8
United States	119		119		English	Non-Party	Very High	Maize, soybean, cotton, canola, sugarbeet, alfalfa, papaya, squash	66.8
South America									
Argentina	15	5	11		Spanish, English	CBD	High	Soybean, maize, cotton	22.9
Brazil	36	12	12	12	Portuguese, English	CBD & CPB	High	Soybean, maize, cotton	25.4
Colombia	57	20	39	8	Spanish, English	CBD & CPB	High	Cotton	0.05-0.1

Nation	Number of Records as of Nov. 2009[1]				Document language(s)	CBD[i] & CPB[ii] party status[3]	2009 United Nations - Human Development Index[4]	Living modified crop(s)[5]	Area of cultivation (million hectares)[5]
	Total	Law(s), regulation(s) or guideline(s)	Country's decisions or any other communications	Risk assessment					
ASIA									
China	66	43	23		Mandarin, English	CBD & CPB	Medium	Cotton, papaya, poplar, tomato, sweet pepper	3.5
India	1	1			English	CBD & CPB	Medium	Cotton	9.4
Japan	174	2	93	78	Japanese, English	CBD & CPB	Very High		<0.05
Malaysia	1	1			English	CBD & CPB	High		<0.05
EUROPE									
Germany	39	15	11	13	German, English	CBD & CPB	Very High	Potato	0.05-0.1
Norway	10	8	2		Norwegian, English	CBD & CPB	Very High		<0.05
OCEANIA									
Australia	30	1	29		English	CBD	Very High	Cotton, canola	0.7
New Zealand	78	11	23	44	English	CBD & CPB	Very High		<0.05

[i] Convention on Biological Diversity

[ii] Cartagena Protocol on Biosafety

In addition to the criteria relating directly to Annex III of the CPB (see Appendix: CPB – Annex III), we examined the documents to determine what LMO regulatory structure existed in the country in question and to answer questions such as who is the regulatory authority, what is the scope of their authority, what triggers a risk assessment, whether different types or uses of LMOs are regulated differently, and who makes the final decision for approval. The guidance documents, when available, indicated what information should be included in an application for LMO use and/or how the pertinent authority should evaluate a submitted risk assessment. Some of these documents provided detailed lists of the items to be considered when conducting an assessment, such as donor organism and LMO characteristics and information on the receiving environment. Risk assessments and risk assessment summaries often provided concrete details of the assessment process, for example, the specific adverse effects considered.

In most but not all cases, the primary sources were available in languages in which our group is competent (i.e., English and Spanish). Documents that were available in other languages were translated using a web-based machine translation software (Google Translate). The individual country summaries (Ch. 3 – 11) state whether translation was necessary and which documents were translated.

V. Comparative process

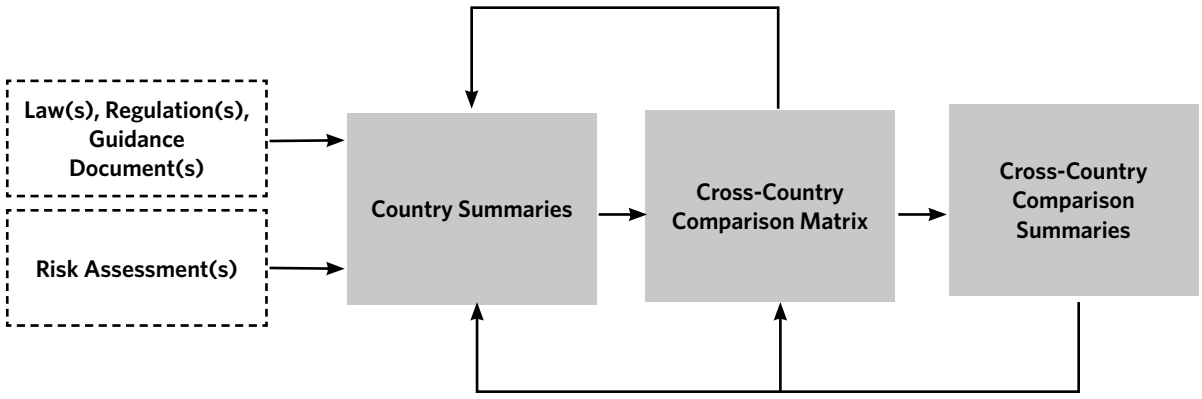
We compared approaches to risk assessment using an iterative process (Fig. 2.1). For each selected country, we examined the legal, regulatory and guidance documents available and determined how each component fit within the CPB Annex III structure. We then read at least one risk assessment, if available, noting procedural details as well as the ways an actual risk assessment varied from the process prescribed by the corresponding laws and regulations. We summarized each country's risk assessment framework (Ch. 3-11), and encapsulated the findings into comparative matrices (Ch. 12). Commonalities and divergences among countries that were observed in the matrices were then discussed in multi-country comparison summaries (Ch. 12). The country summaries, matrices, and comparison chapters were peer-reviewed within the group and by University of Minnesota faculty mentors who have substantial experience in risk assessment and policy analysis. All chapters were also revised in an iterative fashion (Figure 2.1) as new information became available and as further consideration led to reassignment of framework components to different categories corresponding to Annex III of the CPB.

This was done to increase reliability and consistency in country summaries and multi-country comparisons.

Commonalities and divergences among countries that were observed in the matrices were then discussed in multi-country comparison summaries

Due to the number, variability, and complexity of the risk assessment frameworks considered, we focused our comparison on living modified plants considered for release into the environment (i.e. uncontained use) and further differentiated release into the environment as either restricted use (e.g. experimental use or isolated field trials) or unrestricted use (e.g. deregulated, commercial use, placing on the market). The individual country summaries also discuss other types of LMOs or contained use, where such discussion helped to clarify the risk assessment framework in question.

FIGURE 2.1: Iterative processes for development of the country and multi-country summaries and comparison matrices. Dotted lines indicate primary sources.



VI. Strengths and limitations of this methodology

This report represents our best current understanding of the reviewed risk assessments and risk assessment frameworks. It is an independent analysis based on publicly available documents, conducted by an interdisciplinary team and reviewed by experts in risk assessment. The introduction and methods chapters (Ch. 1, 2) along with country summaries and matrices were submitted to the competent national authorities for review. Some countries' competent national authorities chose to provide comments and additional documentation, however, the competent national authorities were not allowed to review the comparison and conclusion chapters (Ch. 12 and 13).

> This report is an independent analysis based on publicly available documents, conducted by an interdisciplinary team and reviewed by experts in risk assessment.

Due to time constraints, we only analyzed nine countries in-depth. This consideration, combined with our choice to use publicly-available documents, required us to focus our work primarily on countries that were particularly active participants on the BCH and that had documents available in English or Spanish. In regards to the countries whose source documents required translation (i.e. China and Germany), we were limited by the capability of the machine translation service. When points were unclear after translation, we sought confirmation from other sources such as the websites or personnel of the pertinent competent national authorities. However, all errors of fact and interpretation are our own. Our analysis is primarily descriptive and comparative. We refrain from making normative judgments about the overall quality of each individual country's ERA LMO framework.

VII. Organization of this report

For each of the nine countries we reviewed, the summaries of the risk assessment frameworks are presented as individual chapters (Ch. 3 – 11). In those chapters as well as in the comparative matrix (Ch. 12) and the multi-country comparison (Ch. 12), the headings "General principles" and "Methodology" and most of the associated subheadings are taken directly from Annex III. Additional headings and subheadings appearing in Chapters 3 – 12 are inserted to provide clarity (items are indicated by asterisks) and because they represent themes that may be of interest but do not readily fall within CPB Annex III categories.

Chapter 3. Australia: Elements of risk assessment for LMOs

I. Abstract

Regulation regarding living modified organisms (LMOs) in Australia is triggered by genetic modification, and the approval process for LMO release activities is regulated by a single regulatory body and was created under the Gene Technology Act 2000[1] and the Gene Technology Regulations 2001.[2] Risks to human health and safety and the environment are the only ones considered by the Act for regulation. The regulatory process distinguishes between applications for contained dealings and environmental releases; environmental releases are further divided into limited release (also called field trials) and large-scale commercial release. A risk management plan is a necessary component of the completed risk assessment for a LMO application in Australia. Australia takes a qualitative approach to risk assessment of LMOs but quantitative evidence can be incorporated into the assessment at many points. Risk estimates consider the likelihood and consequences of a risk as well as any associated uncertainty, and the framework details how these components should be estimated using qualitative class values.

II. Overview of legislative & regulatory framework

The Gene Technology Act 2000 (further referred to as the "Act") and Gene Technology Regulations 2001 are the primary legislative documents in Australia addressing the release of LMOs. As a result of this legislation, an independent office holder, the Gene Technology Regulator (also known as the Regulator) was appointed. The Regulator is a single person responsible for making decisions regarding release of living modified organisms (LMOs) in Australia and is an independent statutory office holder responsible for reviewing all submitted Risk Assessment and Risk Management Plans (RARMP) for licensing of LMOs. A separate regulatory body, the Office of the Gene Technology Regulator (OGTR), provides administrative support to the Regulator. (See Appendix 3.A for a flow chart summary of the Australian National Gene Technology Regulatory System.) The Act does not regulate LMO products, however; this falls to other governmental agencies, depending on the type/use of product.

To assist in risk communication and transparency as well as to improve the quality of RARMPs, the OGTR published the Risk Analysis Framework (RAF),[3] a key document for informing applicants, stakeholders and the public about the Regulator's approach to risk assessment and risk management

1 Gene Technology Act 2000. 2000. "Act No. 169 of 2000 as amended". Australian Government. Accessed 2 November 2009. http://www.frli.gov.au/comlaw/Legislation/ActCompilation1.nsf/0/51A2449A3EBB9A1CCA257475001ECD9C?OpenDocument.

2 Gene Technology Regulations 2001. 2001. "Statutory Rules 2001 No.106 as amended." Australian Government: Federal Register of Legislative Instruments. Australian Government. Accessed 2 November 2009. http://www.comlaw.gov.au/ComLaw/Legislation/LegislativeInstrumentCompilation1.nsf/current/bytitle/50A20AC6364C7697CA2575AC0012A890?OpenDocument&mostrecent=1.

3 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Accessed 20 October 2009. http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/riskassessments-1.

process as outlined in the Act for the release of LMOs. Since its first version, the RAF has undergone several revisions, the most recent being in 2009. The RAF does not differentiate between different types of LMOs, and excluding LMO products, all other LMOs go through the same risk assessment process. Australia's RAF is the primary reference document we used for this summary. Decision documents, completed RARMPs, summary documents, and documents for public comment are made available on the OGTR website.[4]

For this summary document, a completed LMO risk assessment was also reviewed to see how the risk assessment framework is implemented.[5] The completed RARMP document addresses confined experimental release (field trials) of three genetically modified (GM) *Gossypium barbadense* cotton lines in Australia. These stacked lines contain combinations of genes for insect resistance and herbicide tolerance; each of these resistance genes have previously been approved for commercial release in Australia in other LMO cotton lines (GM *Gossypium hirsutum*).[6]

> For our purposes, a DNIR is analogous to a contained laboratory studies, and a DIR includes a release into the environment, whether for experimental purposes or a large-scale commercial release.

In Australia, all activities regarding LMOs are referred to as "dealings with GMOs", and a license must first be approved and granted for any activity to occur. Dealings are separated into two categories: 1) "Dealings not involving intentional release" (DNIR) and 2) "Dealings involving intentional release" (DIR). For our purposes, a DNIR is analogous to a contained laboratory studies, and a DIR includes a release into the environment, whether for experimental purposes or a large-scale commercial release.

Regulation of LMOs in Australia is process-based, but the trigger for a risk assessment is product-based. For reference, LMOs are referred to as GMOs in all Australian legislative documents. (See Appendix 3.C and 3.D to view flow charts of Australia's risk assessment application process for environmental release of a LMO.)

III. General principles

A. SCIENTIFICALLY SOUND

Australia's regulatory framework for LMOs was created through consultation with experts, the public, existing risk assessment models such as the Australian New Zealand Risk Management Standards 4360:2004, and guideline documents from the World Health Organization, Food and Agriculture Organization of the United Nations, Annex III (Cartagena Protocol), the United States' National Research Council "Red Book", and the Organisation for Economic Co-operation and Development.[7] The Regulator is required by the Act to consult with scientific experts, and the Regulator can also require that further scientific evidence be provided. In addition, scientific experts may be consulted when adequate scientific evidence is not provided or available. Finally, staff working on LMOs is required to receive updated training to maintain scientific expertise and best practice in risk analysis.[8]

The use of sound scientific information is vital to Australia's LMO regulatory process. Although much of the LMO risk assessment process is qualitative, sound scientific evidence must be used for estimates of risk likelihood, consequence, the overall risk estimate, and risk management. The RAF lists criteria for determining the quality of sources and scientific information.[9] Table 3.1 summarizes these criteria.

4 Office of the Gene Technology Regulator. 2009. Website. Accessed 21 October 2009. http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/home-1.

5 Technical Summary of the Risk Assessment and Risk Management Plan for Application No. Dir 074/2007 from Monsanto Australia Limited. 2007. Office of the Gene Technology Regulator. Accessed 22 October 2009. http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/dir074-2007.

6 Technical Summary of Dir 074/2007. 2007. Executive Summary pIII.

7 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 2 p12.

8 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 2 p19.

9 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 4 p 42-43.

TABLE 3.1: Criteria used in Australia's Risk Analysis Framework to determine quality of evidence.[9]

Criteria for Considering Quality of Evidence	Description
Appropriateness	The degree to which the data are relevant and applicable to the risk assessment question
Reliability	The accuracy and integrity of experimental design, methodology, and statistical analysis used to report data and conclusions
Transparency	The clarity and completeness with which all key data, methods and processes, as well as the underlying assumptions and limitations, are documented and available
Expertise	The standing of the author(s) or expert(s) presenting the data
Strength	The quantity of data available to support the conclusion in the scientific literature; whether there is conflicting data and the strength of the conflicting data
Robustness	If data are from disparate sources, whether experiments or researchers support similar conclusions.

B. TRANSPARENCY

The Australian RAF states that transparency and risk communication are important in the LMO risk assessment process. Transparency is considered one of the "Guiding principles of risk analysis".[10] In Australia's risk assessment framework, risk communication "establishes an interactive dialogue between the Regulator and stakeholders to provide open, transparent and consultative risk-based regulation of GMOs",[11] and a significant component to risk communication is demonstrating the rationale used by the Regulator in making LMO decisions.

An entire chapter in the RAF is dedication to the importance of risk communication and how/where this should occur for each LMO risk analysis.[12]

> Transparency is considered one of the "Guiding principles of risk analysis"

Australia maintains a transparent risk assessment process in other ways as well. One is through the development of numerous governmental policy documents related to LMOs. These documents aim to clarify particular aspects of the regulatory framework. For example, one document is entitled "Policy on licensing of plant GMOs in which different genetic modifications have been combined (or 'stacked') by conventional breeding".[13] Another example is a monitoring and compliance framework document.[14] The OGTR also maintains a website that includes all RARMPs, licenses issued by the Regulator authorizing environmental releases of LMOs, locations of field trials, reports of Regulator activities, biology documents, and other various policy and guidance documents.[15] Finally, Australia incorporates external comment, including (but not limited to) the public and Australian government agencies, into the risk assessment process by requiring the Regulator to seek consultation on RARMPs; these documents are advertised in a national newspaper, the Australian Government Gazette, and the OGTR website.[16] The final version of the RARMPs form the basis of the decision by the Regulator on whether to issue a license for the environmental release of a LMO.

10 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 2 p18.
11 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Executive Summary p iv.
12 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 6 p61.
13 Policy on licensing of plant GMOs in which different genetic modifications have been combined (or 'stacked') by conventional breeding. 2007. Office of the Gene Technology Regulator. Australian Government. Accessed 20 October 2009. http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/policies-1.
14 Monitoring and compliance framework: In accordance with the *Gene Technology Act 2000*. 2007. Office of the Gene Technology Regulator. Australian Government. Accessed 20 October 2009. http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/monprot-3/$FILE/02%20M&C%20Framework%20July%202007.pdf,
15 Office of the Gene Technology Regulator. 2009. Website. Accessed 21 October 2009. http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/home-1.
16 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Appendix A Stage 7 p93.

The final RARMPs also include a summary of issues raised from the public comment period in an Appendix, which is exemplified in the GM cotton risk assessment document we reviewed.[17]

C. LACK OF SCIENTIFIC KNOWLEDGE OR CONSENSUS DOES NOT INDICATE LEVEL OR ABSENCE OF RISK

In dealing with scientific uncertainty, Australia's Act outlines a precautionary approach that states "where there are threats of serious or irreversible environmental damage, a lack of full scientific certainty should not be used as a reason for postponing cost-effective measures to prevent environmental degradation".[18] The RAF raises two other important points concerning uncertainty in risk. The first is that uncertainty can also be useful, for example, uncertainty analysis could be used to "highlight areas where more information may be needed to make risk estimates and areas where cautionary measures should be taken".[19] The second point addresses the advantages and disadvantages of a precautionary approach. For example, in the RAF, "the Act indicates that the Regulator is required to take protective measures as a prudent and sound response in the face of a lack of full scientific certainty", but the RAF also acknowledges that "Critics argue that precautionary strategies invoke less scientifically rigorous information and can lead to arbitrary regulatory decisions."[20]

> In dealing with scientific uncertainty, Australia's Act outlines a precautionary approach that states "where there are threats of serious or irreversible environmental damage, a lack of full scientific certainty should not be used as a reason for postponing cost-effective measures to prevent environmental degradation".

17 Risk Assessment and Risk Management Plan (RARMP) for DIR 074/2007: Limited and controlled release of GM insect resistant and/or herbicide tolerant *Gossypium barbadense* cotton. 2007. Office of the Gene Technology Regulator. Appendix C, p104. Accessed 21 October 2009. http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/dir074-3/$FILE/dir074rarmp1.pdf.

18 Gene Technology Act 2000. 2000. Act Section 4(aa).

19 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 2 p17.

20 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 1 p7.

D. RISK CONSIDERED IN THE CONTEXT OF RISK POSED BY NON-MODIFIED RECIPIENTS OR PARENTAL ORGANISMS

The RAF states that LMO risks are estimated through a comparative assessment with a parental/baseline organism in a specific environment. If the parental organism itself poses some human or environmental risk (e.g. weediness), then that risk is considered part of the baseline. As stated in the RAF, "The focus of the assessment is whether modified properties of the GMO arising from gene technology increase the level of risk, or give rise to additional risks."[21]

E. CASE-BY-CASE BASIS

Australia's RAF explicitly states that all applications for dealings with LMOs in Australia be dealt with on a case-by-case basis. The Regulator must take a "case-by-case approach, weighing the available evidence against any uncertainty of likelihood or consequence, and the availability of management measures, to arrive at a prudent judgment".[22] The RAF does not formally define a case, but Australia's published individual RARMPs represent examples of what is considered a case for genetic modification or transformation and risk assessment for an individual LMO (i.e. case-by-case basis). The framework also makes a distinction in the criteria between releases into the environment (DIR) and confined experimental work with LMOs in the laboratory (DNIR).

Australia has a stated policy on dealing with multiple modifications or stacked event LMOs. The Regulator deals with each of these events on a case-by-case basis as well, but any previously prepared RARMPs for the release of individual parent LMOs must be consulted. Unless new risks are identified, a new risk assessment is unlikely to be triggered.[13] In the case of GM cotton, the use of a new recipient species (*G. barbadense*) triggered the submission of a new LMO license application and the preparation of a new RARMP by the Regulator, even though the resistance genes were previously approved for commercial release in different species of cotton LMOs.

21 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 1 p4.

22 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 5 p51.

IV. Methodology

A. IDENTIFICATION OF NOVEL GENOTYPIC AND PHENOTYPIC CHARACTERISTICS ASSOCIATED WITH LMO, THAT MANY HAVE ADVERSE EFFECTS ON BIOLOGICAL DIVERSITY IN THE LIKELY RECEIVING ENVIRONMENT, ALSO TAKING INTO ACCOUNT RISKS TO HUMAN HEALTH.

1. Recipient/Parental Organism

In Australia's framework, the comparison of the LMO to the non-modified parent organism is critical for identifying adverse effects.[23] As much information as possible should be provided in the risk assessment regarding the parental organism, including (but not limited to) origin, taxonomy, uses, ecology, biological characteristics, and morphology.[24] The information may come from sources both in Australia as well as abroad.[25] It must be noted that the baseline for comparison may not be limited to the parent organism alone. In the case study reviewed on GM-*Gossypium barbadense,* both the non-GM parent *G. barbadense* and GM-*G. hirsutum* (the commercial standard, making up 90% of cotton grown in Australia) were used for baseline comparisons;[26] examples of the information used in the RA include nutritional requirements of both the GM and the parent cotton lines, average seed yield, history of hybridization, and known similarities/differences between the two cotton lines. The toxicity, allergenicity, and weediness of each cotton species were specifically described in detail to help identify adverse effects.[27] For a number of major plant crops, review documents such as "The biology and ecology of cotton (*Gossypium hirsutum)* in Australia" have been prepared by the OGTR to use as a source of information on recipient/parental organisms in comparison with their respective LMOs.[28]

2. Donor Organism

The donor organism is mentioned infrequently within the documents reviewed. The donor organism is mentioned once in the GT Regulations to define what constitutes a LMO.[29] In the RAF, the donor organism is referred to as the "source organism" and is mentioned in the context of characterizing the LMO by providing information on "the source organism and any known adverse effects it may have on human health and safety or the environment".[24] In the GM cotton risk assessment, the source organisms of all inserted genes are identified to at least the generic level, and since at least one source organism (*Agrobacterium tumefaciens*) is a plant pathogen, the document states that the inserted sequence is not capable of causing disease.[30]

3. LMO Characteristics

The RAF provides guidance on the importance of considering information on LMO characteristics because this information is used in a comparative analysis with the parent organism for identifying risks. The RAF also provides guidance on how information such as "genotypic and phenotypic properties of the GMO" is used in risk assessment.[31] Specifics on the method(s) of genetic modification used, number of copies inserted for a particular genetic sequence, observable unintended effects, and future stability of the modification may all be addressed in the risk assessment.[32] Information on the proposed dealings of the LMO, including information on use, supply, transport, production, breeding, and propagation of the LMO, should be considered in identifying risks.[33] In the GM cotton risk assessment, the source,

23 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Executive Summary p viii.
24 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 3 p27.
25 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Appendix A p87.
26 Risk Assessment and Risk Management Plan for DIR 074/2007. 2007. Technical Summary p4.
27 Risk Assessment and Risk Management Plan for DIR 074/2007. 2007. Section 3.
28 The biology and ecology of cotton (*Gossypium hirsutum*) in Australia. 2002. Office of the Gene Technology Regulator. Accessed 20 October 2009. http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/cotton-3/$FILE/biologycotton.pdf.
29 Gene Technology Regulations 2001. 2001. Page 30.
30 Risk Assessment and Risk Management Plan for DIR 074/2007. 2007. Page 1.
31 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 4 p35.
32 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 3 p26.
33 Risk Assessment and Risk Management Plan for DIR 074/2007. 2007. Section 2 p39.

sequence, degradation process, toxicity, and allergenicity properties of all inserted genes were described in detail.[34] The license application form for a LMO release in Australia outlines the type of information considered necessary to prepare a RARMP.[35]

4. Receiving Environment

Information on the receiving environment is used in a comparative analysis of the LMO to its parent organism. In LMO applications, information on environmental conditions, current production/work practices, presence of related and sexually compatible relatives, and presence of similar genes should be included. Within the RAF, specific mention is made to include information on management/farming practices for a LMO crop plant.[24] Consideration of scale of the release environment is important because legislation makes a distinction between "limited and controlled" releases (i.e. confined field trials) and "all others" (i.e. commercial releases).[36] The case study risk assessment on LMO cotton exemplifies a "limited and controlled" release into the environment where the spatial scale was set at a specified number of locations (13) with limited size each (2 hectares maximum) and the temporal scale set for two growing seasons.[37] The risk assessment example also stipulated the distance from natural waterways (>50m), crop destruction after harvest, and destruction of any volunteer LMO cotton post-harvest for twelve months.[38]

The risk assessment should also take into consideration information available from previous releases of the LMO, whether in Australia or overseas.[32] The GM cotton risk assessment provides this information for each genetic modification that has been approved both within Australia and overseas. For example, all countries that have approved Bollgard II® for commercial release are listed, as well as the year of approval, intended use of the LMO, and the regulatory agency.[39] The RAF also recognizes that receiving environments may not be static. For example, extensive adoption of GM cotton in Australia increased beneficial insects in the environment through reduced insecticide dependency. This resulting effect from extensive use of a LMO must be considered in the baseline comparisons.[24]

> The risk assessment should also take into consideration information available from previous releases of the LMO, whether in Australia or overseas.

B. EVALUATION OF THE LIKELIHOOD OF THESE ADVERSE EFFECTS BEING REALIZED, TAKING INTO ACCOUNT THE LEVEL AND KIND OF EXPOSURE OF THE LIKELY POTENTIAL RECEIVING ENVIRONMENT TO THE LIVING MODIFIED ORGANISM

1. Intended use of the LMO compared to recipient or parental organism

The Australian RAF provides guidance on conducting a detailed comparative analysis of the LMO to the parental organism. Likelihood is qualitatively assessed using the information described above (Section IIIA). For LMO crops, the Australian framework does make some distinction between controlled releases and commercial releases. In the GM cotton RARMP example, all introduced genes for resistance were previously approved for commercial release in Australia, and therefore the results of these previous RAs were taken into consideration.

Within the GM cotton RARMP, allergenicity and toxicity were both addressed regarding adverse effects to human health. The reversibility of toxicity, type of toxicity, and potential exposure pathways were all addressed. The document also states that for contained releases where the LMO is not intended for human food or animal feed and must be destroyed, this lack of potential exposure must be considered.

34 Risk Assessment and Risk Management Plan for DIR 074/2007. 2007. Section 4.

35 Application for license for dealings with a GMO involving intentional release of the GMO into the environment (DIR). 2009. Office of the Gene Technology Regulator.

36 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Appendix B p104.

37 Risk Assessment and Risk Management Plan for DIR 074/2007. 2007. Tech Summary p1.

38 Risk Assessment and Risk Management Plan for DIR 074/2007. 2007. Section 2.2 p10.

39 Risk Assessment and Risk Management Plan for DIR 074/2007. 2007. Table 2 p36.

2. Characteristics of relevant potential receiving environment

Details required for characterizing the receiving environment were mentioned in Section IV.4 (see previous section). Consideration for temporal scale of release becomes important in likelihood evaluation. The RAF mentions that in the case of a LMO being released for a very short time period (for limited/controlled releases), any human or environmental effect(s) that could occur beyond the limited release period must be considered.[40] In the case of GM cotton, the limited size and short duration of the proposed release would limit the exposure of people and the environment to the LMO.

3. How incidental exposure to the environment could occur

The RAF emphasizes the need to identify all steps in the exposure pathway because each step may be critical in determining likelihood. The Australian risk assessment process also takes into consideration the number of steps in an exposure pathway. Assessing likelihood for complex exposure pathways with many links is inherently more difficult than a simple pathway, and the RAF discusses how the number of steps in the pathway can affect the likelihood. They give the example of a simple exposure pathway where the LMO gene product is toxic to non-target organism; in this case because there is likely to be more evidence of a direct correlation between dose and toxin, the likelihood estimate will be more robust.[40]

In the GM cotton RARMP, exposure pathways for each identified adverse effect is described individually.[41] Human-mediated exposure to the environment, such as pollen transfer on clothing, is one example mentioned. Gene transfer to a non-modified related crop growing nearly is another example.

4. Conclusion of evaluation of likelihood of exposure

Likelihood evaluation is a qualitative process in Australia. A likelihood assessment is conducted for each identified adverse effect, and a likelihood value (Table 3.2) is assigned by the Regulator based on information provided on the parent organism(s), the genetic modification, the receiving environment, scope of release, use of LMO, and the LMO itself.[42] Within the GM cotton risk assessment, the likelihood estimates were not explicitly stated and only an estimate of risk was provided.

TABLE 3.2: Scale for the likelihood assessment of LMOs in Australia.[43]

Likelihood	Likelihood assessment definitions
Highly unlikely	May occur only in very rare circumstances
Unlikely	Could occur in some circumstances
Likely	Could occur in many circumstances
Highly likely	Is expected to occur in most circumstances

C. EVALUATION OF THE CONSEQUENCES SHOULD THESE ADVERSE EFFECTS BE REALIZED

Consequence evaluation is also a qualitative process in Australia, and as with likelihood, each identified risk undergoes its own consequence assessment on a case-by-case basis.[44] The Regulator determines a consequence value for each identified risk. The consequence values in Table 3.3 provide broad descriptive definitions so that all potential risks can be included somewhere.[45]

40 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 4 p40.
41 Risk Assessment and Risk Management Plan for DIR 074/2007. 2007. Chapter 2.
42 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 4 p39.
43 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 4 Table 4.2. p39.
44 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 4 p32.
45 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 4 p41.

To assist in consequence evaluation, Australia has developed a set of generic "consequence criteria" to use as the basis for developing measurable assessment endpoints (Appendix 3.B).[46] The Australian RAF further considers magnitude of adverse impact, spatial extent, temporal occurrence (short- or long-term), temporal extent (duration and frequency), and reversibility in consequence evaluation of the risk. Within the receiving environment, the RAF notes that in consequence evaluation, "the potential existence of vulnerable individuals, populations, species, communities or ecosystems is also considered".[45]

TABLE 3.3: Australian consequence assessment scale for the health of people and the environment. [47]

Consequences	Consequence assessment definitions relation to the health of people and the environment
Marginal	Minimal adverse health effects. Minimal or no damage to the environment or disruption to biological communities.
Minor	Adverse health effects that are reversible. Damage to the environment or disruption to biological communities that is reversible and limited in time and space or numbers affected.
Intermediate	Adverse health effects that are irreversible. Damage to the environment or disruption to biological communities that is widespread but reversible or of limited severity.
Major	Adverse health effects that are severe, widespread and irreversible Extensive damage to the environment or extensive biological and physical disruption of whole ecosystems, communities or an entire species that persists over time or is not readily reversible.

D. ESTIMATION OF THE OVERALL RISK POSED BY THE LMO BASED ON THE EVALUATION OF THE LIKELIHOOD AND CONSEQUENCES OF THE IDENTIFIED ADVERSE EFFECT BEING REALIZED

A qualitative process is used in Australia to estimate overall risk.[48] The Act only addresses those risks that affect the health and safety of humans or the environment (Section 3), and once those risks are identified, they are characterized by the seriousness of the harm (consequence) and likelihood. A risk matrix that uses the likelihood and consequence values (determined by the Regulator) helps determine the overall risk value (Table 3.4a and b). Other considerations are made in assessing overall risk. For example, consideration is made for whether the risk requires control or mitigation measures. Another consideration regards the uncertainty within the likelihood and/or consequence estimates. One last consideration is for the quality and sources of evidence provided for the likelihood/consequence estimates.[49]

> A qualitative process is used in Australia to estimate overall risk.

Each adverse effect identified in the GM cotton RARMP was assigned a risk value. If no risk was identified, the risk was considered insubstantial (not realistic) and was not considered any further. For each adverse effect, all the vital information used to make that risk estimate decision was provided and a summary rationale paragraph provided to validate the decision in the RARMP.

46 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 3 Table 3.1 p25.
47 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 4 Table 4.3 p42.
48 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 4 Table 4.4 p45.
49 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 4 p42.

TABLE 3.4A: Australia's scale for the level of LMO risk.[50]

Risk estimate	Risk estimate definitions
Negligible	Risk is insubstantial and there is no present need to invoke actions for mitigation
Low	Risk is minimal, but may invoke actions for mitigation beyond normal practices
Moderate	Risk is of marked concern that will necessitate actions for mitigation that need to be demonstrated as effective
High	Risk is unacceptable unless actions for mitigation are highly feasible and effective.

TABLE 3.4B: Australian risk matrix to estimate the level of risk from a combination of outcomes of likelihood and consequence assessments.[50]

		Risk Estimate			
Likelihood Assessment	**Highly Likely**	Low	Moderate	High	High
	Likely	Low	Low	Moderate	High
	Unlikely	Negligible	Low	Moderate	Moderate
	Highly Unlikely	Negligible	Negligible	Low	Moderate
		Marginal	**Minor**	**Intermediate**	**Major**
		Consequence Assessment			

50 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 4 Table 4.4 and Figure 4.3 p45.

E. RECOMMENDATION AS TO WHETHER THE RISKS ARE MANAGEABLE, INCLUDING, WHERE NECESSARY, IDENTIFICATION OF STRATEGIES TO MANAGE THESE RISKS

Risk management is an important component of Australia's LMO regulatory process. Without a risk management plan, the Regulator cannot make a licensing decision on a particular LMO (thus the reason for the name risk assessment and risk management plan (RARMP) rather than simply risk assessment). Within Australia's RAF, all risks rated higher than "negligible" on the risk estimate scale are considered for risk management. The "Risk Evaluation" process outlined in the RAF determines qualitatively which risks need management. Consideration is made to the safety of humans and the environment. Factors used in the risk evaluation include risk criteria, estimated risk level, uncertainty in the risk estimate, and interactions between potential risks.[51] The causal pathway(s) for a particular risk is also considered because it may identify ideal points for management.[22]

> In addressing risk management, Australia demonstrates a preference for preventative over curative management strategies

In addressing risk management, Australia demonstrates a preference for preventative over curative management strategies. In creating a management plan, current or existing management practices as well as the scale (spatial and temporal) of the release are considered.

Scale is particularly important in DIR (release into the environment) risk mitigation (e.g. isolation distances, monitoring zones). Contingency plans are required for all LMO releases into the environment and the details are provided in the RARMPs.[52] The RAF also addresses several concerns raised regarding risk mitigation, and these concerns include whether a particular management option creates new risks,[53] management options actually mitigate the risks, management options are feasible, and management options can be monitored.[54] Monitoring in risk management is not a requirement but may be stipulated in the license (particularly for an unrestricted release into the environment) so that the Regulator can stay informed or collect post-release information on the LMO.[55]

Resistance management is often an important component of management plans for LMO crops. An important point to make about Australia's risk assessment process is that resistance management is not considered by the Regulator. In Australia if resistance management is required, it is the responsibility of other agencies, depending on the type of LMO. In the case study on GM-cotton, the Australian Pesticides and Veterinary Medicines Authority (which regulates pesticides in Australia) "…can impose conditions on the use of agricultural chemical products including the implementation of an insect resistance or herbicide resistance management plans…", and therefore, in the final RARMP the Regulator does not impose license conditions for resistance monitoring or management.[56]

51 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 5 p52.

52 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 5 p55.

53 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 5 p50.

54 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 5 p54.

55 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 5 p58.

56 Risk Assessment and Risk Management Plan for DIR 074/2007. 2007. p78 .

F. WHERE THERE IS UNCERTAINTY REGARDING THE LEVEL OF RISK, IT MAY BE ADDRESSED BY REQUESTING FURTHER INFORMATION ON THE SPECIFIC ISSUES OF CONCERN OR BY IMPLEMENTING APPROPRIATE RISK MANAGEMENT STRATEGIES AND/OR MONITORING THE LMO IN THE RECEIVING ENVIRONMENT

Dealing with uncertainty in risk assessment is an integral part of Australia's LMO risk assessment process. The Australian RAF directly addresses uncertainty in the risk estimate, and Australia even goes so far as to describe the types of uncertainty (variability, incertitude, descriptive, and cognitive) that may arise in risk assessment and provides examples of each.[57] An example of how Australia may deal with uncertainty in risk is in the following: "Risk treatment measures would be devised to take account of such uncertainty. For instance, the size of a reproductive isolation distance for a GM plant would be based on the overall distribution of pollen, and not just on the median distance pollen might travel".[54] The Regulator can also request more information if the information or data submitted for an environmental release proves to be insufficient.[58]

V. Discussion

Australia's risk assessment process of LMOs is a very thorough process with rationale, methodology, and examples laid out in detail for nearly every step. Although Australia takes a qualitative approach to estimating risks from LMOs, each step of the risk analysis process is laid out in detail in the RAF and RARMPs to make the decision-making process transparent to applicants and stakeholders alike. The RAF even provides justification for the use of a qualitative rather than quantitative risk assessment.[59] While Australia's RAF does not differentiate between different groups of LMOs (such as plants vs. microbials), these LMO groups are separately covered in the LMO license application. The risk estimation matrix and consideration for many types of uncertainty are other significant aspects of Australia's risk assessment framework that are explicitly described within the guideline documents.

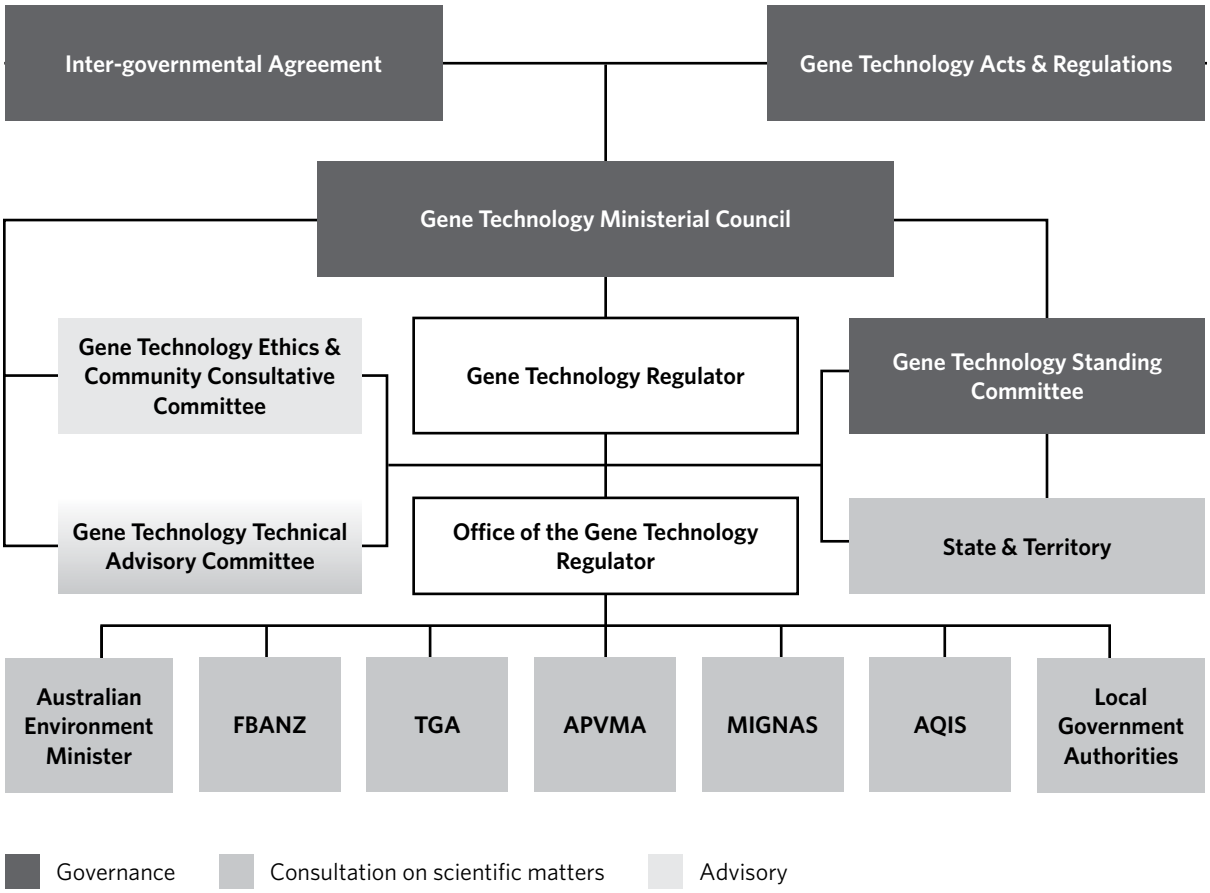
> Although Australia takes a qualitative approach to estimating risks from LMOs, each step of the risk analysis process is laid out in detail in the RAF and RARMPs to make the decision-making process transparent to applicants and stakeholders alike.

Australia's LMO RAF identifies several elements of the risk analysis process not explicitly addressed in Annex III. The first is risk communication. Within Australia's LMO regulatory framework, this is a vital part of the risk analysis that incorporates stakeholders and experts into the process and increases transparency of the decision-making process. Another unique point is that the Regulator can seek advice on ethical and social issues raised by gene technology.[60] Finally, Australia also requires information on the stability of the genetic modification.

57 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 2 p15.
58 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 4 p42.
59 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 4 p37.
60 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Executive Summary p vii.

APPENDIX

APPENDIX 3.A: Australian gene technology regulatory system.[61]



1 Amendements to the legislation replace the Gene Technology Ethics Committee and Gen Technology Community Consultative committee with GTECCC from 1 January 2008.

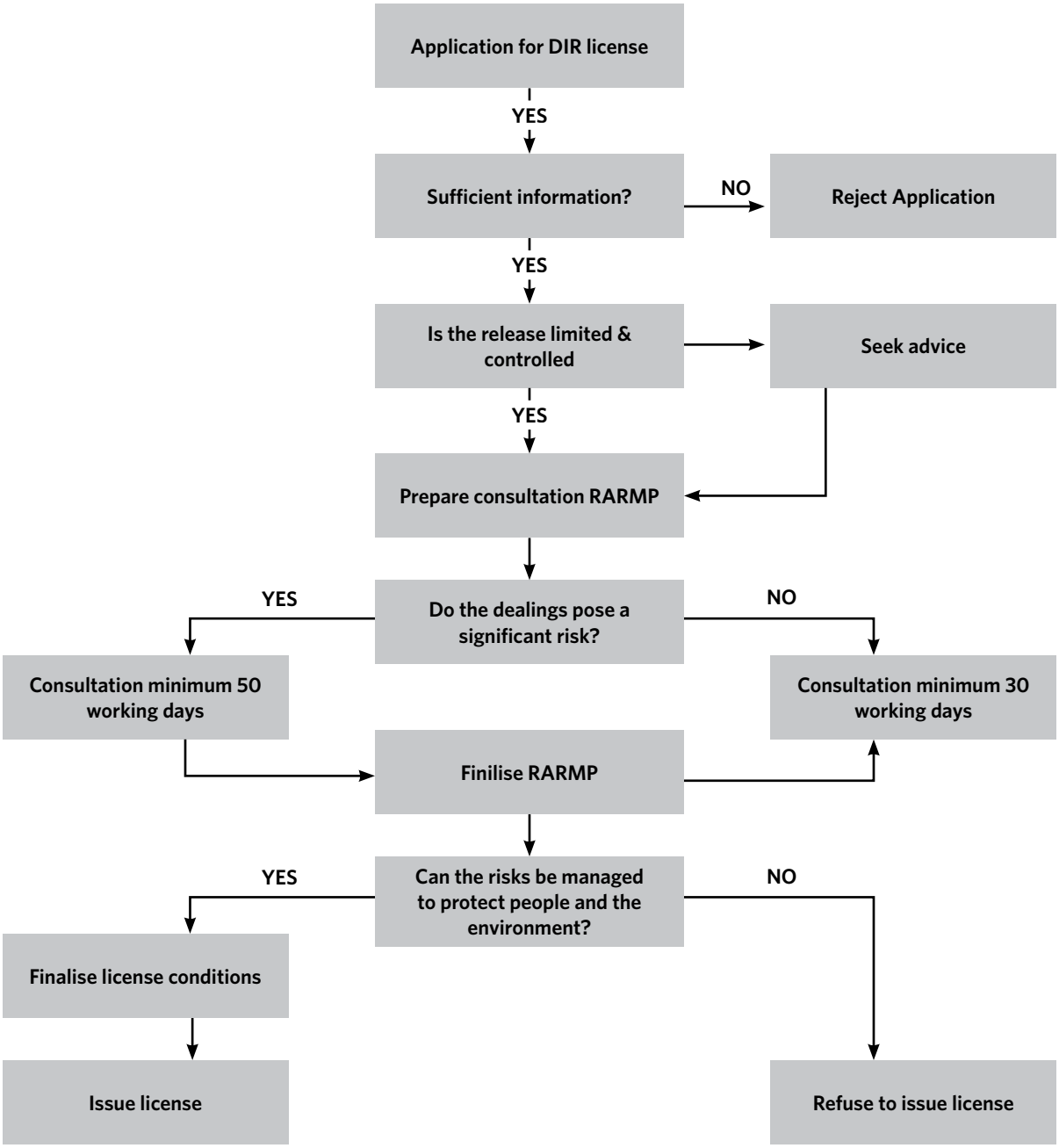
61 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Appendix A p81.

APPENDIX 3.B: Australian criteria for the nature and types of LMO consequences and how they might be measured.[62]

Generic criteria for consequences	Examples of specific consequence criteria developed during license application consideration (assessment endpoints)	Examples of measurable properties for specific consequence criteria (measurement endpoints)
Negative effects on species diversity of genetic diversity within a species	• Increased production of endogenous glycoalkaloids • Production of an allergen • Production of an immunosuppressant compound	• Biochemical, physiological, physical or developmental abnormalities • Frequency of infection • Growth rate • Mortality
Negative effects on valued organisms (including protected species and secondary impacts)	• Reduced population size of valued lepidopteran • Production of a chemical toxic to protected marsupials	• Population morbidity • Genotype frequency • Presence and abundance • Yield/production • Biochemical, physiological, physical or developmental abnormalities
Negative effects on species diversity or genetic diversity within a species	• Formation of monoculture in natural environments	• Presence and abundance of species • Genotype frequency • Yield/production • Biochemical, physiological, physical or developmental abnormalities
Creating a new or more vigorous weed, pest, or pathogen	• Reduced establishment of other organisms • Increased host range of pathogen	• Occurrence in new environment, new population or species of host • Size/frequency of attack or invasion • Intensity of disease symptoms • Yield/production • Species richness of the community where the weed, pest or pathogen occurs
Disruptive effects on biotic communities and ecosystems	• Production of an allelopathic chemical	• Species richness • Diversity indices • Extent and area • Production • Indices of food web structure • Carbon, nitrogen and phosphorous fluxes
Degradation of the abiotic environment	• Reduced soil water table level • Hotter, more frequent fire regimes	• Frequency and intensity of floods • Low flows and fire • Pollutant concentrations • Physical damage • Soil structure

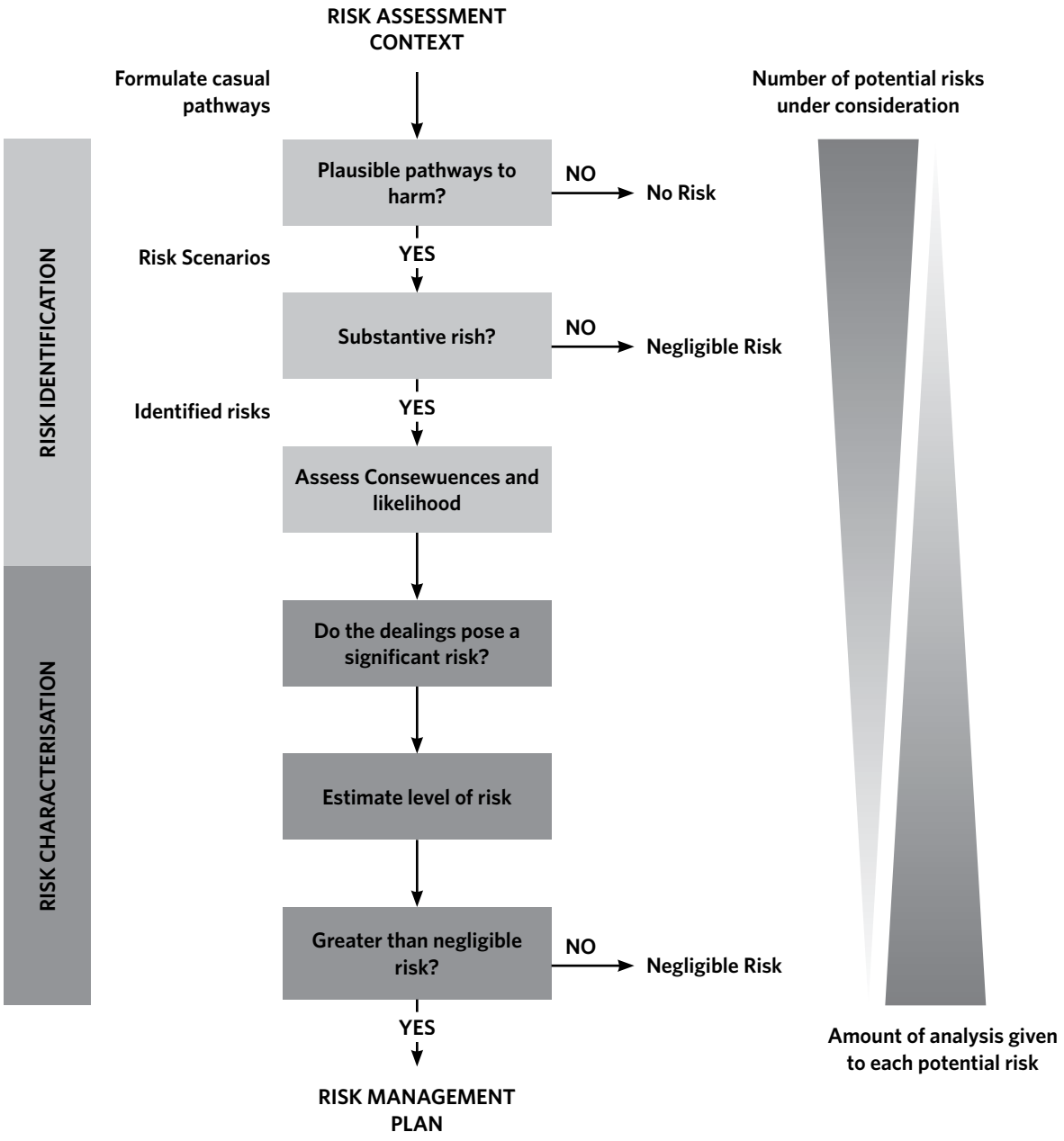
62 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 3 p25.

APPENDIX 3.C: Dealings of intentional release (DIR) assessment process in the Australian LMO Risk Assessment Framework.[63]



63 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Appendix A p83.

APPENDIX 3.D: Summary of Australia's methodology for preparing a risk assessment for LMO release into the environment.[64]



64 Australia Risk Analysis Framework. 2009. Office of the Gene Technology Regulator. Chapter 4 p47.

Chapter 4. Brazil: Elements of risk assessment for LMOs

I. Abstract

The National Biosafety Technical Commission (CTNBio), in cooperation with the National Biosafety Council (CNBS) is the government body responsible for all risk assessment of living modified organisms (LMOs) and their derivatives in Brazil. Risk assessments are triggered by the use of recombinant DNA genetic engineering techniques and are categorized by the receiving organism. Companies or institutions seeking approval to conduct research on or commercialize a LMO must submit an application to the CTNBio. Information within the application is then used by a panel of experts convened by CTNBio to evaluate potential risks and to make recommendations about the approval of the LMO. The CTNBio may also request or gather additional information in the event that uncertainty within the supplied data is encountered. Decisions, referred to as "technical opinions" made by the CTNBio are subject to approval by the CNBS, which may approve or reverse the decision. Completed decisions are published on the Commission's website along with documented information used to make each decision. Additionally, the Federal Gazette publishes risk decisions and abstracts of LMOs for which approval is sought. Brazil's published risk assessment frameworks closely follow the language of Annex III of the Cartagena protocol. LMOs are compared to their un-modified counterparts and potential additional risks posed by these LMOs are identified and evaluated.

Although the frameworks for risk assessment clearly indicate compliance with the Cartagena Protocol, details of how the goals of the protocol will be met are limited. While this allows for great flexibility, it also increases the responsibility of the members of CTNBio. In keeping with this, members are required to "carry out their duties in strict compliance with ethical-professional principles.[1]

II. Overview of legislative & regulatory framework

Assessing the possible risks to human health and the environment of Living Modified Organisms (LMOs) in Brazil is the responsibility of the National Biosafety Technical Commission (CTNBio)[2], a part of the Ministry of Science and Technology.[3] Its risk assessment procedures are outlined in the original Decree 5,591 and elaborated in subsequent supporting documents,- especially Normative Resolutions 2, 5 and 6. Institutions or companies seeking the release of a GMO must submit an application to CTNBio for approval. The CTNBio conducts a risk assessment and its members then vote on whether or not to approve the release. In addition to regulating LMOs for release into the environment, CTNBio regulates all other research and commercial use of LMOs and their derivatives including manipulation, transportation, importation, exportation, storage, release and disposal[2].

1 Decree 5591. Brazil. November 22, 2005. Article 14.
2 Decree 5591. Brazil. November 22, 2005. Article 5.
3 Decree 5591. Brazil. November 22, 2005. Article 4.

Another important governmental aspect in Brazil's risk assessment framework is the National Biosafety Council (CNBS).[3] This body is composed of the ministers for each of the primary departments of government[4] and performs a range of tasks, including establishing guidelines and principles for how other federal agencies carry out their respective biosafety mandates[5] analyzing important matters pertaining to LMOs on a national scale,[6] and serving as a board of appeals for rejected applications for LMO testing[7]. Conversely, if the CNBS determines that a LMO approved by the CTNBio represents too great a risk, it may reverse the decision of the CTNbio[5].

> In addition to regulating LMOs for release into the environment, CTNBio regulates all other research and commercial use of LMOs and their derivatives including manipulation, transportation, importation, exportation, storage, release and disposal[2].

The legal and decision documents relating to the regulation of LMOs are available through the Biosafety Clearing House[8] and on the CTNBio[9] website in both English and Portuguese. We were also able to obtain technical opinions for LMOs for release into the environment, but we could not ascertain whether these were the full risk assessments used by the CTNBio and CNBS to make final decisions about approval for LMOs. Additionally, it must be recognized that even the English documents may have been translated, albeit officially, from their original language of drafting. It is therefore possible that our interpretations of certain passages differ from that in the original Portuguese documents.

In the analysis that follows we will conform to the Cartagena Protocol on biological biodiversity's convention of using the term "LMOs" to refer to the modified organisms assessed in these frameworks. However, Brazil's legal and decision documents refer to these organisms as genetically modified organisms or "GMOs" and any quoted language will reflect this. In the Brazilian documents, GMO and LMO are largely equivalent because the term "organism" in GMO is defined as "every biological entity capable of reproduction or of transferring genetic material, including viruses and other classes that may come to be known."[10] This definition excludes the non-living products of GMOs, which are referred to as "GMO derivatives."[10]

This description is based on the regulatory framework documents available through the CTNBio website as well as technical opinions on NK603 Maize[11] and Widestrike Cotton[12], which summarize the risk assessments conducted and any dissenting opinions. Additional information was gathered from a document titled "Communication 1," which provides guidelines for biosafety practices used in the production of genetically modified maize[13] and "Communication 2," which provides guidelines for biosafety practices related to the production of modified eucalyptus.[14]

III. General principles

A. SCIENTIFICALLY SOUND

Brazil's frameworks do not reference specific guidelines from international organizations,[15] although it is stated that monitoring of LMOs "shall be guided by internationally recognized scientific methodology and experimental designs adequate to the inferences made."[16] Furthermore, applications submitted for commercial release are required to be "duly documented by scientific reports"[17] on the results of studies.

4 Decree 5591. Brazil. November 22, 2005. Article 49.
5 Decree 5591. Brazil. November 22, 2005. Article 48.
6 Decree 5591. Brazil. November 22, 2005. Article 50.
7 Decree 5591. Brazil. November 22, 2005. Article 52.
8 Convention on Biological Diversity Biosafety Clearing-House. Website. Accessed October, 2009. http://bch.cbd.int/.
9 National Biosafety Technical Commission. Website. Accessed October, 2009. http://www.ctnbio.gov.br/.
10 Decree 5591. Brazil. November 22, 2005. Article 3.
11 Technical Opinion no. 1596/2008. Commercial release of genetically modified corn, Roundup Ready 2 Corn (NK 603). Brazil. September, 2008.
12 Technical Opinion no. 1757/2009. Commercial release of genetically modified cotton, WideStrike Cotton. Brazil. March, 2009.
13 Communication no. 1. Brazil. August, 2006. Accessed online. October, 2009 http://www.ctnbio.gov.br/index.php/content/view/12844.html.
14 Communication no. 2. Brazil. July, 2007. Accessed online. October, 2009 http://www.ctnbio.gov.br/index.php/content/view/12844.html.
15 National report on the implementation of the Cartagena Protocol, Article 23 (49).
16 Normative Resolution 5. Brazil. March, 2008. Annex I (5).
17 Normative Resolution 5. Brazil. March, 2008. Article 20.

Experimental evaluation of risks as well as expert opinions are used.[18] Additionally, Brazil takes into account the results of LMO monitoring when the LMO under consideration has already been released in another country.[19] Although Brazil emphasizes the importance of scientific risk assessments, social concerns are taken into consideration- for example, when planning field tests of LMOs, a "description of neighboring cultures and, whenever possible, include a sketch of their location[20]" must be provided.

B. TRANSPARENCY

Members of CTNBio are appointed by the Minister for Science and Technology according to a set of legally mandated criteria[21] and must disclose their potential conflicts of interest prior to their involvement on the panel.[22] Meeting minutes are recorded and technical opinions are accompanied by a written record of dissenting votes and the rationale behind them.[23] The government and public have access to these technical opinions in the "Federal Gazette", which publishes each member's opinion and justification.[24] The Federal Gazette also publishes abstracts of applications for LMO releases prior to evaluation.[2] Additionally, there are procedures in place for members of government agencies or public groups to seek permission from CTNBio to attend hearings regarding LMO risk assessment.[25] Institutions that use genetic engineering techniques must establish an Institutional Biosafety Committee (CIBio).[26] These bodies are responsible for documenting all research activities, conducting monitoring of ongoing LMO projects, and "keeping workers and members of the community informed about all health and safety related issues."[27]

Furthermore, Brazil's framework documents specifically outline the biological information that applicants must provide[28,29,30,31] as well as the ecological considerations that should be made before releasing a LMO into the environment.[32]

C. LACK OF SCIENTIFIC KNOWLEDGE OR CONSENSUS DOES NOT INDICATE LEVEL OR ABSENCE OF RISK

Legislation describes a primary function of the CTNBio as "the observance of the precautionary principle for environmental protection."[33] For LMOs that have already been released, monitoring "shall be conducted under strict observance of the principles of precaution, transparency and scientific independence."[34] We were not able to find an explicit statement of how this precaution should be applied.

> For LMOs that have already been released, monitoring "shall be conducted under strict observance of the principles of precaution, transparency and scientific independence."[34]

D. RISK CONSIDERED IN THE CONTEXT OF RISK POSED BY NON-MODIFIED RECIPIENTS OR PARENTAL ORGANISMS

A risk assessor from the CTNBio writes "in the risk assessment one pursues the qualitative and quantitative characterization of potential adverse effects based on the concept of substantial equivalence.[11] Brazil's risk assessment framework stipulates that characteristics of interest of new LMOs be considered "in comparison with the GMO kindred organism in a conventional production system."[31] This type of comparison is evident in a technical opinion on genetically modified cotton, in which ecological risks are compared to the risks posed by conventional cotton, taking into consideration both the characteristics of the cotton plants themselves as well as agricultural practices used with each crop.[12]

18 Decree 5591. Brazil. November 22, 2005. Article 24.
19 Normative Resolution 5. Brazil. March, 2008Annex IV (A12).
20 Normative Resolution 6. Brazil. November 6, 2008. Annex IV (7).
21 Decree 5591. Brazil. November 22, 2005. Article 16.
22 Decree 5591. Brazil. November 22, 2005. Article 13.
23 Decree 5591. Brazil. November 22, 2005. Article 32.
24 Decree 5591. Brazil. November 22, 2005. Article 24
25 Decree 5591. Brazil. November 22, 2005. Article 43.
26 Decree 5591. Brazil. November 22, 2005, Article 61.
27 Decree 5591. Brazil. November 22, 2005, Article 62.
28 Normative Resolution 5. Brazil. March, 2008. Annex I.
29 Normative Resolution 5. Brazil. March, 2008. Annex II.
30 Normative Resolution 5. Brazil. March, 2008. Annex III.
31 Normative Resolution 5. Brazil. March, 2008 Annex IV (A).
32 Normative Resolution 2. Brazil. July, 2007. Article 7.
33 Decree 5591. Brazil. November 22, 2005. Article 1.
34 Normative Resolution 5. Brazil. March, 2008. Annex I (4).

Further demonstrating the comparison of risks between modified and unmodified varieties, LMOs that are deemed safe are placed in the same risk class as the recipient organism[35] unless the inserted DNA might cause the organism to be "more able to survive on the environment than the native organisms.[35]

E. CASE-BY-CASE BASIS

Although we did not find a formal definition of "case" within Brazil's risk assessment frameworks, part of the mandate of CTNBio is to conduct "risk assessment analysis, on a case-by-case basis." In general each new combination of donor gene/recipient species is subjected to a new risk assessment, although a simplified risk assessment is possible in the case of new transformation events that combine "the same genetic construct used in a GMO of a same species."[36] Stacked events resulting from conventional breeding of multiple LMOs may also be subject to a new risk assessment at the discretion of CTNBio.[37] Stacked events may also be subject to "amplified areas of isolation and monitoring…defined case per case…according to the genes, to the environment and to the experimental practices proposed."[14] The steps required for application for commercial release also suggest that ecological considerations are based on how the LMO might interact with organisms in its specific intended receiving.

In general each new combination of donor gene/recipient species is subjected to a new risk assessment, although a simplified risk assessment is possible in the case of new transformation events that combine "the same genetic construct used in a GMO of a same species."

35 Normative Resolution 2. Brazil. July, 2007. Article 8.
36 Normative Resolution 5. Brazil. March, 2008. Article 3.
37 Normative Resolution 5. Brazil. March, 2008. Article 4.

IV. Methodology

A. IDENTIFICATION OF NOVEL GENOTYPIC AND PHENOTYPIC CHARACTERISTICS ASSOCIATED WITH THE LMO, THAT MAY HAVE ADVERSE EFFECTS ON BIOLOGICAL DIVERSITY IN THE LIKELY POTENTIAL RECEIVING ENVIRONMENT, ALSO TAKING INTO ACCOUNT RISKS TO HUMAN HEALTH

1. Recipient/Parental Organism

Brazil's risk assessment framework documents require those applying to release a LMO to report the taxonomic classification of the recipient organism to the most detailed resolution possible (e.g. strain or cultivar);[38] the history of safe use of the parental organism as it relates to human, animal, and environmental safety;[31] the areas within Brazil where the organism is found[31], and others.[31] A technical opinion published by CTNBio of the risk of development of insect resistance to Bt cotton considered additional parameters such as germination rate, plant vigor, nutrient composition, and presence of aflatoxins.[39]

2. Donor Organism

We were not able to locate required information for donor organisms within the legal documents we reviewed. However, technical opinions on genetically modified cotton and genetically modified maize specified the taxonomic classification of the donor organism down to strain.[11,12] Information regarding the source and biological characteristics of the donor organism was not required by the risk assessment framework documents we were able to review or within the technical opinions reviewed. Instead, these frameworks focus on the characteristics of the inserted genes and how these interact with the recipient.

3. LMO Characteristics

Brazil's legal framework for LMO risk assessment require that the identity and host range of the

38 Normative Resolution 6. Brazil. November 6, 2008. Annex II.
39 Technical Opinion 513/2005. Commercial Release of Genetically Modified cotton, Bollgard Cotton (531). Brazil. March, 2005.

vector used to insert introduced genes be explicitly stated.[29,38] Additionally, the "genetic mapping used in transformation process" and the function of the inserted DNA must be described in detail.[29,38] For example, in a risk assessment for a stacked variety of cotton (insecticidal properties and resistance to herbicide), the mechanism by which Bt endotoxins kill Lepidopterans was explained in detail.[12] In addition to intended actions of inserted transgenes, applicants must describe the potential existence of pleiotropic or epistatic effects of inserted genes,"[40] as well as unintended consequences such as "genetic changes introduced in the GMO that may affect its ability to reproduce, survive, disseminate or the transfer of inserted genes to other organisms."[41] Risk assessors also consider the other ways in which the LMO is phenotypically different from its non-modified counterpart, including but not limited to its effects on soil composition,[42] its impact on associated organisms,[43] increased resistance to chemical agents,[44] and its rate of degradation.[45]

Applications for permission to release LMOs into the environment are required to provide data on the location of release and its climatic,[47] geographic,[46,47] ecological,[38] and soil[47] characteristics. Additionally, human cultures in the vicinity of the release must be described.[20]

4. Receiving Environment

Applications for permission to release LMOs into the environment are required to provide data on the location of release and its climatic,[48] geographic,[46,47] ecological,[38] and soil[47] characteristics. Additionally, human cultures in the vicinity of the release must be described.[20] Assessment of the biological diversity of the release site is implied, but not explicitly stated. Applicants must describe "whether the planned release is likely to affect the characteristics or abundance of other species, and how this will be monitored,"[46] and consider potential non-target effects on "relevant indicator organisms[48]" and species of concern.[12] The presence of sexually compatible varieties[38] and pollinators[48] must also be evaluated.

B. EVALUATION OF THE LIKELIHOOD OF THESE ADVERSE EFFECTS BEING REALIZED, TAKING INTO ACCOUNT THE LEVEL AND KIND OF EXPOSURE OF THE LIKELY POTENTIAL RECEIVING ENVIRONMENT TO THE LIVING MODIFIED ORGANISM

1. Intended use of the LMO compared to recipient or parental organism

Brazil's ERA framework requires the applicant to report the intended use of the LMO because different uses (e.g. agriculture, biological control, bioremediation, etc) require different kinds of data for consideration[30,31] in the risk assessment process. A technical opinion on NK603 glyphosate-tolerant maize not only specified that the maize would be for commercial, agricultural use, but also reported on herbicide use in conventional maize and compared this to potential herbicide use when using NK603 maize.[11]

2. Characteristics of relevant potential receiving environment

See "Receiving Environment" in the Methodology section, above.

3. How incidental exposure to the environment could occur

We were unable to locate an explicit discussion of the ways in which the environment might be exposed to LMOs or their derivatives. However language used in the framework documents suggests that the primary pathways for exposure that are considered in risk assessments for LMO plants are "horizontal transference [of genes] to soil microbiota,"[49] escape of pollen by means of insect vectors[50] and wind,[42] and dispersal away from propagation areas of repro-

40 Normative Resolution 5. Brazil. March, 2008. Annex II (13).
41 Normative Resolution 5. Brazil. March, 2008. Annex II (16).
42 Normative Resolution 5. Brazil. March, 2008Annex IV (A9).
43 Normative Resolution 5. Brazil. March, 2008Annex IV (A8).
44 Normative Resolution 5. Brazil. March, 2008Annex IV (A11).
45 Normative Resolution 5. Brazil. March, 2008Annex IV (A10).
46 Normative Resolution 6. Brazil. November 6, 2008. Annex III.
47 Normative Resolution 6. Brazil. November 6, 2008. Annex IV.
48 Normative Resolution 5. Brazil. March, 2008. Annex IV (A3).
49 Normative Resolution 5. Brazil. March, 2008. Annex IV (A7).
50 Normative Resolution 2. Brazil. July, 2007. Article 18 (III).

duction structures (e.g. seed pods or seeds) in soil and water.[31]

Although quantitative estimates of exposure were not required within the risk assessment frameworks we reviewed, they are sometimes used. For example, a risk assessment for genetically modified, glyphosate tolerant maize used probabilities that maize pollen might travel 1 meter, 200 meters and 500 meters by wind from one study and then used an estimate of the time of viability from another to evaluate the potential for genetically modified maize to cross with un-modified maize. An attached dissenting opinion stated that a weakness in the risk assessment was that the potential impact of insect pollination was not considered. Within the same risk assessment human exposure to maize proteins was estimated using corn consumption per capita in the United States.[11]

Although quantitative estimates of exposure were not required within the risk assessment frameworks we reviewed, they are sometimes used.

4. Conclusion of evaluation of likelihood of exposure

Final decisions regarding likelihood of exposure are rendered by a representative of CTNBio assigned to each case.[51] We were not able to find any guidelines describing how a final judgment of "likelihood of exposure" should be made, but the "risk of dissemination" is taken into account when assigning a GMO to a risk class.[27]

C. EVALUATION OF THE CONSEQUENCES SHOULD THESE ADVERSE EFFECTS BE REALIZED

Brazil's ERA framework requires that the assessment process "identify and assess potential adverse effects of a GMO and its derivatives to human and animal health, environment and plants."[52] During this process, risk assessors may consider the experiences of other countries in dealing with similar LMOs, including whether or not the LMOs were approved, and monitoring and other post-release studies that were conducted.[53] From an ecological perspective, the framework requires that the "possible effects in relevant indicator organisms (symbionts, predators, pollinators, GMO parasites or competitors) where cultivation is intended"[48] must be considered.

In a technical opinion on NK603 glyphosate tolerant maize, the consequences of exposure were evaluated using a literature review of published studies on the impacts of the transgenes and transgene products conferring glyphosate resistance. Acute toxicity data on mice (one high dose) as well as a longer, 8 month study on salmon, and a favorable opinion by the European Food Safety Authority on the maize were used to conclude that toxicity and allergenicity were not likely in humans or other animals.[11] Although the European Union study dealt specifically with NK603 maize, the other studies required extrapolations from proteins generated from *E. coli* to those generated by LM plants or from proteins generated from glyphosate resistant soybean to those from corn. These studies were not conducted in Brazil, however, the technical opinion noted that the protein conferring glyphosate resistance commonly occurs in soils in Brazil and is not known to cause problems.[11]

D. ESTIMATION OF THE OVERALL RISK POSED BY THE LMO BASED ON THE EVALUATION OF THE LIKELIHOOD AND CONSEQUENCES OF THE IDENTIFIED ADVERSE EFFECT BEING REALIZED

We were unable to find a graphical matrix, decision tree, or other formal document qualifying risk estimation in Brazil's ERA framework, but Brazil's initial draft framework document assigned LMOs to either risk class I (low risk) or II (higher risk) based on a review of information provided to the assessor pertaining to the LMO's pathogenicity; the form, function, and stability of genetic inserts; and history of safe use elsewhere.[54] In a subsequent supporting document, this classification system was expanded to four levels, assigning LMOs to a risk class based on criteria such as "the pathogenic potential of the donor and receptor organisms, the transferred nucleotide sequences, their expressions in the receptor organism, the resulting GMO, and its adverse effects to human and animal's health, to vegetables and to

51 Decree 5591. Brazil. November 22, 2005. Article 29.
52 Normative Resolution 5. Brazil. March, 2008. Article 19.
53 Normative Resolution 5. Brazil. March, 2008. Annex IV (A12).
54 Decree 5591. Brazil. November 22, 2005. Annex.

the environment," among others.[32] These criteria are used to determine a LMO's "individual risk" and "risk to the community."[32] We were not able to find a clear definition of these terms, although the descriptions of the risk categories themselves referred to "aggravation to human and animal health" and "risk of dissemination," with varying levels of both contributing to the overall risk categorization.[35]

Estimation of overall risk, as in all steps of the risk assessment process, is in comparison to the overall risk of the non-modified counterpart of a LMO. For example, although Brazil's risk assessors determined that "vertical genetic flow [sic] to local varieties of open pollination is possible" for a modified variety of maize, it was noted that the new strain "carries the same risk caused by the commercial genotypes available on the market," so it did not pose a new risk. Additionally, the consequences of gene flow were considered minimal since there would be no selective advantage to glyphosate resistance in plants like maize that require so much technical assistance to survive.[11]

E. RECOMMENDATION AS TO WHETHER THE RISKS ARE MANAGEABLE, INCLUDING, WHERE NECESSARY, IDENTIFICATION OF STRATEGIES TO MANAGE THESE RISKS

A final judgment regarding whether or not the risks posed by a given LMO are acceptable and warrant approval for testing or release is made by the assembled CTNBio committee, which votes on the opinion presented by the committee member assigned to conduct the assessment. In the case of small-scale experiments only a simple majority of members must assent, while for commercial releases, approval by a 2/3 majority is required.[55] In all cases, decisions rendered by the CTNBio are reviewed by the CNBS, which may approve or reject the CTNBio's findings. If an application is not approved by the CTNBio, the applicant may file an appeal with the CNBS, with the decision of that body considered final.[7]

Research on LMOs must be done under biosafety conditions appropriate to the risk classification of the LMO,[56] with each progressively higher risk class requiring increasingly secure biosafety measures. Brazil's framework documents provide explicit biosafety guidelines for LMO research and testing done in isolated settings[57] (e.g. greenhouses and laboratories), but we were unable to find similar regulations for field-testing and cultivation. However, in a description of risk management guidelines for cultivating modified maize, experimental plots were required to be surrounded by ten rows of non-modified corn (spatial isolation). The document further describes how the modified maize must be planted such that the difference in flowering times between the modified and unmodified maize is at least 40 days (temporal isolation).[13] Furthermore, in the application for environmental release, applicants must include "biosafety procedures, isolation conditions, agronomic practices, and procedures for discarding and storage" that will be used.[47]

F. WHERE THERE IS UNCERTAINTY REGARDING THE LEVEL OF RISK, IT MAY BE ADDRESSED BY REQUESTING FURTHER INFORMATION ON THE SPECIFIC ISSUES OF CONCERN OR BY IMPLEMENTING APPROPRIATE RISK MANAGEMENT STRATEGIES AND/OR MONITORING THE LMO IN THE RECEIVING ENVIRONMENT

Brazil's risk assessment framework permits CTNBio to request additional information or documents if any doubt exists regarding any aspect of the GMO application.[58] For outdoor experiments or commercial releases to the environment, Brazil's framework documents also require the applicant to develop and present case-specific post-release monitoring plans.[59] Furthermore, the framework requires the integration of a genetic marker into a LMO that could be used to differentiate it from morphologically similar conspecifics.[32] If monitoring reveals problems, CTNBio decisions may be reversed. The group is tasked with "reassessing its technical decisions on the grounds of new facts or scientific knowledge that may be relevant to the biosafety of the GMO or derivative, upon the request of its members or appeal by the registration and oversight bodies and agencies.[2]

55 Decree 5591. Brazil. November 22, 2005. Article 19.

56 Normative Resolution 2. Brazil. July, 2007. Article 9.
57 Normative Resolution 2. Brazil. July, 2007. Article 10.
58 Normative Resolution 8. Brazil. July, 2009. Article 12.
59 Normative Resolution 5. Brazil. March, 2008. Annex I (1).

Although the above policies make it possible for Brazil to continue to collect data and reduce some sources of uncertainty even after a decision is issued, these framework documents do not address how risk assessors should handle the inherent uncertainties that cannot be eliminated through further scientific study. A CTNBio risk assessor writes, "zero risk coupled with absolute safety is an inexistent combination in the biologic world" and then goes on to require post-release monitoring of an approved LMO.[11]

> For outdoor experiments or commercial releases to the environment, Brazil's framework documents also require the applicant to develop and present case-specific post-release monitoring plans.

V. Discussion

Brazil's risk assessment framework delegates LMO risk assessment to the National Biosafety Technical Commission (CTNBio), with the National Biosafety Council responsible for reviewing the decisions and considering appeals of CTNBio decisions brought by applicants. The framework documents do not detail how final risk decisions are reached, but they do outline the basic requirements for approval of LMOs for release into the environment. This has the advantage of allowing the commission the flexibility to handle risks on a case by case basis, streamlining the procedure for minimal risks and going into more depth in assessing relatively unknown risks. On the other hand, this flexibility does make Brazil's framework less transparent. Brazil handles this by requiring publications of risk decisions and by holding commission members responsible for their views by making their opinions accessible. Although Brazil does not seem to have established steps for post–release monitoring, applicants are required to submit a monitoring plan and send a yearly updates on monitoring results for 5 years after release of a GMO.[29]

Brazil's framework also does not clearly address how uncertainty should be handled or how the probability of adverse effects occurring will be estimated and provides explicit risk management measures only for contained (laboratory or greenhouse) research and testing; biosafety measures used for field trials are not described.

In our review of Brazil's risk assessment framework we found a statement that the "GMO risk class shall not be inferior to the risk class of the receptor organism,"[35] but we were not able to locate information about how a recipient organism is assigned to a risk class. It may be that the same information and approach applied to the classification of LMOs[35] is used to determine the risk class of the recipient organism, but this was not clear. This could be due to our inability to find an accompanying document, or to an error in translation.

> The framework documents do not detail how final risk decisions are reached, but they do outline the basic requirements for approval of LMOs for release into the environment.

Overall, Brazil's system of notification and documentation of LMO applications and decisions makes risk assessment in Brazil accessible to interested parties, and most guidelines seemed clear. However, further clarification is needed regarding the types of risks considered, biosafety measures that may be used in field trials, the types of data that may be used in risk assessment, and how those data are used to make final decisions of whether a LMO is approved for production or not.

Chapter 5. Canada: Elements of risk assessment for LMOs

I. Abstract

Environmental release of living modified plants (LMP) in Canada is regulated under the *Plant Protection Act*[1] and the *Seeds Act*[2], and these acts contain the most detailed directive for risk assessment of all types of organisms modified through modern biotechnology in Canada. The process and necessary information that are required as part of an application for unconfined release in Canada is outlined in *Directive 94-08: Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits*[3]. As defined by this directive, plants with novel traits (PNT) may or may not include LMPs. *Directive 94-08* describes the role that data, expert opinions, and scientific literature play in the development of the risk assessment. It also outlines "substantially equivalent" as the context for the consideration of risk posed by non-modified recipients or parental organisms. This context along with novel traits as the regulatory hook helps inform what is considered a new case in addition to being the trigger for a risk assessment.

Annex III of the Cartagena protocol[4] is used as an outline to delineate the major components of a risk assessment for plants with novel traits. These components describe the risk assessment process in Canada for PNTs and include the identification of novel genotypic and phenotypic characteristics with the potential to cause adverse effects, evaluation of the likelihood and the consequences of these adverse effects, estimation of the overall risk, identification of strategies to manage these risks, and how to address uncertainty.

II. Overview of legislative & regulatory framework

The risk assessment and regulation of living modified organisms (LMO) for environmental release in Canada are divided into four main categories based on the LMO being considered: plants with novel traits, animals, fish, and veterinary biologics (see Table 5.1). The regulating government agency for LMO risk assessment therefore varies depending upon which category the LMO falls into.

The Plant Biosafety Office (PBO) of the Canadian Food Inspection Agency regulates living modified plants (LMPs) for environmental release (see Appendix 5.G) under the *Plant Protection Act*[1] and the *Seeds Act.*[2] LMPs with novel traits have a risk assessment process that must be undertaken which

1 Plant Protection Act [1990, c. 22]. Canadian Food Inspection Agency. Website: http://laws.justice.gc.ca/en/P-14.8/index.html.

2 Seeds Act [R.S., 1985, c. S-8]. Canadian Food Inspection Agency. Website: http://laws.justice.gc.ca/en/S-8/index.html.

3 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml.

4 Convention on Biological Diversity. 2000. Cartagena Protocol on Biosafety to the Convention on Biological Diversity. Annex III. Website: http://www.cbd.int/doc/legal/cartagena-protocol-en.pdf.

is outlined in *Directive 94-08: Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits.*[3] This directive provides the most detailed description of the risk assessment process in Canada, and it informs most of this document. In addition to *Directive 94-08*, seven decision documents (see Appendix 5.A) provide a sample of the risk assessments conducted under the directive, however, we were unable to locate detailed risk assessments through the Bio-Safety Clearing House (BCH) or the Canadian Food Inspection Agency website to use as a case study example. A single decision document was reviewed for each crop type that had a decision document from approved LMOs for release into the environment. When a crop type had multiple decision documents, the LMO with the most novel trait(s) and the most current approval status was chosen for review. We were unable to locate any decision documents in which a LMO was not approved for release.

> The Plant Biosafety Office (PBO) of the Canadian Food Inspection Agency regulates living modified plants (LMPs) for environmental release

Living modified animals (LMA) produced through modern biotechnology for environmental release are regulated by Environment Canada and Health Canada under the *Canadian Environmental Protection Act 1999*[5] and the *New Substances Notification Regulations.*[6] Producers of LMAs must complete a risk assessment for potential impacts to the environment administered by Environment Canada.

Living modified fish produced through modern biotechnology for environmental release are subject to the same regulations as LMAs. In addition to administration by Environment Canada, risk assessments of living modified fish are also administered by the Department of Fisheries and Oceans. This department, according to *Fish Products Derived Through Modern Biotechnology: Roles and Responsibilities of the Government of Canada,*[7] is in the process of developing regulations under the *Fisheries Act*[8] for aquatic organisms derived through modern biotechnology.

Living modified veterinary biologics produced through modern biotechnology for environmental release are regulated under the *Health of Animals Act.*[9] Specific guidelines for living modified veterinary biologics are outlined in the *Veterinary Biologics Guideline 3.2E: Guideline for the Regulation of Veterinary Biologics produced by Biotechnology.*[10]

As part of the identification of plants subject to *Directive 94-08,* it is important to fully define the types of plants considered. The term "plant" as defined by the scope of *Directive 94-08* covers includes agricultural and horticultural crop plants and forest trees but specifically excludes aquatic plants. The PNT "may be developed through mutagenesis, somaclonal variation, intra-specific and inter-specific crosses, protoplast fusion, recombinant DNA technology, or other techniques."[11] The Canadian regulations directive defines a plant with novel traits as "a plant containing a trait not present in plants of the same species already existing as stable, cultivated populations in Canada, or is present at a level significantly outside the range of that trait in stable, cultivated populations of that plant species in Canada."[12] Determination of novelty is a product-based approach to identification and independent of the process used to create the novelty. Therefore, living modified plants (LMP) developed through modern biotechnology are subject to *Directive 94-08* only if they contain novel traits.

5 Canadian Environmental Protection Act [1999, c. 33]. Environment Canada. Website: http://laws.justice.gc.ca/en/C-15.31/FullText.html.

6 New Substances Notification Regulations (Organisms) [SOR/2005-248]. Environment Canada. Website: http://laws.justice.gc.ca/en/C-15.31/FullText.html.

7 Fish Products Derived Through Modern Biotechnology: Roles and Responsibilities of the Government of Canada. Canadian Food Inspection Agency. Website: http://www.inspection.gc.ca/english/sci/biotech/gen/fispoi_bioe.shtml.

8 Fisheries Act [F-14]. Department of Fisheries and Oceans.

9 Health of Animals Act [1990, c. 21]. Canadian Food Inspection Agency, Animal Health and Production Division - Veterinary Biologics Section. Website: http://laws.justice.gc.ca/en/H-3.3/FullText.html.

10 Veterinary Biologics Guideline 3.2E: Guideline for the Regulation of Veterinary Biologics produced by Biotechnology. Canadian Food Inspection Agency. Website; http://www.inspection.gc.ca/english/anima/vetbio/info/vb302e.shtml.

11 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Section 2.1.

12 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Section 1.

TABLE 5.1: Canadian government agencies regulating LMOs and associated legislation

Government Agency	Types of LMOs regulated	Legislation
Canadian Food Inspection Agency (CFIA) – Plant Biosafety Office (PBO)	Living modified plants (LMPs)	Plant Protection Act and Seed Act
Canadian Food Inspection Agency (CFIA) – Veterinary Biologics Section (VBS)	Living modified veterinary biologics (LMVB)	Health of Animals Act
Environment Canada and Health Canada	Living modified animals (LMAs), Living modified fish (LMFs)	Canadian Environmental Protection Act 1999, New Substances Notification Regulations
Department of Fisheries and Oceans (DFO).	Living modified fish (LMFs)	Fisheries Act

III. General principles

A. SCIENTIFICALLY SOUND

The Canadian documents describe four mains ways in which a risk assessment must be conducted to take into account scientific soundness. The first is through the use of "peer-reviewed scientific literature, as appropriate, to guide their safety assessments."[13] The second way is that information provided in a risk assessment should be on the level provided by the peer-reviewed scientific literature: "Applicants should clearly describe the test procedures followed in developing the test data, including test methods, reference products, quality control, quality assurances procedures, appropriate statistical analysis, together with bibliographic references, including numbered patents, where these are appropriate. The generation of field trial data should be produced using statistically valid experimental designs and protocols."[14] The third way to incorporate scientific soundness is to ensure that "the PBO may consult relevant scientific experts on specific issues with regards to the environmental safety of a PNT."[15] The fourth way is that information provided should not be exhaustive and "be updated as appropriate to reflect current scientific knowledge and acquired field experience".[12] Additionally, if "... at any time after providing notification of the proposed unconfined release or receiving authorization for the unconfined release of a particular PNT, the applicant becomes aware of any new information regarding the environmental safety of the PNT… the applicant must immediately provide the PBO with the new information."[16]

B. TRANSPARENCY

The application process, including the guidelines, is publicly available at the Canadian Food Inspection Agency's website. Decision documents for PNTs are also available, however, we were unable to locate detailed risk assessments.

13 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Section 6.2.

14 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Section 7.3.

15 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Section 6.3.

16 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Section 9.

C. LACK OF SCIENTIFIC KNOWLEDGE OR CONSENSUS DOES NOT INDICATE LEVEL OR ABSENCE OF RISK

We were unable to locate this information with the documents reviewed.

D. RISK CONSIDERED IN THE CONTEXT OF RISK POSED BY NON-MODIFIED RECIPIENTS OR PARENTAL ORGANISMS

Due to its regulation as a plant with one or more "novel" traits, the risks posed by a LMP must be considered relative to risks posed by its counterpart. Not only is the counterpart the basis for comparison, but the new transformation event must also create a LMO with "novel" traits not already present in cultivated populations in Canada for a complete a risk assessment to be required.

> the risks posed by a LMP must be considered relative to risks posed by its counterpart

As part of the required "Information on the Biology and Interactions of the PNT," an applicant must compare the phenotypic characteristics of the PNT to its counterpart. The phenotypic comparison must look at compositional analysis, levels of known naturally expressed toxicants, antinutrients, and allergens.[17,18] In addition, characteristics of the LMO which influence reproductive and survival biology - including habitat, life cycle, life history, outcrossing frequency, impact on pollinators species, stress adaptations, and the ability to overwinter - must be compared to its counterpart.[19]

Any data collected and information provided in the application process must also be conducted in the context of the LMO's counterpart. The information provided in a risk assessment "consists of appropriate data and relevant scientific information describing the environmental risk of the PNT relative to its counterpart(s) already present in the Canadian environment."[13] When considering confined research field trials, the experiments should be "carefully designed to generate data demonstrating the agronomic/silvicultural and environmental characteristics of the PNT relative to its counterpart."[13]

> The information provided in a risk assessment "consists of appropriate data and relevant scientific information describing the environmental risk of the PNT relative to its counterpart(s) already present in the Canadian environment."

The idea of being "substantially equivalent." is an important concept in the Canadian directive in regards to risk relative to its unmodified counterpart This concept is defined as a PNT which "in terms of its specific use and safety for the environment…should pose no greater risk to the Canadian environment compared with its counterpart."[12] An implication of this definition is that an LMP "may be exempted from the notification and authorization requirements."[12]

---

17 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Section 3.3.

18 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Section 3.4.

19 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Section 3.2.

E. CASE-BY-CASE BASIS

The use of novel traits as the criteria by which plants are subject to risk assessment has implications for how a case is defined in the Canadian directive. A plant must be determined as novel to be considered a new case, "irrespective of the method used to introduce it."[11] The determination of novelty is the responsibility of the proponents and conducted on a case-by-case basis using both "their expertise and relevant scientific literature reviews, to determine the range of the selected trait in cultivated populations of the plant species in Canada."[11]Following an authorization for unconfined release, PNTs - even when crossed, trait stacked, re-transformed, or re-mutated - may not require additional risk assessments. In the case of intra-specific crosses a PNT's progeny and sister lines from the original transformation are authorized for unconfined release.[20] In the case of inter-specific crosses a risk assessment of the first inter-specific cross - but not further lines - may be necessary.[21] Intentional trait stacking, common in modern biotechnology, does not constitute a new case, so there is no requirement for a risk assessment.[22] However, notification to the PBO is required, therefore allowing the PBO to determine if any possible safety concerns exist. Re-transformation and re-mutation, also common in modern biotechnology, do not constitute a new case provided that 1) the method utilized is identical, 2) intended uses are the same, and 3) the novel gene are expressed at similar levels.[23]

IV. Methodology

A. IDENTIFICATION OF NOVEL GENOTYPIC AND PHENOTYPIC CHARACTERISTICS ASSOCIATED WITH LMO, THAT MAY HAVE ADVERSE EFFECTS ON BIOLOGICAL DIVERSITY IN THE LIKELY POTENTIAL RECEIVING ENVIRONMENT, ALSO TAKING INTO ACCOUNT RISKS TO HUMAN HEALTH

1. Recipient/Parental Organism

The most important aspect of the Canadian risk assessment process in regards to the recipient/parental organism is the required species-specific biology documents. These documents are produced by the PBO and outline the characteristics of a plant species that has been submitted or may be submitted for unconfined release. Required information includes the biology (e.g. use, centers of origin, reproduction, agronomic practices, weediness, and ecology) of the species and related species.[24] The intent of these documents is to create a standard reference for the comparison of the PNT with its counterpart. Proponents who wish to submit an application for a PNT where a biology document for the species is not available must notify the PBO six months prior to submission in order to allow time for the PBO to author a new biology document for that species.[25] These documents are "drafted using subject matter experts, published peer-reviewed literature, and consensus documents developed by the Organization for Economic Cooperation and Development (OECD)."[26]

20 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Section 2.2.

21 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Section 2.3.

22 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Section 2.4.

23 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Section 2.5.

24 Biology Document BIO1992-02. The Biology of Brassica rapa L. Canadian Food Inspection Agency - Plant Biosafety Office of the Plant Health and Production Division. Website; http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9902e.shtml.

25 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Section 7.2.

26 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Section 7.2.

In addition to the biology document the proponent of the PNT must also select a suitable counterpart (Table 5.2). In general this is the isogenic line closest to the PNT and can be a previously authorized PNT.

TABLE 5.2: Sample of recipient/parental organisms from seven Canadian decision documents

Alfalfa Events J101 and J163[27]	Line R2336
Canola MS8, RF3 (MS8xRF3)[28]	*B. napus* variety "Drakkar"
Corn MON 88017[29]	corn hybrid A x Hi-II
Flax FP967 (CDC Triffid)[30]	flax cv. Norlin
Potato New Leaf™ Plus line: RBMT22-082[31]	Russet Burbank (RB)
Soybeans Event 356043[32]	Soybean (*Glycine max* (L.) Merr.)
Sugar Beet Line H7-1[33]	KWS multigerm line 3S0057

27 Decision Document DD2005-53. Determination of the Safety of Monsanto Canada Inc.'s Roundup Ready® Alfalfa (Medicago sativa L.) Events J101 and J163. Canadian Food Inspection Agency - Plant Biosafety Office of the Plant Health and Production Division. Website: http://www.inspection.gc.ca/english/plaveg/bio/dd/dd0553e.shtml.

28 Decision Document 96-17: Determination of Environmental Safety of Plant Genetic Systems Inc.'s (PGS) Novel Hybridization System for Rapeseed (Brassica napus L.). Canadian Food Inspection Agency - Plant Biosafety Office of the Plant Health and Production Division. Website: http://www.inspection.gc.ca/english/plaveg/bio/dd/dd9617e.shtml.

29 Decision Document 2006-57. Determination of the Safety of Monsanto Canada Inc.'s Glyphosate-Tolerant, Corn-Rootworm-Protected Corn (Zea mays L.) Event MON 88017. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dd/dd0657e.shtml.

30 Decision Document 98-24: Determination of the Safety of the Crop Development Centre's 'CDC Triffid', a Flax (Linum usitatissimum L.) Variety Tolerant to Soil Residues of Triasulfuron and Metsulfuronmethyl. Canadian Food Inspection Agency - Plant Biosafety Office of the Plant Health and Production Division. Website: http://www.inspection.gc.ca/english/plaveg/bio/dd/dd9824e.shtml.

31 Decision Document DD2002-36: Determination of Environmental Safety of RBMT22-082 Colorado Potato Beetle and Potato Leaf Roll Virus Resistant Potato Line Developed by Monsanto Canada Inc. Canadian Food Inspection Agency - Plant Biosafety Office of the Plant Health and Production Division. Website: http://www.inspection.gc.ca/english/plaveg/bio/dd/dd0236e.shtml.

2. *Donor Organism*

Information requirements in regards to the donor organism (Table 5.3) include the source, portion, and size of the sequence vector (Table 5.4).[34] In addition the proponent must indicate if the genetic component, donor organism, or related organism "is responsible for disease or injury to plants or other organisms, and is a known toxicant, allergen, pathogenicity factor, or irritant."[35] The proponent must also comment on the history of safe use of the donor organism.

TABLE 5.3: Sample of donor organism from seven Canadian decision documents

Alfalfa Events J101 and J163[27]	*Agrobacterium* sp. strain CP4
Canola MS8, RF3 (MS8xRF3)[28]	*Streptomyces hygroscopicus*
Corn MON 88017[29]	*Agrobacterium tumefaciens*
Flax FP967 (CDC Triffid)[30]	T-DNA region of an *A. tumefaciens* plasmid
Potato New Leaf™ Plus line: RBMT22-082[31]	*B. thuringiensis* subsp. Tenebrionis, ORF-1 and ORF-2 regions from *PLRV*
Soybeans Event 356043[32]	*Bacillus licheniformis* enzymes
Sugar Beet Line H7-1[33]	*Agrobacterium* sp. strain CP4

32 Decision Document DD2009-77: Determination of the Safety of Pioneer Hi-Bred Production Ltd.'s Soybean (Glycine max (L.) Merr.) Event 356043. Canadian Food Inspection Agency - Plant Biosafety Office of the Plant Health and Production Division. Website: http://www.inspection.gc.ca/english/plaveg/bio/dd/dd0977e.shtml.

33 Decision Document DD2005-54: Determination of the Safety of Monsanto Canada Inc. and KWS SAAT AG's Roundup Ready® Sugar Beet (Beta vulgaris ssp vulgaris L.) Event H7-1. Canadian Food Inspection Agency - Plant Biosafety Office of the Plant Health and Production Division. Website: http://www.inspection.gc.ca/english/plaveg/bio/dd/dd0554e.shtml.

34 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Section 7.1

35 Directive 94-08: Appendix 3, Sections 2-4, 8.

TABLE 5.4: Sample of vectors from seven Canadian decision documents

Alfalfa Events J101 and J163[27]	double border, binary, PV-MSHT4
Canola MS8, RF3 (MS8xRF3)[28]	disarmed non-pathogenic *Agrobacterium tumefaciens*
Corn MON 88017[29]	binary plasmid vector
Flax FP967 (CDC Triffid)[30]	disarmed *A. tumefaciens Ti*-plasmid vector pGV3850
Potato New Leaf™ Plus line: RBMT22-082[31]	*Agrobacterium tumefaciens*
Soybeans Event 356043[32]	Microprojectile bombardment (gene gun) mediated transformation
Sugar Beet Line H7-1[33]	disarmed binary PV-BVGT08

3. LMO characteristics

Canada's framework identifies three main categories of information requested in regards to the LMO. These include 1) the identity and origin of the PNT, 2) the properties of the novel gene and its gene products, and 3) the relative phenotypic expression of the PNT compared to its counterpart.[36] Details of the information required are also outlined, including requested information specific to LMPs such as how the LMP was modified, taxonomic information, and a description of the novel traits (Table 5.5).[37] For the taxonomic information requirements, transgenic PNTs must have a unique identifier for each transformation event according to the *OECD Guidance for the Designation of a Unique Identifier for Transgenic Plants*.[38] Toxicity of the novel gene must be specified if applicable.

TABLE 5.5: Sample of inserted genes and novel traits of LMOs from seven Canadian decision documents

	Inserted Gene	Novel Traits
Alfalfa Events J101 and J163[27]	CP4 EPSPS	Glyphosate Tolerance
Canola MS8, RF3 (MS8xRF3)[28]	*barnase* gene from *Bacillus amyloliquefaciens*	Nuclear Male Sterility, Fertility Restoration, Glufosinate Ammonium Tolerance
Corn MON 88017[29]	*cp4 epsps, cry3Bb1*	Resistance to Rootworm (CRW), Glyphosate Tolerance
Flax FP967 (CDC Triffid)[30]	mutant als and kanamycin resistance	Tolerance to soil residues of triasulfuron and metsulfuron-methyl; kanamycin (antibiotic) resistance; production of nopaline.
Potato New Leaf™ Plus line: RBMT22-082[31]	*cry3A, PLRVrep, CP4 EPSPS*	Colorado potato beetle and potato leaf roll virus resistance, and glyphosate tolerance
Soybeans Event 356043[32]	*gat4601, gm-hra*	Glyphosate tolerate, ALS-inhibiting Herbicides tolerance
Sugar Beet Line H7-1[33]	*cp4 epsps*	Glyphosate Tolerance

36 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Section 7.1.

37 Directive 94-08: Appendix 3, Sections 2-4, 8.

38 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Appendix 3, Section 2.4.

In addition to the requests above, the PBO "prepared a series of checklists to be used by reviewers in the assessment process for the following six analytical techniques: Southern blot, Western blot, Northern blot, polymerase chain reaction, RNA dot blot, enzyme- linked immunosorbent assay (ELISA), and enzyme assays."[39]

4. Receiving environment

Information in regards to the potential receiving environment is contained in the biology document of the non-modified plant species and is also supplemented by the proponent. Within the biology documents, Part B describes the current environment in which the non-modified plant species resides in Canada, including the primary crop production areas and the environment of any wild relatives.[40] As part of the risk assessment the proponent must address "anticipated or known relative effects on the environment resulting from the release."[41]

> Information in regards to the potential receiving environment is contained in the biology document of the non-modified plant species and is also supplemented by the proponent.

B. EVALUATION OF THE LIKELIHOOD OF THESE ADVERSE EFFECTS BEING REALIZED, TAKING INTO ACCOUNT THE LEVEL AND KIND OF EXPOSURE OF THE LIKELY POTENTIAL RECEIVING ENVIRONMENT TO THE LIVING MODIFIED ORGANISM

Directive 94-08 considers five major categories of adverse effects for LMP released into the environment. These include:[42]

- Potential of the PNT to become a weed of agriculture or be invasive of natural habitat
- Potential for gene flow to wild relatives whose hybrid offspring may become weedier or more invasive
- Potential for the PNT to become a plant pest
- Potential impact of the PNT or its gene products on non-target species, including humans
- Potential impact on biological diversity

1. Intended use of LMO compared to recipient or parental organism

Section 4 of Directive 94-08: Appendix 4 outlines the information requested as part of the risk assessment related to the use of a PNT for cultivation. This includes a description of the current regions of cultivation and whether or not the "modification permits cultivation of the species in regions in Canada outside the area of current cultivation."[43] In addition, cultivation practices for the PNT must also be described. This includes: land preparation, fertilizer usage, weed and pest control, harvest, post-harvest protocols, and others.

2. Characteristics of relevant potential receiving environment

See section A.4 above for details.

39 Reviewers' Checklists - Plant Biosafety Office of the Plant Health and Production Division. Website: http://www.inspection.gc.ca/english/plaveg/bio/usda/usda04e.shtml.

40 Biology Document BIO1994-09. The Biology of Brassica napus L (Canola/Rapeseed): A companion document to Directive 94-08. Canadian Food Inspection Agency - Plant Biosafety Office of the Plant Health and Production Division. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9409e.pdf.

41 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Section 7.1.

42 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Section 6.1.

43 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Appendix 4, Section 4.

3. How incidental exposure to the environment could occur

There are four main ways in which the Canadian Directive considers how incidental exposure may occur: gene-flow, pollinator feeding, seed feeding and weediness or becoming a plant pest.[44]

In addition the proponent must indicate the overwintering ability of the PNT as this is an important aspect of consideration of continued incidental exposure to the environment due to Canada's climate.

Likelihood of gene flow is a significant component of the risk assessment. The risk assessment must consider outcrossing frequency, cross-fertilization frequency, sexually compatible species including wild relatives and the stability of inheritance, and the expression of novel traits.[44] Quantitative measurement of many of the gene-flow parameters is required as part of confined field trials. In addition to general gene-flow issues, the risk assessment must address specific issues regarding wild relatives including trait similarity in wild relatives and changes in reproductive fitness, selective advantage, establishment and spread.[45]

Likelihood of non-target effects including seed feeding and the visiting of flowers by pollinators must be addressed. "Information on whether the same pollinator species have been seen in the field or have there been changes in the pollinators that visit the flowers"[46] is required to assess the likelihood of adverse effects to pollinators. This information, including any changes, may be determined through the confined field trials. Secondary or pleiotropic effects due to changes in composition of the PNT's seed has the potential to impact seed feeders. This requires identification of parameters including protein, lipids, fiber, and others when appropriate.

The weediness or plant pest potential must be considered in each risk assessment conducted. All of the decision documents that we examined indicated that there was no altered weedy or invasive potential (see Appendix 5.H). Reasons given include "does not possess the potential to become weedy due to traits such as lack of seed dormancy, the non-shattering nature of corn cobs, and the poor competitive ability of seedlings."[29]

4. Conclusion of evaluation of likelihood of exposure

Directive 94-08 does not require a specific qualitative or quantitative conclusion of the likelihood of exposure. The decision for authorization for unconfined release is concluded qualitatively in the estimation of the overall risk.

> The decision for authorization for unconfined release is concluded qualitatively in the estimation of the overall risk.

C. EVALUATION OF THE CONSEQUENCES SHOULD THESE ADVERSE EFFECTS BE REALIZED

There are two main considerations in regards to the impact of the PNT or its gene products on non-target species: toxicity and secondary or pleiotropic effects, the most detailed being the former. As part of the risk assessment the proponent must detail the animal diets that consist of LMP parts that express the novel gene. Additionally, the possibility of persistent toxic substances must also be considered and are determined through residual effects studies conducted by crop rotation; "direct measurements in soil microbial communities may be indicated if microbial toxins are expected in root exudates."[47] Effects on "metabolism, growth, development, or reproduction of animals, plants, or microbes" must be identified in the risk assessment.[48] Additionally, "potential physiological and behavioral effects to

44 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Appendix 4.

45 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Appendix 4, Section 5.4.

46 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Appendix 4, Section 3.1.

47 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Appendix 4, Section 6.3.

48 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Appendix 4, Section 6.2.

other organisms including insect, avian, aquatic, or mammalian species" must be considered.[47] Special consideration is given to threatened or endangered species and beneficial organisms (pollinators, predators, parasites, biological control organisms, soil microbes).[47] In the decision document for corn the proponent indicated "there are no coleopteran species currently listed by the Committee on the Status of Endangered Wildlife in Canada as being a threatened or endangered species."[29] The information provided can be in the form of primary data, secondary data, and other supporting information.

D. ESTIMATION OF THE OVERALL RISK POSED BY THE LMO BASED ON THE EVALUATION OF THE LIKELIHOOD AND CONSEQUENCES OF THE IDENTIFIED ADVERSE EFFECT BEING REALIZED

Final determination of the overall risk is made by the Plant Biosafety Office in the Canadian Food Inspection Agency. Its directive is to weigh the evidence provided to authorize or refuse to authorize the unconfined release of the PNT:

> *Where the proposed release of a PNT poses a minimal apparent risk to the environment, the PBO may authorize the unconfined release of the PNT, and may, where necessary, impose conditions for the management of the apparent risk. Conditions will be imposed on an indeterminate basis.*[49]

> *Where the proposed release of a PNT has been assessed to pose unacceptable risk to the environment, the PBO may refuse to authorize the unconfined environmental release of the PNT, and will provide reasons for the refusal.*[49]

E. RECOMMENDATION AS TO WHETHER THE RISKS ARE MANAGEABLE, INCLUDING, WHERE NECESSARY, IDENTIFICATION OF STRATEGIES TO MANAGE THESE RISKS

Management plans may be required in Canada for LMPs that exhibit "minimal apparent risk to the environment."[49] In addition to this conditional requirement there are two other components to the risk management strategy of LMPs in Canada: confined field trials and stewardship plans. The first component is the use of confined field trials to initially minimize the exposure of the LMPs to the environment while conducting research to evaluate the performance and collect data to inform the risk assessment for unconfined environmental release. The second component includes management plans that target the development of evolutionary resistance in pest and weed populations.

There are two components to the risk management strategy of LMPs in Canada: confined field trials and stewardship plans. The first component is the use of confined field trials to initially minimize the exposure of the LMPs to the environment. The second component includes management plans that target the development of evolutionary resistance in pest and weed populations.

Confined field trials of LMPs in Canada "provide researchers with the opportunity to evaluate the PNTs in the field under conditions which minimize their exposure to the environment." (see Appendix 5.F)[50] This is done by limiting the size, number, and locations of the confined field sites (see Appendix 5.B) and reproductively isolating LMPs (see Appendix 5.C).[50] Of the seven decision documents reviewed for this summary, all of the products underwent confined field trials in Canada prior to the application for unconfined release (Table 5.6). Four of the decision documents (i.e. alfalfa, corn, soybeans, sugar beets) also indicated field trials in the United States. One of decision documents (sugar beets) indicated that field trials had been conducted in Europe (i.e. France, Germany). Data from some of the field trials, including field trials outside Canada, were used as supportive information.

49 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Section 8.1.

50 Directive 2000-07 – Conducting Confined Research Field Trials of Plant with Novel Traits in Canada. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/plants/plants-with-novel-traits/applicants/directive-dir2000-07/eng/1304474667559/1304474738697. Section 3.2.

TABLE 5.6: Confined field trials conducted prior to approval of seven LMOs in Canada

Alfalfa **Events J101 and J163**[27]	Canada, United States
Canola **MS8, RF3 (MS8xRF3)**[28]	Canada
Corn **MON 88017**[29]	Canada, United States
Flax **FP967 (CDC Triffid)**[30]	Canada
Potato **New Leaf™ Plus line:** **RBMT22-082**[31]	Canada
Soybeans **Event 356043**[32]	United States, Canada
Sugar Beet **Line H7-1**[33]	North America, Europe (France, Germany)

The primary objective of reproductive isolation is to minimize potential gene flow from the PNT field plot to "neighboring related commercial crops, breeding nurseries, seed multiplication plots, other trials, and sexually compatible wild relatives."[51] In addition to geographically limiting the field plants, alternative methods may be used such as harvesting before flowering and bags, nets, or cages to prevent pollen exchange.[52]

Two stewardship management plans are intended to delay the resistance of crop pests and weeds: insect resistance management and herbicide tolerance management. The first plan involves insect resistance management for LMPs "…expressing novel insect resistance (including those expressing *Bacillus thuringiensis* (Bt) endotoxins) grown in fields of greater than one hectare in size."[53] These plans must be part of the application for unconfined release and be specific to the target insect. The insect resistance management plans must also integrate available laboratory and field research and computer modeling. The intent of these plans is "to delay the development of resistance in the insect to the active compound(s) and thereby prolong the lifespan and usefulness of the technology."[53] Current plans include refugia planting for Bt corn and Bt potatoes to allow potentially resistant insects to interbreed with insects that have not been exposed to the novel compounds. These plans must include the most recent scientific information including reproductive biology, behavior, dispersal, resistance allele frequency, and target life cycle (see Appendix 5.D).[49]

The second plan targets herbicide tolerance in environments where novel herbicide tolerant crops are being cultivated. These plans attempt to delay resistance of plants that grow environment similar to PNTs with novel herbicide resistance. Further, these plans must address the control of volunteers, selection of herbicide tolerance, introgression of novel traits, management of herbicide tolerant crops and effectiveness of plan.[54]

It is also important to note that a "PNT with a novel herbicide tolerance that could be introgressed to related species, resulting in hybrids that have no effective or sustainable control options, will not be authorized."[54]

Detection and identification are also required to support the management plans that have been developed. Applicants must submit appropriate test methodologies including test type, limit of detection, procedural clarity, cross reactivity, reference material, and contact information.[55]

51 Directive 2000-07 – Conducting Confined Research Field Trials of Plant with Novel Traits in Canada. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/plants/plants-with-novel-traits/applicants/directive-dir2000-07/eng/1304474667559/1304474738697. Section 3.3.

52 Directive 2000-07 – Conducting Confined Research Field Trials of Plant with Novel Traits in Canada. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/plants/plants-with-novel-traits/applicants/directive-dir2000-07/eng/1304474667559/1304474738697. Section 3.3.2.

53 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Section 7.5.1.

54 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Section 7.5.2.

55 CFIA Detection and Identification Method Criteria. Canadian Food Inspection Agency. Website: http://www.inspection.gc.ca/english/plaveg/bio/detecte.shtml.

F. WHERE THERE IS UNCERTAINTY REGARDING THE LEVEL OF RISK, IT MAY ADDRESSED BY REQUESTING FURTHER INFORMATION ON THE SPECIFIC ISSUES OF CONCERN OR BY IMPLEMENTING APPROPRIATE RISK MANAGEMENT STRATEGIES AND/OR MONITORING THE LMO IN THE RECEIVING ENVIRONMENT

Uncertainty regarding the level of risk is addressed using both confined research field trials and a post-release monitoring plan. The primary goals of the confined field trials beyond limiting exposure are to "address the criteria and information requirements considered in the environmental safety assessment of PNTs for unconfined releases".[56] The confined field trial provides data to the proponent for cultivation purposes and also informs the risk assessment for unconfined environmental release.

> Uncertainty regarding the level of risk is addressed using both confined research field trials and a post-release monitoring plan.

A post-release monitoring plan must be part of an application for unconfined environmental release. The goal of such a plan is "to monitor for unintended or unexpected environmental effects."[57] Stewardship management plans such as those for herbicide tolerant and insect resistant LMPs may be used to meet this requirement. New information obtained by the proponent as part of this plan regarding risk to the environment must be given to the PBO.

V. Discussion

The risk assessment process in Canada is detailed in its information requirements for plants with novel traits. Living modified plants (LMPs) developed through modern biotechnology techniques that do not express novel traits are not subjected to the same risk assessment directives. Except for plants with novel traits (PNTs), LMPs are assessed according to the overarching regulations the *Plant Protection Act* and the *Seeds Act*.[1,2] These acts have no specific requirements for organisms produced through modern biotechnology or contain novel traits.

Usage of novelty as the regulatory hook for plants has implications for the comparison context and what constituents a new case. Novelty designation and the concept of substantial equivalence also suggest that the baseline for consideration of risks changes with each authorization for unconfined release.

The risk assessment requirements for PNTs in general do not make conclusions on the level of likelihood or impacts of exposure. Conclusion on the overall risk is considered in the decision process but estimation methods are not explicit.

Plants with novel traits are not strictly required to undergo confined field trials; however, it appears that these field trials are conducted to provide the necessary data to develop the application for unconfined release. Confined field trials are used as a mechanism to allow proponents to study PNTs for their own purposes and collect data to resolve uncertainty in the risks associated with the environmental release. These limited field plots allow for small-scale research on the field risks associated with PNTs.

Inclusion of a post release monitoring plan aids in the dissemination of data after a PNT has been approved for unconfined release. These data can help inform stewardship and management plans. Use of stewardship management plans that are specific to the novel traits of a PNT can provide additional management techniques that go beyond general guidelines.

56 Directive 2000-07 – Conducting Confined Research Field Trials of Plant with Novel Traits in Canada. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/plants/plants-with-novel-traits/applicants/directive-dir2000-07/eng/1304474667559/1304474738697. Section 1.1.

57 Directive 94-08 – Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits. Canadian Food Inspection Agency - Plant Biosafety Office. Website: http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml. Section 7.6.

APPENDIX

APPENDIX 5.A: Decision Documents Examined for Canada's Summary

Plant Species	Product / Designation	OECD Unique Identifier	Applicant at time of application	Novel Trait(s)	Approval for unconfined release into the environment	Variety Registration
Medicago sativa L.	Alfalfa Events J101 and J163	J101: MON-00101-8; J163: MON-00163-7	Monsanto Canada Inc.	Glyphosate tolerance	Yes (July 28, 2005) DD2005-53	No varieties registered
Brassica napus L.	Canola MS8, RF3 (MS8xRF3)	MS8: ACS-BN005-8; RF3: ACS-BN003-6	Plant Genetic Systems (currently Bayer CropScience)	Male sterility / fertility restoration / glufosinate ammonium tolerance	Yes (October 21, 1996) DD96-17	Yes
Zea mays L.	Corn MON 88017	MON-88017-3	Monsanto Canada Inc.	Western and Northern Corn Rootworms resistance/ Glyphosate tolerance	Yes* (February 20, 2006) DD2006-57	Not subject to variety registration
Linum usitatissimum L.	Flax FP967 (CDC Triffid)	CDC-FL001-2	University of Saskatchewan	Sulfonylurea tolerance	Yes (May 8, 1996) DD98-24	No longer registered
Solanum tuberosum L.	Potato New Leaf™ Plus line: RBMT22-082	NMK-89896-6	Monsanto Canada Inc.	Colorado Potato Beetle resistance / Potato Leafroll virus resistance	Yes* (August 13, 2001) DD2002-36	Yes
Glycine max (L.) Merr.	Soybeans Event 356043	DP-356043-5	Pioneer Hi-Bred Production Ltd.	Tolerance to glyphosate herbicide and tolerance to ALS-inhibiting herbicides	Yes (August 26, 2009) DD2009-77	No varieties registered
Beta vulgaris ssp vulgaris L.	Sugar Beet Line H7-1	KM-000H71-4	Monsanto Canada Inc. and KWS SAAT AG	Glyphosate tolerance	Yes (September 13, 2005) DD2005-54	Not subject to variety registration

APPENDIX 5.B: Restrictions on the size and number of confined research field trial site locations (Dir2000-07 3.2)

1 hectare per trial location site.
10 trial site locations per submission per province (includes locations submitted in new applications and renewal of authorizations).
5 hectares cumulative per submission per province (includes locations submitted in new applications and renewal of authorizations)

APPENDIX 5.C: Alternative reproductive isolation methods (Dir2000-07 3.3.2)

Harvest of plants before flowering requires close monitoring at the onset of flowering.
Bags, nets or cages placed over flowering plants to prevent pollen exchange, provided that scientific rationale is provided in writing in the application to justify the effectiveness of such measures.
Removal of floral parts before pollen maturity.
Guard rows/Pollen traps must be seeded no greater then 10 meters and no less then 3 meters from the trial.

APPENDIX 5.D: Insect Resistance Management Plan Scientific Evidence (Dir94-08 7.5.1)

Reproductive biology and behaviour of the insect pest;
Mobility of the larvae;
Ability of adults to disperse from the natal field before and after mating;
Estimate of resistance allele frequency in the insect population;
Impact of management practices such as insecticide use in the refuge;
Targeted life cycle stage of the insect pest.
History of insect resistance to the active compound(s).

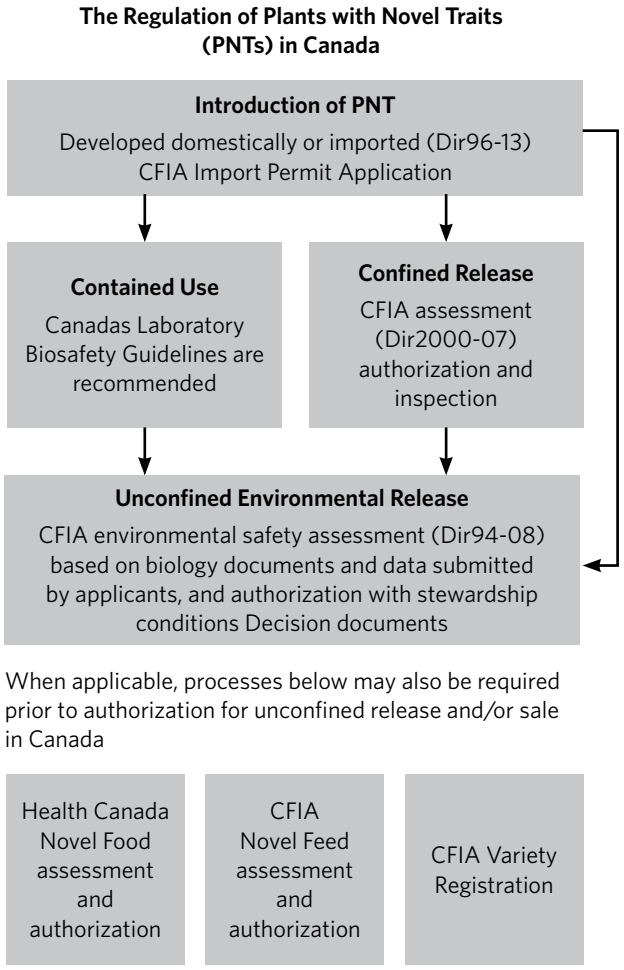
APPENDIX 5.E: Herbicide Tolerance Management Plan Elements (Dir94-08 7.5.2)

Control of volunteers, more specifically, any changes in usual agronomic practices that may arise from the novel herbicide tolerance and which could result in reduced sustainability or have significant impacts on soil conservation;
Selection of herbicide tolerance in weeds resulting from the potential continued application of the same herbicide in subsequent rotations;
Introgression of novel trait into related species;
Management of the herbicide tolerant crop during the growing season, particularly where multiple herbicide tolerances, due to cross pollination, could arise in subsequent growing seasons;
Communication to growers as well as an efficient mechanism allowing growers to report problems to developer;
Monitoring of effectiveness of the stewardship plan.

APPENDIX 5.F: Opportunities for developers from confined research field trial program (Dir2000-07 1.1)

Evaluate the performance of PNTs.
Study the environmental safety of these modified plants.
Address the criteria and information requirements considered in the environmental safety assessment of PNTs for unconfined releases and.
Generate data for variety registration purposes.

APPENDIX 5.G: Opportunities for developers from confined research field trial program (Dir2000-07 1.1) Source: http://www.inspection.gc.ca/english/plaveg/bio/pntchae.shtml



APPENDIX 5.H: Risk assessment for potential adverse effects on LMP in the environment

	Alfalfa Events J101 and J163	Canola MS8, RF3 (MS8xRF3)	Corn MON 88017	Flax FP967 (CDC Triffid)	Potato New Leaf™ Plus line: RBMT22-082	Soybeans Event 356043	Sugar Beet Line H7-1
Become weed or invasive	Alfalfa not invasive in unmanaged habitats, no pest or weed characteristics, should take steps to prevent tolerance development	Reproductive and survival biological characteristics in line with commercial varieties based on applicants' information	Reproductive and survival biological characteristics in line with commercial varieties based on applicants' information	Reproductive and survival biological characteristics in line with commercial varieties based on applicants' information, can appear in other crops in subsequent years, but non-competitive with other crops	Reproductive and survival biological characteristics in line with commercial varieties based on applicants' information	No demonstrated invasiveness of soybeans, does not differ from commercial counterparts, should take steps to prevent tolerance development	No demonstrated invasiveness of sugar beets in unmanaged areas, does not differ from commercial counterparts, should take steps to prevent tolerance development
Gene-flow to wild relatives causing invasive-ness	Unlikely for gene flow to one wild relative, M. lupulina	No pollination of other species since male sterile, could spread to B. rapa, weed in cultivated lands, if resistance develops chemical / mechanical control will be required	No wild relatives that can naturally hybridize with corn	No wild relatives that can freely hybridize with this species, outcrossing occurs up to 5% of time	No wild relatives that can naturally hybridize with PNT	Can hybridize with, Glycine soja, not naturalized in N. America, soybeans self-pollinating so <1% chance of cross-pollination	No wild relatives that can naturally hybridize with PNT
Become a plant pest	Novel traits not related to plant pest potential	Novel traits not related to plant pest potential, Susceptible to same diseases as parent	Novel traits not related to plant pest potential	Novel traits not related to plant pest potential	Novel traits not related to plant pest potential, Susceptible to same diseases as parent	Novel traits not related to plant pest potential	Novel traits not related to plant pest potential, if tolerance develops can manage through alternative herbicides
Impact on non-target species	Does not results in altered toxic or allergenic properties, mouse tests revealed lack of oral toxicity to protein	Does not results in altered toxic or allergenic properties	Cry3Bb1 toxic only to Coleopteran species, none on CA's End. Wildlife List, both genes non-toxic to humans based on previous tests	Tests with monocots and dicots shown no differences, no data on effect of dicots grown on soils previously grown with CDC flax	Non-toxic to range of species (honeybee, ladybird beetle, green lacewing, parasitic wasp, Collembola sp., earthworm, mice, bobwhite quail)	Does not results in altered toxic or allergenic properties	Does not results in altered toxic or allergenic properties

	Alfalfa Events J101 and J163	Canola MS8, RF3 (MS8xRF3)	Corn MON 88017	Flax FP967 (CDC Triffid)	Potato New Leaf™ Plus line: RBMT22-082	Soybeans Event 356043	Sugar Beet Line H7-1
Impact on biological diversity	No risk of spread beyond current geographic range, only could spread to feral alfalfa	Potential outcross species could appear in managed / cultivated lands	No risk of spread beyond current geographic range, could reduce presence of pest (CRW) in area	No risk of spread beyond current geographic range, should not be used in consecutive years	No risk of spread beyond current geographic range, could reduce use of chemicals in environment	No risk of spread beyond current geographic range, reduces weeds in cultivated areas unlikely to affect wild areas	No risk of spread beyond current geographic range
Tolerance development in target species	NA	NA	IRM management plan in place to prevent tolerance development in species	NA	Known tolerance development in CPB to Cry3A requires adherence to management practice (refuge, education, etc)	NA	NA
Tolerance development in other species	NA	NA	Could develop herbicide tolerance in volunteer crops and weeds, requires management	NA	NA	NA	NA

Chapter 6. China: Elements of risk assessment for LMOs

I. Abstract

Risk assessment of living modified organisms (LMOs) in China is a concerted effort involving national and local governments and the entities involved in LMO research. National administration of the overall risk assessment process is under the jurisdiction of the Ministry of Agriculture, although similar functions are also carried out on a more local scale by the relevant county or provincial agricultural departments. Risk assessments are triggered by the use of recombinant DNA technologies and are carried out by a scientific body established by the LMO developer. These assessments are then internally reviewed and forwarded to the relevant government agencies for further review and consideration. One primary framework document and a number of supporting documents, all of which are available from multiple official internet sources, guide and inform this process. Risk assessments conducted according to these documents employ comparisons across a broad range of biological and ecological characteristics between a proposed LMO and its unmodified counterpart to generate a qualitative risk classification for the LMO. Various risk management strategies are then employed depending on the risks associated with the LMO. If a proposed LMO is approved for environmental release, the developer is issued a "Safety Certificate". Uncertainty is addressed during this process by the use of elevated risk classifications and expert judgment in cases where information is lacking.

II. Overview of legislative & regulatory framework

It is important to point out that the description of China's approach to risk assessment presented here is based on our interpretation of documents that have been translated from the language of their initial drafting, Mandarin Chinese. Three of the documents, *Regulations on Safety of Agricultural Genetically Modified Organisms*, *Implementation Regulations on Risk Assessment of Agricultural Genetically Modified Organisms*, and *Implementation Regulations on the Safety of Import of Agricultural Genetically Modified Organisms* were acquired in English from the English version of the National Biosafety Clearing House of China (NBCHC) website[1], and are presumably official translations produced by the relevant government authority. *Notice No. 953*, also referenced in this review, was acquired in Chinese from the Convention on Biological Diversity's Biosafety Clearing-house (BCH) website[2] and translated to English using a web-based translator (www.google.com/translate). In both cases (official and unofficial translation) our interpretation of the details of some of these document sections, particularly regulatory and administrative terminology, may differ from an interpretation based on the original documents. Under the Chinese system, the subject of regulation is a "Genetically Modified Organism"

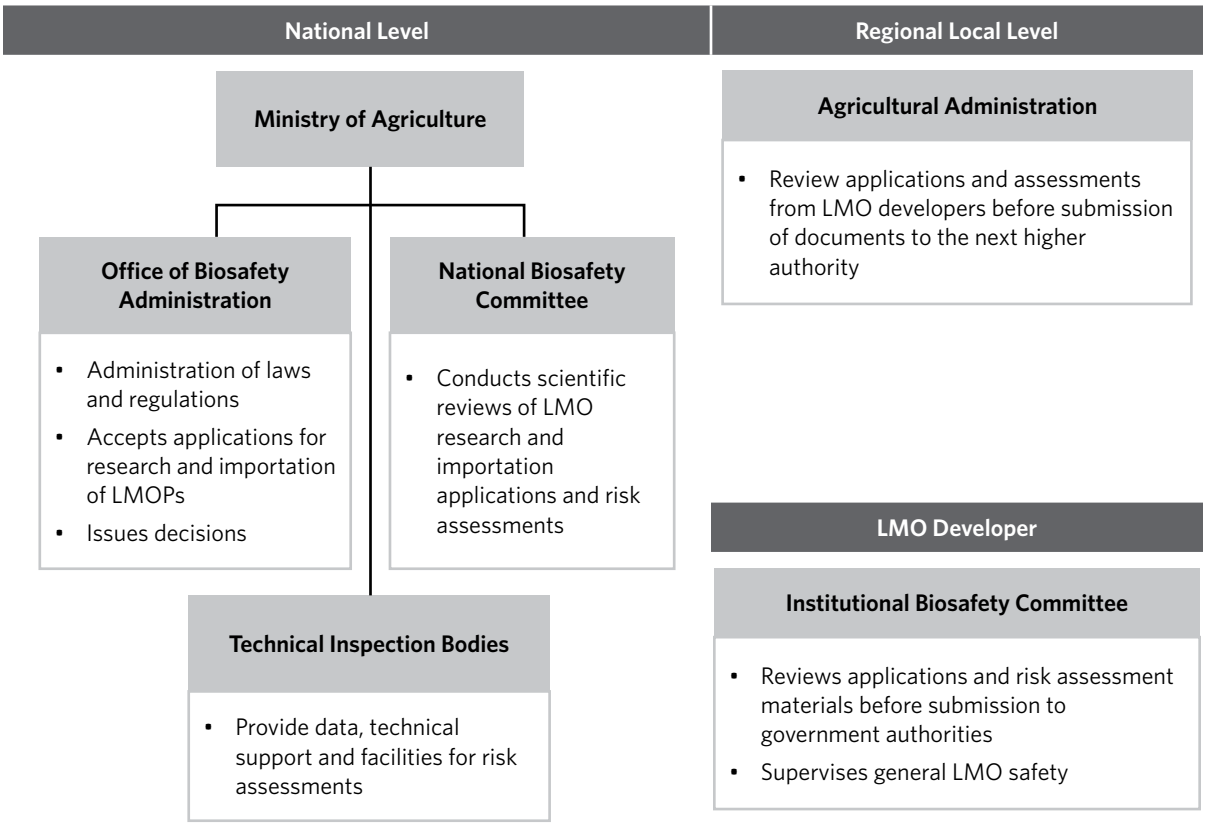
1 National Biosafety Clearing-House of China. Accessed October, 2009. http://english.biosafety.gov.cn/

2 Biosafety Clearing-House: Country Profile (China). Accessed October, 2009. http://bch.cbd.int/about/countryprofile.shtml?country=cn

(GMO), which includes any organism possessing a genome that has been modified by recombinant DNA methods ("genetic engineering technologies"[3]) and any products derived from such an organism.[4] This definition differs from that used in Annex III of the Cartagena Protocol on Biosafety, where the term "Living Modified Organism" (LMO) does not include LMO-derived products. China's LMO regulatory terminology also differs from Annex III in its use of "safety assessments" rather than "risk assessments," although for all intents and purposes, these appear to be synonymous. For the purposes of maintaining semantic consistency with the other country summaries in this report, and taking into account the purpose of the report, we have used the Annex III language ("LMO" and "risk assessment") here, except when quoting directly from China's framework documents.

China's administrative structure for LMO regulation involves jurisdiction at multiple levels (Figure 6.1). Most of the authority regarding regulation of LMOs is based in the Ministry of Agriculture, an administrative unit of the State Council[5]. Within the Ministry is the Office of Biosafety Administration (OBA),[6] which approves research plans for LMOs submitted by developers[7] and reviews applications and progress reports submitted by entities developing or planning to import LMOs into China.[8]

FIGURE 6.1: Administrative structure of LMO regulation in China.



3 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Article 44.

4 Regulations on Safety of Agricultural Genetically Modified Organisms (RSAGMO). 2001. Ministry of Agriculture, People's Republic of China. Article 3.

5 Regulations on Safety of Agricultural Genetically Modified Organisms (RSAGMO). 2001. Ministry of Agriculture, People's Republic of China. Article 4.

6 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Article 5.

7 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Article 20.

8 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Article 15.

Gaining approval for commercial production of a new agricultural LMO in China involves four distinct levels of testing that occur at increasing spatial scales.[9] Before a LMO may progress to the next stage, an applicant must submit a report containing a summary of the previous stage's work, a risk classification of the LMO, a justification for that classification, and biosafety measures used to the OBA for review and approval (Figure 6.2). Only after a safety certificate has been issued can a LMO be used in commercial production.

In addition to the OBA, the Ministry of Agriculture also appoints a National Biosafety Committee for agricultural LMOs. This body is composed of experts in various fields pertaining to LMOs (e.g. public health, environmental protection, and related biological research) and serves as the scientific arm of risk assessment administration[6]. The primary duty of this group is to review all risk assessments of LMOs that are submitted to the Ministry of Agriculture.

Gaining approval for commercial production of a new agricultural LMO in China involves four distinct levels of testing that occur at increasing spatial scales.

A third contribution of the Ministry of Agriculture towards the risk assessment process is the creation of Technical Inspection Bodies (TIBs).[10] These groups provide technical support and data for entities conducting risk assessments and conduct them when applicants lack the appropriate facilities.

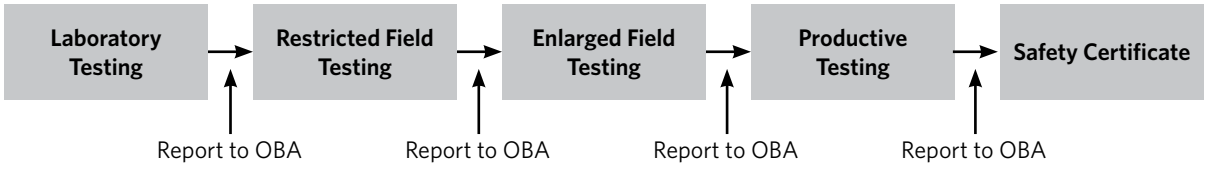
Supervision and administration of some LMO assessment activities also occurs at smaller administrative scales, including at county, municipality, or province levels. Based on the text of the framework documents, this involvement appears to amount to approving applications and reports for research and testing of new LMOs before they are sent to the OBA for review.[11]

III. General principles

A. SCIENTIFICALLY SOUND

China's LMO risk assessment framework explicitly states that assessments "shall be carried out on scientific…basis."[5] This commitment is embodied in the establishment of TIBs, as defined above, and in the requirement that any entity conducting research on LMOs in China must establish an Institutional Biosafety Committee (IBC) to internally oversee and review risk assessments before the final application is submitted to the OBA.[12] In addition, applications for laboratory research and field-testing of LMOs must include detailed descriptions of experimental design, including "the main indexes and analytic methods" used.[13] Examples provided in the framework documents of studies that should be carried out include tests of genetic stability, survival and competitive ability, and expression of the novel trait in different organs of the LMO.[13]

FIGURE 6.2: The different steps involved in the process of receiving authorization to commercially produce an agricultural LMO in China.



9 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Appendix I. § III.

10 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Article 7.

11 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Article 17.

12 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Article 6.

13 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Appendix I. § III (1.5).

The exact methods for conducting these studies are left to the discretion of the scientific committee of the applying institution or TIB conducting the assessment, but *Notice No. 953*[14] contains a set of explicit guidelines (including detailed experimental protocols) for experiments that should be conducted when performing an assessment of environmental safety for herbicide-tolerant maize.

> China's LMO risk assessment framework explicitly states that assessments "shall be carried out on scientific...basis."

B. TRANSPARENCY

China's risk assessment guidance documents provide a detailed description of 1) the kinds of information required by the relevant authorities to make a decision regarding applications for LMOs and 2) the underlying process by which those decisions are made. Furthermore, the framework documents guiding these processes are available for download from the websites of the BCH and the CBCH.

C. LACK OF SCIENTIFIC KNOWLEDGE OR CONSENSUS DOES NOT INDICATE LEVEL OR ABSENCE OF RISK

We were not able to locate in the available framework documents any explicit references to the principle of precaution. However, when determining the "safety type" of genetic manipulations, those manipulations of the recipient organism "with an undetermined influence on human health or the environment" are automatically given a higher (greater risk) safety type[15] (Table 6.1). This is significant because an elevated classification at this stage may, pending the expert judgment of the assessor, result in a higher overall classification of risk for the LMO.

D. RISK CONSIDERED IN THE CONTEXT OF RISK POSED BY NON-MODIFIED RECIPIENTS OR PARENTAL ORGANISMS

China's approach to risk assessment relies on comparisons between unmodified recipient organisms and proposed LMOs, but this is most evident in the concept of the safety type of the genetic manipulation. Briefly, those manipulations that increase, do not change, or decrease the safety of a recipient organism relative to its unmodified recipient organism are classified as "safety type 1," "safety type 2," or "safety type 3," respectively (Table 6.1).

TABLE 6.1: General criteria used to determine the "safety type" of a genetic manipulation.[14]

Safety Type	Effect of Manipulation	Example
1	Increases Safety	Removal of hazardous gene
		Inhibition of expression of hazardous gene(s)
2	Same Safety	Modification with no effect on environmental or human health
		Modification with non-harmful effect(s) on environmental or human health
3	Decreases Safety	Modification that may have harmful influence on human and environmental health
		Modification with unknown influence on human and environmental health

14 Notice No. 953. Evaluation of environmental impact of genetically modified plants and its derivative products. Ministry of Agriculture, People's Republic of China. Released March 3, 2001.

15 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Article 12.

E. CASE-BY-CASE BASIS

Risk assessment for agricultural LMOs in China is carried out on a case-by-case basis where each new combination of recipient organism and recombinant DNA modification triggers an assessment.[16]

Risk assessment for agricultural LMOs in China is carried out on a case-by-case basis where each new combination of recipient organism and recombinant DNA modification triggers an assessment.[16]

IV. Methodology

A. IDENTIFICATION OF NOVEL GENOTYPIC AND PHENOTYPIC CHARACTERISTICS ASSOCIATED WITH LMO THAT MAY HAVE ADVERSE EFFECTS ON BIOLOGICAL DIVERSITY IN THE LIKELY POTENTIAL RECEIVING ENVIRONMENT, ALSO TAKING INTO ACCOUNT RISKS TO HUMAN HEALTH

1. Recipient/Parental Organism

The first step in the risk assessment process for a LMO in China is assignment of the recipient organism to a safety class.[17] This determination is based on information pertaining to the biology, potential to become harmful, and the ability of known hazards associated with the recipient organism to be avoided or mitigated (Table 6.2).[17] In addition to basic taxonomic information (e.g. scientific and common names), assessors require such background as the current use of the plant (particularly in China), place of origin, and any records (domestic or international) pertaining to past safe use or negative impacts on human health and the environment. Further information regarding the biology of a proposed recipient organism, such as life history (annual vs. perennial), means of reproduction (wind vs. insect pollination), toxicity, rate of hybridization, and environmental tolerances, also inform the risk assessment process. Details of the recipient plant's genetic structure, such as its genetic stability and the ability of the plant to exchange information with either other plants or microorganisms in close association with it, provide the final information necessary to place a potential recipient plant into a safety class.[18]

TABLE 6.2: Summary of the general criteria used to assign a recipient organism to a safety class.[17]

Safety Class	Criteria
I	History of safe use regarding human and environmental health
	Low potential to become hazardous to human and environmental health
	Short-lived and unlikely to survive outside of laboratory conditions
II	May pose a low risk to human and environmental health
	Minimal risks can be entirely avoided through safety control measures
II	May pose a medium risk to human and environmental health
	Medium risks can be basically avoided through control measures
IV	May pose a high risk to human and environmental health
	Likely to have a high rate of genetic exchange with other organisms
	Escape is unpreventable with known control techniques
	No effective control strategies are known in the event of escape

16 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Article 4.

17 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Article 11.

18 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Appendix I. § I (1).

2. Donor Organism

In China's risk assessment framework, only limited information regarding the donor organism (i.e. the name) is required during the risk assessment process. It further appears that, in the event that multiple donor organisms are used (for example, if one provides the promoter and terminator while the other provides the marker and reporter genes), the name is required of each.[19]

3. LMO Characteristics

As described in section III.D above, China's risk assessment process includes conducting an assessment of the "safety type" of the genetic manipulation used to create a new LMO. To do this, assessors consider information pertaining to the vector used in the transformation event, the genetic information inserted into the genome of the recipient organism, and the expected changes in phenotype of the resulting LMO.[20]

When considering the vector, primary information of interest is the name, structure, and the source of the vector itself. In addition, the pathogenicity of the vector, particularly its potential to become pathogenic as a result of the manipulation process, is considered. Within these categories, one specific piece of information required by the framework documents is the physical map of the vector organism's genetic material, including where in the target gene it is found.[21]

Additional information used to assess the safety of the genetic manipulation utilized to create an agricultural LMO are the specific structure and function of the inserted genetic material (DNA sequence of the introduced gene, promoter, terminator, marker genes, reporter genes, and any regulatory sequences involved) and the technique used to accomplish the insertion.[20] The risk assessment of the genetic manipulation further requires information regarding the structure(s) within the plant where traits coded for by the inserted material are expected to be expressed and how that expression can be identified and quantified.[22] We were not able to find in the framework documents details regarding how this identification should be done, but the BCH and CBCH both host several documents describing polymerase chain reaction (PCR) techniques that have been approved for this purpose.

As a final step towards determining the safety type of the transformation event used to produce a LMO, comprehensive data regarding the new organism, particularly its genetic stability[23] and how it differs biologically from the recipient organism[24] must be collected and offered for review. Key parameters of interest for assessing differences between the LMO and its parent organism include form and rate of reproduction, dispersal ability, survival and competitive abilities, ability to transfer genetic material to other organisms in close association with it, and the potential for the LMO to become a weed. In the specific case of LMOs modified with insect resistance traits, impacts on target and non-target organisms[24] must also be determined (see *Report No. 953*[14] for an example). When applicable, additional information pertaining to human health, such as toxicity, allergenicity, and antibiotic resistance, must also be considered when making the final risk classification decision.[25]

> geographic and ecological information regarding the receiving environment must be presented in an experimental plan for any proposed field trials

19 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Appendix I. § I (2.4).

20 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Appendix I. § I (2).

21 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Appendix I. § I (2.3).

22 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Appendix I. § I (2.6).

23 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Appendix I. § I (3.1).

24 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Appendix I. § I (3.2).

25 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Appendix I. § I (3.3).

4. Receiving Environment

While not explicitly playing a role in the categorization of LMOs to a risk class (the environment in which the recipient organism is found is considered during that process[26]), geographic and ecological information regarding the receiving environment must be presented in an experimental plan for any proposed field trials. Information required in all cases include topographic and isolation maps[27] and "actual position"[28] of the experimental site (we could not find a clear definition of the latter term), general climatic characteristics, and a list of animal species around the site (including their conservation status, if any). If other plants are nearby, a list of present species must be produced, with particular attention paid to their weediness. Furthermore, a description of any environmental factors that may affect (positively or negatively) the ability of the LMO to survive, reproduce, disperse, or spread into the surrounding environment, with particular attention paid to how these factors affect the possibility of gene transfer from the LMO to nearby organism, must also be provided for review. These data are required for all cases, but slight differences exist between assessments for LMOs tested in an "agricultural ecosystem" versus those tested in a "natural ecosystem." In the former case, information regarding diseases and pests of the crop, along with their prevalence and severity, must be provided, while in the latter case the distance from the test plots to areas of agriculture is required.[28]

B. EVALUATION OF THE LIKELIHOOD OF ADVERSE EFFECTS BEING REALIZED, TAKING INTO ACCOUNT THE LEVEL AND KIND OF EXPOSURE OF THE LIKELY POTENTIAL RECEIVING ENVIRONMENT TO THE LIVING MODIFIED ORGANISM

1. Intended use of LMO compared to recipient or parental organism

We were not able to find any text in the framework documents requiring comparison of the intended use of the LMO to that of the unmodified the recipient organism when determining the likelihood of occurrence of any risks associated with an LMO.

2. Characteristics of relevant potential receiving environment

We were not able to locate within the text of the framework documents any references to the role(s) that the characteristics of a potential receiving environment might play in affecting the likelihood of occurrence of adverse effects resulting from the release of an LMO.

3. How incidental exposure to the environment could occur

We were not able to locate within the framework documents an explicit requirement to consider specific pathways of exposure of LMOs to the environment. However, based on the list of information required during the risk assessment process and the detailed biosafety regulations provided therein, it appears that the primary pathways of concern involve the transport of pollen by insects or wind from experimental laboratories and field sites into the environment. These concerns are evident in the requirement that the form of reproduction, including if it is accomplished with the aide of insect or wind pollination, must be identified[29.] Furthermore, the biosafety framework documents stipulate that in laboratories working with safety class II organisms "a solarium to prevent entry of insects" must be set

26 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Article 13.

27 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Appendix I. § III (1).

28 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Appendix I. § II (1).

29 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Appendix I. § I (1.2).

up[30]. In the case of field tests, isolation distances for several major crops are also provided for use in risk management (Appendix 6).

4. Conclusion of evaluation of likelihood of exposure

We were not able to find any specific references in the primary framework documents requiring a determination of the likelihood of exposure of the environment to a LMO. *Notice No 953,*[14] however, describes an experiment designed to determine the distance that herbicide-resistance may be conveyed by airborne pollen. Furthermore, during the process of assigning a recipient organism to a safety class, the ability to avoid adverse effects through the use of biosafety practices plays a role in determining the safety class of the recipient organism.[17] As the ability to avoid these adverse effects decreases (i.e. as likelihood of exposure increases), the safety class of the recipient organism also increases.

C. EVALUATION OF THE CONSEQUENCES SHOULD ADVERSE EFFECTS BE REALIZED

Based on the language used in the framework documents, it appears that the primary consequences of interest are those resulting from weediness of the LMO, gene flow from a LMO to neighboring organisms (including plants, animals, and microorganisms), development of insect resistance to LMOs,[31] development of herbicide tolerance in plants located near LMOs containing those traits, and general non-target effects.[24]

We were not able to find in the framework documents a specific description of the expected consequences, but the experiments described in *Notice No 953*[14] measure herbicide tolerance of unmodified plants grown near herbicide-resistant maize and changes in abundance of insects in LMO and unmodified treatment plots.[14]

the ability to avoid adverse effects through the use of biosafety practices plays a role in determining the safety class of the recipient organism

D. ESTIMATION OF THE OVERALL RISK POSED BY THE LMO BASED ON THE EVALUATION OF THE LIKELIHOOD AND CONSEQUENCES OF THE IDENTIFIED ADVERSE EFFECT BEING REALIZED

The third step in China's risk assessment process for LMOs is an assessment of the modified organism itself. This process involves an integration of the recipient organism safety class as described in Section IV 1A above with the safety assessment of the manipulation as described in Section III D. Instructions are provided within the framework documents that indicate how different combinations of recipient organism safety class and manipulation type determine the final safety class of a proposed LMO.[26] These instructions are not so much strictly formulaic as they are guidelines for assessors to work within, which allows for professional judgment when necessary. For example, a LMO generated through a type 1 or type 2 manipulation of a safety class I recipient organism can be classified as either safety class I or safety class II, whereas a LMO generated through a type 3 manipulation of a safety class I or safety class II organism may classified as a safety class I, II, or III, depending on the change in safety, the ability to avoid risks, and the ability to mitigate consequences[26] (Table 3). Since genetic manipulations may affect different organisms in different ways, this judgment-based system allows species-specific information to be considered during the assessment process.

30 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Appendix IV (2.2.1).

31 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Appendix I. § III (4.5.10).

TABLE 6.3: Determination of the safety class of the final LMO based on the integration of the safety class of the recipient organism with the safety type of the genetic manipulation. Roman numerals in the boxes are possible options for safety class for a LMO for each combination of recipient risk class and manipulation safety level. Darker levels of shading represent increasing maximum safety class for the LMO. The presence of a '*' indicates a combination where professional judgment regarding relative changes in the safety of the LMO compared to the recipient organism plays a role in determining the final risk classification.[26]

Matrix of Risk Classifications of LMOs				
Safety Level of Manipulation	Safety Class of Recipient Organism			
	I	II	III	IV
1	I	I,II*	I,II,III*	I,II,III,IV*
2	I	II	III	III,IV*
3	I,II,III,IV*	II,III,IV*	III,IV*	III,IV*

We were not able to find in China's framework documents a discussion of the relative risks associated with stacked events or interactions of existing genes with introduced genetic material. Risks to biological diversity, the environment, and human health posed by a LMO are all considered during the process of assigning a LMO to a safety class.

E. RECOMMENDATION AS TO WHETHER THE RISKS ARE MANAGEABLE, INCLUDING, WHERE NECESSARY, IDENTIFICATION OF STRATEGIES TO MANAGE THESE RISKS

The final decision regarding whether risks are manageable is incorporated into the final risk classification for a LMO, as described in the immediately preceding section. China's risk assessment framework documents provide extensive risk management guidelines for studies conducted in both laboratory and field settings.[32] These risk management strategies, designed to "restrict the survival and spread of genetically modified organism [*sic*] and its products outside the experimental areas"[3] are divided into physical, chemical, biological, environmental, and scale controls.

The final decision regarding whether risks are manageable is incorporated into the final risk classification for a LMO

Examples of these controls include installation of fences, disinfection of tools and facilities, spatial and temporal isolation, artificially controlling photoperiod or other environmental parameters, and reducing the number of LMOs in cultivation, respectively. The exact set of risk management practices used varies depending on the safety class of the LMO in question (e.g. LMOs of safety class I are subject to the minimal standards of safety class I controls, while higher-risk LMOs of safety class 3 are subject to the more stringent safety class III controls; see Table 6.4)

32 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Appendix IV.

TABLE 6.4: Different control (i.e. risk management) measures required by China's framework documents for experiments conducted in the field using LMOs of different safety classes.[33]

Safety Class	Control Measures
I	Biological isolation
II	Safety Class I +
	Solarium to restrict movement of insects
	Sterilize tools
III	Safety Class II +
	Specialized facilities for raising and disposing of LMOs
	Prevent LMOs being carried outside of experimental areas
	Eliminate plants, animals, and microorganisms that are not associated with the experiment
	Control the experimental scale
	Sterilize or destroy any residual LMO material
IV	More stringent versions of Safety Class III

China's framework documents stipulate that identification of plant LMOs should be possible during all periods of testing, but we did not find prescribed ways in which this should be done. However, China has published a series of documents on the Convention on Biological Diversity's Biological Clearing House website detailing the different methods (mostly involving PCR analyses) that have been developed since the publication of the framework documents for detecting specific combinations of recipient organism and novel trait.[2]

Administrative oversight of the monitoring of LMOs in their respective receiving environments is within the domain of the Ministry of Agriculture[34] as well as the agriculture administrative departments at the county and province level.[35]

However, we were not able to determine which specific subunit of the Ministry has that function. It appears that the entity conducting LMO research and testing is responsible for actually conducting monitoring activities during normal research and testing operations.[36] China's framework documents explicitly refer to standard monitoring activities in and around experimental plots only after the final harvest and conclusion of a field test.[37]

> China's framework documents require that emergency measures for reacting to an accidental release of LMOs or their derivatives to the environment be provided at the time of application for a permit to conduct field experiments.[38]

China's framework documents require that emergency measures for reacting to an accidental release of LMOs or their derivatives to the environment be provided at the time of application for a permit to conduct field experiments.[38] In the event of accidental spreading of LMOs, research sites must be closed and an investigation into the cause and consequences of the escape must be conducted. If the consequences impact human health, personnel who may have been exposed must be treated. Finally, the affected areas must be continuously monitored until all risks associated with the LMO escape have been neutralized.[39] We were not able to find examples of explicit methods for countering specific exposure events.

33 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Appendix IV (2).
34 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Article 31.
35 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Article 32.
36 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Article 34.
37 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Appendix I. Section II (3.5).
38 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Appendix I. Section II (3.3).
39 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Appendix IV (3).

F. WHERE THERE IS UNCERTAINTY REGARDING THE LEVEL OF RISK, IT MAY BE ADDRESSED BY REQUESTING FURTHER INFORMATION ON THE SPECIFIC ISSUES OF CONCERN OR BY IMPLEMENTING APPROPRIATE RISK MANAGEMENT STRATEGIES AND/OR MONITORING THE LMO IN THE RECEIVING ENVIRONMENT

In general, uncertainty regarding the level of risk posed by a LMO is addressed during the qualitative assessments of both the recipient organism and the genetic manipulation. In both cases, uncertainty results in classification of that parameter in a higher risk category. Integration of these higher risk rankings then results in a higher safety classification of the LMO (see Table 6.3). This, in turn, results in stricter biosafety controls at research and development sites.[33] In the event than a LMO is found to be hazardous to the environment, the Ministry of agriculture may recall the safety certificate and ask the developer to destroy any remaining LMO tissues.[40]

V. Discussion

The framework documents require that a report be submitted to the OBA following completion of one stage of testing before the next stage can begin, but it was not clear if that report constituted an entire risk assessment or if it was a small-scale progress report. It was also not clear from the framework documents why this step-wise process had been adopted. It is entirely possible that it is a precautionary approach whereby risks and consequences are reassessed at each increasing spatial scale, but we were not able to find language to that effect and we felt it would be inappropriate to speculate in our review as to the purpose of this design.

China's risk assessment process also contains one additional level of assessment, in which the products of LMO are assigned to a safety class based on the degree to which the risk associated with them changes as a result of processing.

As described in the framework documents, this did not appear to apply to environmental release, so it was not included in this review. Provision of some examples of processing techniques would have clarified if this referred to harvesting practices, in which case it would likely be applicable to this review, or methods used in production facilities, which would probably not qualify.

In general, uncertainty regarding the level of risk posed by a LMO is addressed during the qualitative assessments of both the recipient organism and the genetic manipulation. In both cases, uncertainty results in classification of that parameter in a higher risk category.

We were not able to find within the framework documents any explicit references to "transparency" in the risk assessment process. Transparency has nonetheless been achieved in part through the availability of framework documents for public viewing and also through the detailed description of the general processes used to arrive at assessment decisions. Additional aspects of transparency, such as public comment and participation or promulgation of completed risk assessments in a federal publication akin to the Federal Register in the United States or the Federal Gazette in Brazil, were not located within the framework documents. The fact that the National Biosafety Clearing-House of China website is not described in the framework documents and yet exists as a forum for public education and document presentation may be an indication that additional efforts towards achieving transparency have been made since the publication of the primary framework documents.

We were unable to find any references to risks associated with LMOs in the context of their intended use compared to their corresponding unmodified recipient organisms. This may be because most genetic manipulations are conducted for the purposes of enhancing an existing trait or adding a new trait while not changing the intended use.

40 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Article 38.

We did not find any language in the framework documents specifically referring to determining the 'probability' or 'likelihood' of occurrence of adverse effects associated with LMOs. One example of language hinting at this concept stipulated that a recipient organism might be assigned to a low-risk safety classification if it had 'little possibility to survival [sic] in a natural enviroment after the completion of experiments17.' This suggests that the overall risk classification of an LMO might vary depending on release location (e.g. a lower risk classification at a site at which environmental conditions are harsher and thus exposure of the environment to the organism lower). However, as we found no additional language to support this hypothesis, it should be considered speculative.

At times we experienced great difficulty interpreting China's approach to risk assessment of agricultural LMOs because many of the sections of the framework documents that we reviewed contained vague terminology. For example, we were unable to determine what constitutes 'high' or 'low' risks (as used in Table 6.2, above) to human or environmental health. Similarly, the term 'harmful influences' as used in Table 6.1 (above) was not defined. Some aspects of the risk assessment process, such as the kinds of studies that need to be performed to gather sufficient data to make determinations of risk were not found. It was also not clear how many administrative levels an application for research or testing must go through before it reaches the OBA. The text of the framework documents only stipulates that the relevant agricultural department at or above the county level must approve it first. This could mean that it is reviewed only once (county level) or up to three times (county level, prefecture level, and province level). It was also not clear what options are available to an applicant if an application is approved at one level but not approved by another. Another point that was not clear is if the National Biosafety Committee has any legal authority or if its decisions are merely recommendations to be considered by the OBA.

The simplest explanation for the vagueness that we perceived in China's risk assessment framework documents is that, given that even the official versions that we reviewed had been translated from Mandarin Chinese, subtleties in definitions, process descriptions, administrative structure, and references to experimental methods were lost or misinterpreted.

With a few exceptions, most notably the lack of explicit use of the precautionary principle and a lack of discussion of public participation in the risk assessment process, China's framework for risk assessment of agricultural LMO plants satisfies the overall goal of Annex III of the Cartagena Protocol on Biosafety. Risks associated with each new combination of recipient organism and genetic modification are evaluated in the context of an unmodified counterpart and based on data collected using scientifically valid procedures. Strategies to manage the identified risks are then provided, with a range of stringency depending on the relative severity of overall risk of a LMO. Review of application and assessment materials at multiple levels (LMO developer, regional agriculture administration, national administration) may increase the likelihood that critical flaws in experimental design or risk management are caught early, reducing the potential for environmental harm. Only time will tell if China's LMO RA framework, as currently written, is strong enough yet flexible enough to cope with technological developments in what is a rapidly changing field.

APPENDIX

APPENDIX 6: Isolation distance for some crops.[41]

Crop Species	Isolation Distance (m)	Note
Zea mays L.	300	Or isolation of florescent stage for over 25 days
Triticum aestivum	100	Or isolation of florescent stage for over 20 days
Hordeum vulgare	100	Or isolation of florescent stage for over 20 days
Brassica spp.	1000	-
Gossypium spp.	150	Or isolation of florescent stage for over 20 days
Oryza sativa L.	100	-
Glycine max L. Merrill	100	-
Lycopersicum esculentum Mill	100	-
Nicotiana tabacum	400	-
Sorghum vulgare Pers.	500	-
Solanum tuberosum L.	100	-
Cucurbita pepo	700	-
Trifolium repens	300	-
Lolium perenne	300	-
Capsicum annum	100	-

41 Implementation Regulations on Safety Assessment of Agricultural Genetically Modified Organisms (IRSAAGMO). 2001. Ministry of Agriculture, People's Republic of China. Appendix IV (Table 1).

Chapter 7. Cuba: Elements of risk assessment for LMOs

I. Abstract

In 1996, Cuba centralized all risk assessment and management of living modified organisms (LMOs) within the Ministry of the Environment's National Biosafety Center.[1] Cuban regulatory documents require that institutions and companies seeking to use a LMO for research or commerce in Cuba submit information relating to its potential risks. All LMOs are placed in risk classes and subject to associated guidelines for their use in laboratory settings. However, this risk class is not taken into consideration in decisions about release into the environment. Applicants for licenses to study or release a LMO in Cuba must submit descriptions of the biology and taxonomy of the donor and recipient organisms, as well as information on the expression and function of the inserted transgene and its vector. Characteristics of the receiving environment emphasize the biological diversity of the receiving environment and how the environment is used by humans. Unique characteristics of the LMO and its potential interactions with other organisms, including humans, must also be provided. A few potential adverse effects, such as gene transfer, are specifically mentioned, but most must be inferred from the required information. The National Biosafety Center has 90 days to approve, decline or postpone the granting of a biosafety license. Each LMO licensed for use in Cuba is posted on the National Biosafety Center website along with a brief risk assessment summary and a plan to minimize any perceived risks. Regulatory frameworks of Cuba state that a lack of information is not interpreted as the absence of risk.

II. Overview of legislative & regulatory framework

The main body responsible for risk assessment for living modified organisms (LMOs) in Cuba is the National Biosafety Center (CSB), which was established in 1996 and is housed under the Ministry of Science, Technology and the Environment (CITMA).[1] Prior to the establishment of the National Biosafety Center, regulation of LMOs in Cuba was spread out among diverse areas such as public health, plant health, workplace, and the environment.[1] In 1984 the first biosafety commission was developed.[1] and in 1999 Decree 190 charged the CSB under CITMA with centrally regulating "biological agents" and their derivatives.[2] "Biological agents" are placed into 3 categories: 1) Micro-organisms and pests, 2) LMOs, and 3) toxins.[3]

1 Compendio de legislación de seguridad biológica: *Una guía para la gestión. Centro Nacional de Seguridad Biológica.* 2006. (translated as "Compendium of Biosafety Legislation. A Management Guide. National Biosafety Center"). Habana, Cuba. p. 6.

2 Decreto-Ley 190 de La Seguridad Biológica. 1999. (translated as "Decree 190 on Biosafety") Ministry of Science, Technology and the Environment, Republic of Cuba.

3 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. (translated as "Resolution 76. Regulations for the granting of biosafety authorizations.") Annex I, part 3.1-3.3 Ministry of Science, Technology and the Environment, Republic of Cuba.

Three primary responsibilities of the CSB that relate to LMOs are:

1. Organize, direct and execute inspections of institutions and land where biological agents and their derivatives are used or liberated
2. Grant, suspend and revoke authorization for activities related with the use, investigation, tests, production, release, import and export of biological agents and their derivatives.
3. Establish risk classes for biological agents based on risks to the environment, agriculture, and human and animal health.[4]

Any release of a LMO into the environment requires a "biosafety license" which must be granted by the CSB under CITMA.[5] CITMA has 90 days to rule on applications for biosafety licenses[6] and can approve, postpone or deny the granting of a biosafety license.[7] Once granted, the license must be periodically renewed[8] and can be revoked if any terms of the license are not met.[9] In addition to issuing these licenses, CITMA regulates some other activities involving LMOs, such as remodeling labs that handle LMOs, that require only a "biosafety permit"[10] which can sometimes be granted by regional authorities delegated by CITMA.[11]

CITMA also classifies biological agents into risk classes[12] that are used to determine lab safety guidelines, but are not considered in risk assessments for biosafety licenses.[13]

> Once granted, the license must be periodically renewed[8] and can be revoked if any terms of the license are not met.[9]

The legal framework for risk assessment in Cuba is set forth in Decree 190 on Biological Safety and subsequently elaborated in a series of resolutions (Table 7.1).

TABLE 7.1: Cuban Resolutions Elaborating Decree 190, 1999

Resolution/Title	Summary
42/99. Lista oficial de agentes biologicos en grupos de riesgo.	Sets standards for putting organisms into risk classes.
8/00. Reglamento general de seguridad biologica para las instalaciones que manipulan agentes biologicos y sus productos, organismos y fragmentos de estos con informacion genetica	Regulations for labs that manipulate biological agents, LMOs and their products
76/00. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica	Information required for LMO permits
103/02. Reglamento para el establacimiento de los requisitos y procidimientos de seguridad biologica en las instalaciones en las que se hace uso de agentes biologicos y sus productos, organismos y fragmentos de estos con informacion genetica	Elaborated regulations and procedures for labs
2/04 . Reglamento para la contabilidad y el control de materiales biologicos, equipos y tecnologia aplicada a estos.	Accountability and control related to biological materials

4 Decreto-Ley 190 de La Seguridad Biológica. 1999. Ministry of Science, Technology and the Environment, Republic of Cuba, chapter 2, section 1, article 4.

5 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba. Section 1 article 11.

6 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba. Section 1 article 16.

7 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba. Chapter II, Article 6.

8 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba. Chapter III, Section 2, Article 23.

9 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba. Chapter III, Section 1, Article 18.

10 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba. Chapter II, Article 7.

11 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba. Chapter V, Section 3, article 29.

12 Resolución 42. Lista oficial de agentes biologicos en grupos de riesgo. 1999. (translated as "Resolution 42. Official list of biological agents in risk groups"). Ministry of Science, Technology and the Environment, Republic of Cuba.

13 Decreto-Ley 190 de La Seguridad Biológica. 1999, Ministry of Science, Technology and the Environment, Republic of Cuba, Chapter 2, Section 1, part a.

The following description of the risk assessment process in Cuba is based on Decree 190, the resolutions listed in Table 1, a compendium of risk assessment legislation published by the CSB,[14] risk assessment summaries posted on the CSB website,[15] and the Biosafety Clearing House website maintained by the Convention on Biological Diversity.[16]

All documents were posted in Spanish. Cuba uses the terms genetically modified organism (GMO) and living modified organism (LMO) interchangeably within these documents.

III. General principles

A. SCIENTIFICALLY SOUND

Cuba defines risk evaluation as a systemic process of analysis and quantitative and qualitative evaluation of potential risks in the area of concern with the objective of eliminating or controlling risk.[17] Cuba's regulatory frameworks state that risk assessment should be scientifically competent[18] but the term is not defined. A detailed list of biological information is required by applicants for approval for release of a LMO into the environment.[19] Information about human populations nearby, such as the size of neighboring populations and the proximity of the LMO release to important water sources, is also required,[19] suggesting that community concerns may be considered as part of the risk assessment process. Aside from the Cartagena Protocol,[20] references to international risk assessment standards relating to LMOs were not located within the documents reviewed for this analysis.

> Information about human populations nearby, such as the size of neighboring populations and the proximity of the LMO release to important water sources, is also required,[19]

B. TRANSPARENCY

Cuba addresses transparency by explicitly stating the information required of applicants seeking to use or release LMOs in Cuba[19] and by notifying the public of LMO approvals.[21] Although the Cuban documents do not specify the ways in which the public is be notified, the CSB website shows a list of LMOs approved for field studies, along with a brief summary of the risk assessment that was conducted prior to their approval.[15] A more complete list of LMOs approved for study in Cuba is posted on the Biosafety Clearing-House website of the Convention on Biological Diversity.[16] Legislation regarding LMOs is made publicly available on both the CSB and Biosafety Clearing House websites[22] and is published in the Federal Register of Cuba known as the "Gaceta Oficial."

C. LACK OF SCIENTIFIC KNOWLEDGE OR CONSENSUS DOES NOT INDICATE LEVEL OR ABSENCE OF RISK

Regulations published in Cuba state that lack of scientific information does not indicate the absence of risk or of an acceptable risk.[23] The latter part of this statement may indicate that not detecting a risk does not mean that the risk is likely to be small.

14 Compendio de legislación de seguridad biológica: *Una guía para la gestión. Centro Nacional de Seguridad Biológica.* 2006. Habana, Cuba.

15 Centro Nacional de Seguridad Biologica (CBS) website, Informaciones section. National Biosafety Center website, Information section. Accessed December 15, 2009. http://www.medioambiente.cu/oregulatoria/cnsb/Informaciones.html.

16 Biosafety Clearing-House website, Convention on Biological Diversity. Cuba country decisions. Accessed December 15, 2009. http://bch.cbd.int/database/results-v4.shtml?searchid=413768.

17 Resolución 8. Reglamento general de seguridad biologica para las instalaciones que manipulan agentes biologicos y sus productos, organismos y fragmentos de estos con informacion genetica. 2000. (translated as "Resolution 8. General biosafety regulations for facilities manipulating biological agents and their products, organisms and their fragments with genetic information"). Chapter 1, Article 3.

18 Compendio de legislación de seguridad biológica: *Una guía para la gestión. Centro Nacional de Seguridad Biológica.* 2006. Habana, Cuba. Annex III. Number 3, npg.

19 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba. Annex II.

20 Compendio de legislación de seguridad biológica: *Una guía para la gestión. Centro Nacional de Seguridad Biológica.* 2006. Habana, Cuba. p.137.

21 Decreto-Ley 190 de La Seguridad Biológica. 1999, Ministry of Science, Technology and the Environment, Republic of Cuba, Chapter 2, Section 2, c.

22 Centro Nacional de Seguridad Biologica (CBS) website, Legislaciones section. National Biosafety Center website, Legislation section. Accessed December 15, 2009. http://www.medioambiente.cu/oregulatoria/cnsb/legislaciones.html.

23 Compendio de legislación de seguridad biológica: *Una guía para la gestión. Centro Nacional de Seguridad Biológica.* 2006. Habana, Cuba, Annex III, section, 4, npg.

D. RISK CONSIDERED IN THE CONTEXT OF RISK POSED BY NON-MODIFIED RECIPIENTS OR PARENTAL ORGANISMS

> Finally, methods (as well as data on their efficacy) must be provided to distinguish the LMO from non-modified organisms after release.[26]

Comparing the risk of LMOs to that of similar, non-modified organisms is part of the risk assessment framework in Cuba. The stability of the LMO must be compared to that of its non-modified counterpart in a lab setting and that known differences between natural and LMO types should be described by the applicant.[24] A second document implies such a comparison by stating that genotypic and phenotypic characteristics *unique* to the LMO should be considered.[25] Applicants for permission to use a LMO in Cuba must also submit an assessment of "substantial equivalency" to the non-modified counterpart,[24] although we were unable to locate guidelines for the type of data required within this assessment. Finally, methods (as well as data on their efficacy) must be provided to distinguish the LMO from non-modified organisms after release.[26]

E. CASE-BY-CASE BASIS

In reference to "case by case basis," Cuba states that risk assessments will be conducted depending on the LMO, its use, and its likely receiving environment.[27] However, the application information required for LMO research or release permits in Cuba is the same regardless of the type of LMO under consideration.[19]

Risk assessments must be conducted for each "genetically modified organism" (organismo modificado geneticamente), which is defined as "an organism whose genetic material has been modified by man in a way that is different from natural modification" (translated from the original Spanish).[28] This definition could have different meanings depending on what is considered different from natural modification. However, we were unable to locate further detail about what triggers a risk assessment within the documents reviewed.

IV. Methodology

A. IDENTIFICATION OF NOVEL GENOTYPIC AND PHENOTYPIC CHARACTERISTICS ASSOCIATED WITH LMO, THAT MAY HAVE ADVERSE EFFECTS ON BIOLOGICAL DIVERSITY IN THE LIKELY POTENTIAL RECEIVING ENVIRONMENT, ALSO TAKING INTO ACCOUNT RISKS TO HUMAN HEALTH

1. Recipient/Parental Organism

Before releasing a LMO into the environment, applicants are required to assemble detailed information on the biology of the recipient organism. The recipient must be identified to species and, if possible, to biotype. Additionally, the institution and individuals responsible for this identification must be listed and a sample of the organism must be accessible for confirmation. If the recipient is a micro-organism, the method of identification must also be described within the application.[29] The applicant must submit the common name of the organism, the location it was acquired[30] and describe the species' geographic distribution, center or origin and the ecological conditions where the organism develops.[31]

24 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba. , Annex II, section 1.4, 5 a-b.

25 Compendio de legislación de seguridad biológica: *Una guía para la gestión. Centro Nacional de Seguridad Biológica.* 2006. Habana, Cuba, Annex III, section 8, a, npg.

26 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba., Annex II, section 2.2, c and d.

27 Compendio de legislación de seguridad biológica: *Una guía para la gestión. Centro Nacional de Seguridad Biológica.* 2006. Habana, Cuba. Annex III, section 6, npg.

28 Decreto-Ley 190 de La Seguridad Biológica. 1999, Ministry of Science, Technology and the Environment, Republic of Cuba . Chapter 1, Article 3.

29 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba., Annex II. Part 1, 1.1, a-d.

30 Compendio de legislación de seguridad biológica: *Una guía para la gestión. Centro Nacional de Seguridad Biológica.* 2006. , Annex I, e, npg.

31 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II. Part 1, 1.2, a-d.

The applicant is also required to provide characteristics of the parent organism that might relate to biosafety.[30]

The Cuban framework also requires that applicants document how the organism might interact with other species and with its receiving environment. For example, how the organism reproduces, survives, competes and defends itself must be considered and its predators and competitors listed. Additionally, the organism's possibility of crossing with other organisms must be evaluated. Information on the tolerance of the recipient organism to different climates as well as its reproductive cycle, tolerance to disease, and its potential to adapt in its environment must also be submitted.[32]

Within the documents we were able to review, we found no direct statement regarding the specific adverse effects that could be considered during a risk assessment in Cuba. However, the CSB website does show brief risk assessment summaries for LMOs approved for small scale (300m^2 or less) field trials and all of these refer specifically to the potential for gene flow and how it could be minimized[15] so gene flow between the LMO and other organisms or uncontrolled spread of the LMO is an adverse effect that may be considered. The detailed information required on how the parental organism interacts with other species also suggests that non-target effects on species in the receiving environment are considered. Additionally, requiring information on the potential of the parental organism or the LMO to adapt suggests applicants should consider evolutionary processes when identifying adverse effects.

2. Donor Organism

Cuban regulations require that characteristics of the donor be provided by the applicant[33] but the specific information requested includes only its taxonomy[34] and source.[33]

3. LMO Characteristics

Cuba requires that the source, function[35] and intended use of the insert within Cuba[36] be reported by the applicant, in addition to the potential impacts of the insert on human, vegetable or animal health.[35] The nucleic acid sequence and its number of copies, location, and expression in the final product must also be provided.[35] Details on the vector including its complete nucleic acid sequence, natural source, method of insertion and presence in the final product must also be submitted. [37] The concern that the vector could introduce the insert into other hosts is reflected in the requirement to provide information on the stability of the vector and its capacity to transfer and establish itself in other hosts.[37] Cuba also requests information on the previous uses of the LMO (see subsequent section IVB part 1) and on the characteristics of the LMO in comparison to an unmodified counterpart (see previous section IIID).

As biological agents, LMOs are also subject to classification into risk classes by CITMA.[12] Although these risk classes are for the safe handling of biological agents in laboratory settings and are not to be used as part of the risk assessment for release into the environment[13] they do list potential adverse effects to plants, animals and humans (Table 7.2) that presumably would be important in Cuba. These include adverse effects on biological diversity such as impacts to protected plants, adverse economic effects (via harm to plants or animals of commercial importance) and effects to human and animal health.

32 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II. Part 1, 1.3, a-j.

33 Compendio de legislación de seguridad biológica: *Una guía para la gestión. Centro Nacional de Seguridad Biológica.* 2006. Habana, Cuba, Annex I, g, npg.

34 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II, section 1, part 1 a and b.

35 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II, section 1 part 4.

36 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II section 2.

37 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II., section 1 part 3.

TABLE 7.2: Risk classes descriptors based on Resolution 41/1999[12]

	Effects on Humans	Effects on Other Animals	Effects on Plants
Level 1	Individual risk low, community risk low, very unlikely to cause disease in healthy workers	Individual risk low, community risk low, very unlikely to cause disease in animals	Affects plants of minor importance
Level 2	Individual risk moderate, community risk low, can cause disease but no serious risk to healthy workers, community or environment	Have little risk of spread, socio-economic and health consequences are not serious.	Affects protected plant species or could cause economic losses.
Level 3	Individual risk high, community risk low, can spread from an infected person to another but usually there are preventative measure and effective antibiotic treatment	Individual risk high, community risk moderate, causes disease that could have economic impact, limitations on international trade of animals and/or its products, may be in the country.	Cause severe damage in ecologically similar countries, are exotic to the county, represent a high risk for agriculture.
Level 4	High individual risk, high community risk, can cause serious illness in people and can spread from person to person with no specific preventative measures or effective treatment, exotic to the country	Pose high risk to staff due to rapid spread, have serious economic and health impact, restrictions on international trade in relation to their use, exotic to the country	

Increasing Risk ↓

4. Receiving Environment

Applicants seeking permits to use LMOs for research or commerce in Cuba must supply a substantial amount of information about the physical and ecological characteristics of the area in which the LMO might be released (Table 7.3).[38] Additionally, environmental conditions that affect the survival and multiplication of the LMO must be listed,[39] as well as the possibility of an excessive increase in the population of the freed organism in the environment.[40]

38 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II, sections 8 and 9.

39 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II, 3, h.

40 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II, 3, j.

TABLE 7.3: Characteristics of the receiving environment required of applicants for release of LMOs (based on Resolution 76/200038)

Abiotic	Biotic
Geography	Human settlements in proximity
Climate	Flora in proximity
Geology	Fauna in proximity
Soil and subsoil classification	Size of a nearby human population
Soil filtration	Ecosystems with proximity to release site
Presence of heavy metals	Biology of species present
Presence of other chemicals	Ecology of species present
Topography	Biodiversity in the receiving environment
Wind direction, speed, and seasonal variation	
Water temperature, salinity, and nutrients	

B. EVALUATION OF THE LIKELIHOOD OF THESE ADVERSE EFFECTS BEING REALIZED, TAKING INTO ACCOUNT THE LEVEL AND KIND OF EXPOSURE OF THE LIKELY POTENTIAL RECEIVING ENVIRONMENT TO THE LIVING MODIFIED ORGANISM

1. Intended use of the LMO compared to recipient or parental organism

The regulatory framework in Cuba states that the intended use of the LMO must be compared to that of the parental organism, and that this must be done by the National Biosecurity Center under the CITMA.[41] In line with this, the history of use of the LMO[42] as well as its planned use in Cuba and the volume to be used in Cuba[43,44] are required by applicants. The LMO's previous use and current information may be used to indicate that it is innocuous and compatible with long-term health and environment.[45]

> the history of use of the LMO[42] as well as its planned use in Cuba and the volume to be used in Cuba[43,44] are required by applicants.

2. Characteristics of relevant potential receiving environment

Cuba's risk assessment frameworks require documentation of characteristics of the receiving environment[38] (Table 7.3) and an evaluation of the level and type of exposure of the receiving environment to the LMO.[46] Resolution 76/2000 specifies interactions between the LMO and the receiving environment that must be considered. For example, the applicant must respond to whether there are adequate niches for the released LMO[47] and describe the potential competitive advantages of the LMO in relation to organisms present in the ecosystem.[48] Gene transfer between the LMO and organisms in the receiving environment must also be addressed, though the data required are not stated explicitly.[49] Summaries for LMO plants published on the National Biosecurity Center website focus heavily on the potential for gene flow between LMOs and their non-modified counterparts and the conditions under which it could happen.[15]

41 Compendio de legislación de seguridad biológica: *Una guía para la gestión. Centro Nacional de Seguridad Biológica.* 2006. Habana, Cuba, Annex III, section 8, d, npg.

42 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II., 1.5, 2,b.

43 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II, 1.5, c.

44 Compendio de legislación de seguridad biológica: *Una guía para la gestión. Centro Nacional de Seguridad Biológica.* 2006. Habana, Cuba, Annex I, j, npg.

45 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II, 5, b.

46 Compendio de legislación de seguridad biológica: *Una guía para la gestión. Centro Nacional de Seguridad Biológica.* 2006. Habana, Cuba, Annex III, section 8, b.

47 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II, 1.5, 3, e.

48 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II, 1.5, 3, i.

49 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II, 1.5, 3, g.

3. How incidental exposure to the environment could occur

Cuban regulatory documents refer to the need to evaluate the likelihood of adverse effects being realized[46] but the manner in which this is achieved was not described within the documents we reviewed. The required information for applicants does indicate some areas that Cuba regards as potential sources of exposure. For example, it is clear that escape from laboratory settings is considered a route for incidental exposure, because labs must meet strict standards[50] and the lab personnel must receive training in handling potentially hazardous LMOs.[51]Applicants must also submit plans to control human access to the LMO[52] and to keep the LMO isolated from natural organisms.[53]

In cases in which the LMO is not exported, disposal of waste is also a major concern, and those responsible for lab or field studies must report on the byproducts or waste that might be generated, their anticipated volume, their risks, and a plan to dispose of or transport them safely.[54]

For LMOs released into the environment, proximity to human and floral and faunal biological diversity is considered[38] (Table 7.3). Water is another potential exposure pathway; in addition to considering the proximity of sources of drinking water to LMO release sites,[55] soil hydrology and filtration[56] are specifically considered. The possibility that a LMO might spread beyond the planned receiving environment is acknowledged because applicants are required to submit plans to reduce potential spread.[57]

4. Conclusion of evaluation of likelihood of exposure

We were unable to find details on how likelihood of exposure is evaluated within the documents reviewed.

C. EVALUATION OF THE CONSEQUENCES SHOULD THESE ADVERSE EFFECTS BE REALIZED

Legal frameworks in Cuba specifically state that it is necessary to consider the consequences should these adverse effects be realized,[58] however, details on how this is accomplished were not located within the document we reviewed.

D. ESTIMATION OF THE OVERALL RISK POSED BY THE LMO BASED ON THE EVALUATION OF THE LIKELIHOOD AND CONSEQUENCES OF THE IDENTIFIED ADVERSE EFFECT BEING REALIZED

Cuba's legal framework for risk assessment of LMOs states that overall risk should be estimated based on the likelihood and consequences of the identified adverse effect being realized.[41] This information is required as part of the application to release a LMO into the environment.[59] However the way in which data will be combined to get an overall estimation of risk was not explained within the documents we were able to review. The provisions within Cuba's laws recommend more funding and training for conducting biosafety investigations and for training investigators[60] who presumably would be involved in generating data, combining data into an overall estimate of risk, or both.

50 Resolución 8, Reglamento general de seguridad biologica para las instalaciones en las que se manipulan agentes biologicos y sus productos, organismos y fragmentos de estos con informacion genetica. 2000.

51 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex III, c.

52 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II, 2.1., b.

53 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II, 2.1, c.

54 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II, 2.4, a-e.

55 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II, 1.5, m.

56 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II, 8, a-c.

57 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II, 2.3, a.

58 Compendio de legislación de seguridad biológica: *Una guía para la gestión. Centro Nacional de Seguridad Biológica.* 2006. Habana, Cuba, Annex III, 8, c, npg.

59 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II, 1.4, 2, k.

60 Decreto-Ley 190 de La Seguridad Biológica. 1999, Ministry of Science, Technology and the Environment, Republic of Cuba, Chapter 2, b.

E. RECOMMENDATION AS TO WHETHER THE RISKS ARE MANAGEABLE, INCLUDING, WHERE NECESSARY, IDENTIFICATION OF STRATEGIES TO MANAGE THESE RISKS

We were unable to find detailed guidelines for determining acceptable levels of risk within the documents we reviewed. However, after reviewing the application materials, the authorizing authority of the CSB under CITMA may deny granting a biosafety license either because the potential adverse effects are too many or because the risks are not justified by the anticipated benefit.[61] Cuba requires applicants for licenses to study or release LMOs to submit cost/benefit analyses[62] and these can be used to evaluate potential benefits as well as risks. The authorizing authority is required to produce a report detailing the reasons for decisions either to grant or to deny a license.[63] The CSB may grant licenses that are contingent on meeting conditions[9] such as those posted on the Biosafety Clearing House website intended to minimize the likelihood of adverse effects from LMO use.[15]

CITMA may deny granting a biosafety license either because the potential adverse effects are too many or because the risks are not justified by the anticipated benefit.

F. WHERE THERE IS UNCERTAINTY REGARDING THE LEVEL OF RISK, IT MAY BE ADDRESSED BY REQUESTING FURTHER INFORMATION ON THE SPECIFIC ISSUES OF CONCERN OR BY IMPLEMENTING APPROPRIATE RISK MANAGEMENT STRATEGIES AND/OR MONITORING THE LMO IN THE RECEIVING ENVIRONMENT

Cuba's legal frameworks allow the authorizing authority to request more information on issues of concern during the application[64] and a decision can be postponed until there is adequate time to collect more information.[65] When risks are uncertain Cuba may allow limited releases with conditions. For example, field trials for genetically modified sugar cane were approved on the condition that researchers implement strategies such as carefully disposing of any remaining plant material and monitoring the areas around the trials for escape, to minimize potential adverse effects.[15] Monitoring LMOs in the receiving area is required for all releases, and methods to detect LMOs, the sensitivity of detection methods, and the training of those responsible for monitoring must be provided by the applicant.[66] Additionally, those applying to release a LMO into the environment must provide a plan to protect people and the environment from negative effects[67] and for mitigating them in the event they occur.[68] Ultimately, if the LMO is discovered to have adverse effects, the CSB has the right to revoke the biosafety license for its use.[69]

Carefully managing labs where LMOs are studied[70] is another strategy employed by Cuba to manage risks of incidental environmental exposure. The Regulation System of Accountability and Controls was established in 2002 to inspect labs that handle biological agents including LMOs and enforce the guidelines set forth in Resolution 103 by closing insti-

61 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Chapter 3.
62 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II,1.5,a.
63 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Chapter 3, Article 21.
64 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Section I, Chapter 3, Article 9.
65 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Chapter 3 Article 19.
66 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II, 2.2, a-g.
67 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II, 2.3, d.
68 Resolución 76. Reglamento para el otorgamiento de las autorizaciones de seguridad biologica. 2000. Ministry of Science, Technology and the Environment, Republic of Cuba, Annex II, 2.3, e.
69 Decreto-Ley 190 de La Seguridad Biológica. 1999, Ministry of Science, Technology and the Environment, Republic of Cuba, Chapter II, c.
70 Decreto-Ley 190 de La Seguridad Biológica. 1999, Ministry of Science, Technology and the Environment, Republic of Cuba, Chapter 11 g.

tutions found to be non-compliant.[71,72] Applicants for biosafety licenses must also report how lab personnel will be trained and what strategies will be in place to ensure safe handling of LMOs.[51]

> Monitoring LMOs in the receiving area is required for all releases, and methods to detect LMOs, the sensitivity of detection methods, and the training of those responsible for monitoring must be provided by the applicant.

V. Discussion

Each LMO or LMO derivative intended for research or other use in Cuba must be evaluated by the National Biosecurity Center (CSB) under the Ministry for Science, Technology and the Environment. Required information from those seeking biosafety licenses for LMOs in Cuba is clearly stated and the risks of each LMO are considered in comparison to the risks of an un-modified counterpart. Decisions about whether a LMO is approved and the regulations that might accompany that approval are made by the CSB.

Although guidelines for applications for release into the environment are posted publicly, several aspects of risk assessment regulations in Cuba remain unclear, at least within the documents we were able to review. Although a definition of GMO is given and regulations state that all GMOs are subject to risk assessment, the definition is so broad that it could include products of conventional breeding. This could be intended to give the government more jurisdiction and flexibility in choosing what to assess or could be the outcome of a lack of technical expertise. In either case, clarification of the specific trigger for risk assessment seems to be underdeveloped. Information required by applicants seeking to use LMOs or their derivatives in Cuba is stated in Resolution 76. However, how the information compiled by the applicant and the CSB is used to characterize risk is never explained. Similarly, detail is not given regarding whether or how potential adverse effects and potential benefits are used to make a decision about a given biosafety license application. Additionally, whether the final decision of granting, postponing, or denying a biosafety license is made by the individual authority in charge of a case or a group was not clear.

A particularly interesting aspect of the Cuban legal framework is the power of the CSB to deny biosafety licenses on the grounds that the proposed technology does not have sufficient benefits to justify the risks. Weighing both benefits and risks is an approach in decision-making about release of LMOs into the environment that might, in the absence of clear benefits, make any risk unacceptable. This may be part of the reason that, according to records posted on the Biosafety Clearinghouse, Cuba has not approved many LMOs for release.

> guidelines for biosafety licenses require information about education and training that will be provided for researchers and staff working with LMOs

The focus on education in the Cuban legal documents we reviewed was another unique aspect of Cuban risk assessment. Decree 190 declares that training and money will be provided for education of scientists who specialize in biosafety in Cuba and guidelines for biosafety licenses require information about education and training that will be provided for researchers and staff working with LMOs. Additionally, lab safety guidelines specifically reference training for those working in institutions that handle LMOs.

71 Resolution 103. Reglamento para el establacimiento de los requisitos y procidimientos de seguridad biologica en las instalaciones en las que se hace uso de agentes biologicos y sus productos, organismos y fragmentos de estos con informacion genetica. 2002. Regulations for the establishment of the biosafety procedures and requirements in institutions that use biological agents and their products, organisms and their fragments with genetic information. 2002. Ministry of Science, Technology and the Environment, Republic of Cuba.

72 Decreto-Ley 190 de La Seguridad Biológica. 1999, Ministry of Science, Technology and the Environment, Republic of Cuba, Chapter II, h.

Another interesting aspect of Cuban risk assessment for LMOs is that it acknowledges the potential for the interactions between the LMO and its receiving environment to change. Detailed considerations for how the LMO might react to its receiving environment as well as the potential effects of interactions with the LMO on other species are required along with the potential for the LMO to adapt to its surroundings. Perhaps for this reason, monitoring of the LMO in the receiving environment is mandatory even for LMOs considered low risk.

Although Cuba requires public notification of the releases of LMOs into the environment, the dates on the Biosafety Clearing House website and the CSB website suggest that posted information is not current. However, these websites do confirm that Cuba has approved several LMOs for small-scale field trials. Although Cuban regulatory documents do not state that field trials are required, this may suggest that small-scale trials are required prior to unrestricted releases of LMOs in Cuba. Because these websites are not updated, it is unclear what LMOs are currently being studied or used within Cuba.

Chapter 8. Germany: Elements of risk assessment for LMOs

I. Abstract

Genetic engineering in Germany is regulated by the Gene Technology Act (GenTG) of 1990 which transposes the European Commission Directives 2001/18/EC (deliberate release of genetically modified organisms (GMOs) into the environment) and 2009/41/EC (contained use of GMOs) into national law. The GenTG stipulates that the competent federal authority, with input from the Central Commission on Biological Safety, authorizes the deliberate release of GMOs, whereas genetic engineering work (contained use of GMOs) is authorized by the authorities of the German federal states. Genetic engineering work is defined as the production, disposal, destruction, storage or internal transport of GMOs. The GenTG also requires that applications for the contained use of GMOs (i.e., in a containment facility) include particular documents, including a risk assessment of the potential harms to the health, life, or safety of humans, plants, animals, the environment, or material goods. The Directive 2001/18/EC (transposed in the national GenTG) regulates the deliberate release of GMOs into the environment, either for experimental (i.e., confined or isolated field trials) or commercial purposes. That document lists the requirements for applications for deliberate releases, including specific information that must be included in a risk assessment. The term "GMO" is used in both the GenTG and Directive 2001/18/EC rather than the term "living modified organism" (LMO), which appears in the Cartagena Protocol on Biosafety.

In the German framework, the trigger for a new risk assessment is process-based, hinging on the occurrence of genetic modification that does not occur through mating or natural recombination. Risk assessments themselves are product-based, focusing on GMO traits rather than on the modification procedure. The level of exposure to the environment (i.e., containment or release) determines the framework used. The type of organism (higher plant or not) determines what components must be included in the application for deliberate release. Proposed GMOs for contained use are assigned a risk class that partially determines the biological and occupational safety measures that will be required. Applications for deliberately released GMOs are reviewed individually by the competent federal authority and risk management measures are required in each case, as necessary. Post-release monitoring is required both by German and European Union law and safety assessments may be revised in light of monitoring data or improved scientific knowledge.

> The Directive 2001/18/EC (transposed in the national GenTG) regulates the deliberate release of GMOs into the environment, either for experimental (i.e., confined or isolated field trials) or commercial purposes.

The German system provides for transparency and public notification, through making applications public, through incorporating a comment period into the approval process, and through including

representatives of various social groups as well as scientific experts on the Central Commission.

II. Overview of legislative & regulatory framework

A. WITHIN THE EUROPEAN UNION

Genetically modified organisms (GMOs) intended for experimental or commercial release into the environment are regulated within the European Union (EU) by the Directive on the Deliberate Release into the Environment of Genetically Modified Organisms (Directive 2001/18/EC). The Directive defines "deliberate release" as "any intentional introduction into the environment of a GMO or a combination of GMOs for which no specific containment measures are used to limit their contact with and to provide a high level of safety for the general population and the environment."[1] It separately addresses GMOs deliberately introduced for experimental purposes and for placing on the market,[2] thereby encompassing both field trials and commercial releases. The Directive also states that an environmental risk assessment, information on control and remediation methods, and a monitoring protocol are among the items required for the environmental release to be authorized.[3]

In cases of commercial releases (placing on the market), the application ("notification") is first submitted to the competent national authority of one EU member state.[4] The initial environmental impact assessment and scientific safety assessment are reviewed by the national authority, which then sends the documents to the corresponding federal authorities of the other EU member states and to the European Commission (EC).[5] If there are objections to the documents, or if some issues were left unaddressed, a safety assessment is conducted by the European Food Safety Authority. The EC drafts a decision and submits it to a standing committee and, if necessary, to the Council of Ministers for a final decision.[5] Summaries of the notifications that were submitted to the federal authorities, as well as the final decision, are publicly available through the Joint Research Centre of the European Commission.[6] It is important to note that the EC, not individual member states such as Germany, has final authority over the decision to approve a proposed commercial release, whereas applications for experimental releases of GMOs (field trials) are approved by the member state in whose territory the release is proposed to occur.

> It is important to note that the EC, not individual member states such as Germany, has final authority over the decision to approve a proposed commercial release, whereas applications for experimental releases of GMOs (field trials) are approved by the member state in whose territory the release is proposed to occur.

This chapter reviews only the framework for GMO risk assessment in Germany, not the entire regulatory process for GMOs in Germany.

B. GERMAN LAWS AND REGULATIONS

The German law that broadly regulates GMOs is the Gentechnikgesetz (GenTG), variously translated as the Genetic Engineering Act[7] or the Gene

1 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Article 2.

2 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Part B, Part C.

3 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Article 6.

4 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Article 6, Article 13.

5 GMO Compass. http://www.gmo-compass.org/eng/service (accessed 18 Oct. 2009).

6 Deliberate release and placing on the EU market of genetically modified organisms (GMOs). http://gmoinfo.jrc.ec.europa.eu/(accessed 25 Oct. 2009).

7 Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL) website, English-language version. http://www.bvl.bund.de/nn_496812/EN/06__Genetic__Engineering/genetic__engineering.html__nnn=true (accessed 18 Oct. 2009).

Technology Act.[8] It regulates genetic engineering facilities, genetic engineering work ("gentechnische Arbeiten"), the contained use of GMOs, the deliberate release of GMOs, and the placing on the market of products containing, or consisting of, GMOs.[9] The GenTg defines a GMO as a non-human organism that has been genetically altered in a way that does not occur through natural mating or recombination, or that is the product of natural mating, recombination, or propagation of one or more genetically modified organisms.[10] The law has several objectives. First, it is meant to safeguard humans, plants, animals, the environment, and goods against the processes, products, and hazards related to genetic engineering. Second, it ensures the coexistence and marketability of food and feed, whether produced conventionally, organically, or by genetic engineering. Third, it provides for the continued research, development, and promotion of the potential of genetic engineering, with due regard for ethical considerations.[11]

> The German law that broadly regulates GMOs is the Gentechnikgesetz (GenTG), variously translated as the Genetic Engineering Act[7] or the Gene Technology Act.

Other German laws relating to GMOs include those implementing EU regulations regarding food and food additives[12] and the ratification of the Cartagena Protocol on Biosafety.[13] It was not clear from the documents reviewed whether subsequent legislation was required to align German laws and regulations with EU Directive 2001/18/EC. However, the Directive specifically mentions the need to "approximate the laws of the member States"[14] regarding environmental introductions of GMOs, suggesting that harmonization may have been unnecessary.

Various regulations are authorized by the GenTG. These include the Genetic Engineering Safety Ordinance, which regulates the safety classification of, and required safety measures relating to, contained use of GMOs;[15,16] regulations regarding GMO application and regulation forms and procedures;[17] regulations on public awareness and participation;[18] and on the formation and function of the Zentrale

8 Biosafety Clearing House for the Convention on Biological diversity (BCH) website, English-language version. Record ID# 39280. http://bch.cbd.int/database/record-v4.shtml?documentid=39280 (accessed 16 Oct. 2009).

9 Gesetz zur Regelung der Gentechnik (Gentechnikgesetz – GenTG). Translated as "Act regulating the gene (Gene Technology Act - GenTG)". http://bundesrecht.juris.de/bundesrecht/gentg/gesamt.pdf (accessed 14 Oct. 2009). § 2.

10 Gesetz zur Regelung der Gentechnik (Gentechnikgesetz – GenTG). Translated as "Act regulating the gene (Gene Technology Act - GenTG)". http://bundesrecht.juris.de/bundesrecht/gentg/gesamt.pdf (accessed 14 Oct. 2009). § 3.3.

11 Gesetz zur Regelung der Gentechnik (Gentechnikgesetz – GenTG). Translated as "Act regulating the gene (Gene Technology Act - GenTG)". http://bundesrecht.juris.de/bundesrecht/gentg/gesamt.pdf (accessed 14 Oct. 2009). § 1.

12 Gesetz zur Durchführung von Verordnungen der EU auf dem Gebiet der Gentechnik und zur Änderung der Neuartige Lebensmittel- und Lebensmittelzutaten-Verordnung vom 22. Juni 2004. Translated as "Law on the implementation of EU regulations in the field of genetic engineering and modification of novel food and food additives regulation of 22 June 2004". http://bundesrecht.juris.de/eggentdurchfg/index.html (accessed 22 Oct. 2009).

13 Gesetz zu dem Protokoll von Cartagena vom 29. Januar 2000 über die biologische Sicherheit zum Übereinkommen über die biologische Vielfalt. Translated as "Act ratifying the Cartagena Protocol of 29 January 2000 on Biosafety to the Convention on Biological Diversity, 28 October 2003". Cartagena Protocol of 29 January 2000 on Biosafety to the Convention on Biological Diversity, 28 October 2003". http://www.bvl.bund.de/cln_027/DE/06__Gentechnik/00__doks__downloads/01__Nat__Gesetze__VO/Gesetz_20zum_20Protokoll_20von_20Cartagena,templateId=raw,property=publicationFile.pdf/Gesetz%20zum%20Protokoll%20von%20Cartagena.pdf (accessed 22 Oct. 2009).

14 Directive 2001/18/ EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Preamble (7).

15 Verordnung über die Sicherheitsstufen undSicherheitsmaßnahmen bei gentechnischen Arbeiten in gentechnischen Anlagen (Gentechnik-Sicherheitsverordnung - GenTSV). Translated as "Regulation on Security and
Safety of genetic engineering Work in genetic engineering facilities (Genetic Engineering Safety Ordinance - GenTSV)". http://bundesrecht.juris.de/bundesrecht/gentsv/gesamt.pdf (accessed 16 Oct. 2009).

16 Dr. Ulrich Ehlers, pers. comm. 26 Oct. 2009. Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL), Abteilung Gentechnik, Referat 403 "Freisetzung und Inverkehrbringen". Translated as "Federal Office of Consumer Protection and Food Safety, Department for Gene Technology, Unit 403 "Deliberate Release and Placing on the Market"". Mauerstrasse 39-42, D-10117, Berlin.

17 Verordnung über Antrags- und Anmeldeunterlagen und über Genehmigungs- und Anmeldeverfahren nach dem Gentechnikgesetz (GenTVfV). Translated as "Regulation on the application and registration forms and Licensing and registration procedures under the Gene Technology Act". http://bundesrecht.juris.de/bundesrecht/gentvfv/gesamt.pdf (accessed 16 Oct. 2009).

18 Verordnung über Anhörungsverfahren nach dem Gentechnikgesetz (Gentechnik-Anhörungsverordnung - GenTAnhV). Translated as "Regulation on the consultation process under the Genetic Engineering Act (GM Hearing Regulation - GenTAnhV)". http://bundesrecht.juris.de/bundesrecht/gentanhv/gesamt.pdf (accessed 17 Oct. 2009).

Kommission für die Biologische Sicherheit or Central Commission for Biological Safety (hereinafter Central Commission).[19]

C. THE BUNDESAMT FÜR VERBRAUCHERSCHUTZ UND LEBENSMITTELSICHERHEIT (BVL)

The Gene Technology Act (GenTg) and subsequent amendments established the bureaucracy that regulates GMOs in Germany. Since 2004, the Federal Office of Consumer Protection and Food Safety (BVL) has been the federal authority responsible for the authorization of the deliberate experimental release of GMOs into the environment and the coordination of post-release environmental monitoring.[7] In addition, the BVL is the national competent authority for the commercialization of GMOs or products containing GMOs.[7] Authorizations for contained use of GMOs are issued by the authorities of the German federal states. Under the legislative authority granted by the GenTg, different procedures for application and approval of GMOs intended for contained use (i.e., in a containment facility) and GMOs intended for deliberate environmental release, whether experimental (e.g., isolated field trials) or commercial (e.g., large-scale agriculture), have been established.

Contained use of GMOs

The GenTg stipulates the required components of an application for the approval of contained use, which is also referred to as genetic engineering work ("the production of genetic modifications").[20] These components include a risk assessment,[21] although the GenTg does not include specific details on what a risk assessment should entail (e.g., hazard identification) or how risk should be estimated. We were unable to locate risk assessment guidance documents pertaining to contained use; that is, documents advising applicants on specific details of conducting a risk assessment or documents advising reviewers on how to evaluate risk assessments.

Under the legislative authority granted by the GenTg, different procedures for application and approval of GMOs intended for contained use (i.e., in a containment facility) and GMOs intended for deliberate environmental release, whether experimental (e.g., isolated field trials) or commercial (e.g., large-scale agriculture), have been established.

The procedure for approving contained-use applications is also guided by the Genetic Engineering Safety Ordinance. This regulation requires that contained-use GMOs be assigned a "risk class" and that appropriate safety measures be identified. This process includes expert review by the Central Commission. The authority of the federal state in which the contained use facility is located solicits an opinion from the Central Commission regarding the risk class of the pertinent GMO. The Central Commission is comprised of experts in various scientific fields, including microbiology, cellular biology, ecology, virology, plant breeding, genetics, and toxicology. In addition, various social sectors including trade unions, industry, agriculture, environmental protection and conservation, and consumer safety, are represented on the Central Commission.[22] High-risk genetic engineering operations (requiring containment levels 3 and 4) (III.C., below), and level-2 containment genetic engineering operations that are not comparable to similar, previously assessed operations, have to be reviewed. The Central Commission has to give its opinion on these operations. The scientific secretariat of the Central Commission is provided by the BVL.

19 Verordnung über die Zentrale Kommission für die Biologische Sicherheit (ZKBS-Verordnung- ZKBSV). Translated as "Regulation of the Central Commission for Biological Safety (CCBS-Regulation - ZKBSV)". http://bundesrecht.juris.de/bundesrecht/zkbsv/gesamt.pdf (accessed 15 Oct. 2009).

20 Gesetz zur Regelung der Gentechnik (Gentechnikgesetz – GenTG). Translated as "Act regulating the gene (Gene Technology Act - GenTG)". http://bundesrecht.juris.de/bundesrecht/gentg/gesamt.pdf (accessed 14 Oct. 2009). §3.2.

21 Gesetz zur Regelung der Gentechnik (Gentechnikgesetz – GenTG). Translated as "Act regulating the gene (Gene Technology Act - GenTG)". http://bundesrecht.juris.de/bundesrecht/gentg/gesamt.pdf (accessed 14 Oct. 2009). §10.2.5.

22 Gesetz zur Regelung der Gentechnik (Gentechnikgesetz – GenTG). Translated as "Act regulating the gene (Gene Technology Act - GenTG)". http://bundesrecht.juris.de/bundesrecht/gentg/gesamt.pdf (accessed 14 Oct. 2009). §4.1.1 - §4.1.2.

Deliberate release of GMOs

The BVL's procedures for approving applications for experimental releases are guided by Directive 2001/18/EC. Applications must include an environmental risk assessment,[23] the general criteria for which are provided by the Directive.[16] The criteria for GMOs that are higher plants[24] differ from criteria for other taxa.[25] The BVL does not assign a risk class to GMOs proposed for deliberate release; instead, every application is reviewed individually. Upon request, the agency will provide detailed advice to applicants about the requirements for deliberate-release applications.[16] The Central Commission issues an opinion on each application for a deliberate release of GMOs.

D. AVAILABLE DOCUMENTS AND TERMINOLOGY

The national regulations and laws reviewed were available to us only in German. Directive 2001/18/EC, some of the Central Commission's opinion documents, portions of the summaries of risk assessments, and the notification reports, were available in English. Initial translations of German-language documents were performed using a web-based translator.[26] Throughout the German regulations and laws reviewed, the term used is "gentechnisch veränderter Organismus", which translated as "genetically modified organism" (GMO). Directive 2001/18/EC also uses the term "GMO", which is distinct from "living modified organism" (LMO), the term used in the Cartagena Protocol. In the current work, "GMO" is retained when such is the term used in the original text being paraphrased or discussed.

23 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Article 6.2.b, Article 13.2.b.

24 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Annex III B.

25 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Annex III A.

26 Google Translator. http://www.translate.google.com (accessed 15 Oct. 2009).

III. General principles

A. SCIENTIFICALLY SOUND

Directive 2001/18/EC states that environmental risk assessments should be carried out in a scientifically sound manner.[27] We were unable to find the term "scientific soundness" within the national legal and regulatory documents reviewed, although this may be due in part to translation. However, the idea of scientific soundness may be implicit in various sections of the Gene Technology Act (GenTG) and in the regulations for the Central Commission.

One example is the requirement that the Central Commission include experts in various pertinent scientific fields,[28] as detailed in II.C, above. Another example relates to safety procedures implemented by the operators of genetic engineering facilities. They are required to monitor security measures regularly and immediately revise them if there is cause to believe that the pertinent risk assessment no longer represents the latest scientific and technical knowledge ("…die begründete Annahme besteht, dass die Risikobewertung nicht mehr dem neuesten wissenschaftlichen und technischen Kenntnisstand entspricht").[29]

The principle of scientific soundness also appears within informational public documents disseminated by the BVL. For example, the BVL's English-language website mentions "scientific evaluation of molecular, health, and ecological data by experts in the particular fields" and "best currently available scientific data"[7] in connection with its work relating to genetic engineering in Germany.

27 Directive 2001/18/ EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Annex II.B.

28 Gesetz zur Regelung der Gentechnik (Gentechnikgesetz – GenTG). Translated as "Act regulating the gene (Gene Technology Act - GenTG)". http://bundesrecht.juris.de/bundesrecht/gentg/gesamt.pdf (accessed 14 Oct. 2009). §4.1.1.

29 Gesetz zur Regelung der Gentechnik (Gentechnikgesetz – GenTG). Translated as "Act regulating the gene (Gene Technology Act - GenTG)". http://bundesrecht.juris.de/bundesrecht/gentg/gesamt.pdf (accessed 14 Oct. 2009). §6.1.2.

B. TRANSPARENCY

Directive 2001/18/EC states that environmental risk assessments should be conducted in a transparent matter.[27] We were unable to find the term "transparency" within the national legal and regulatory documents reviewed, although the German framework contains several features that exemplify transparency. First, the GenTG explicitly states the process by which an application is approved. It must be submitted to the BVL, which reviews it in conjunction with the safety assessment opinion provided by the Central Commission.[30] Second, the GenTG establishes legal requirements for the contents of a deliberate release application. These requirements include the names of and contact information for the project and the project operator, a description of the proposed release and of the GMO, and a risk assessment.[31] Third, the BVL's requirements for applications for deliberate environmental release of GMOs are given in the publicly-available Directive 2001/18/EC.

We were unable to find the term "transparency" within the national legal and regulatory documents reviewed, although the German framework contains several features that exemplify transparency.

The German approach to risk assessment also incorporates transparency through public consultation. The GenTG mandates the inclusion on the Central Commission of representatives of various social sectors. These groups include trade unions, environmental protection and conservation groups, industrial and agricultural organizations, and groups concerned with consumer protection and the promotion of research.[32] Additionally, an application for deliberate release must include the specific location(s) in which the proposed release is to occur. Notices to that effect must then be posted in the BVL's official publication, as well as in local newspapers.[33] Those notifications must announce that objections may be raised.[34] On this point, as on others, German regulations are congruent with Directive 2001/18/EC, which states that EU members shall "consult the public…on the proposed deliberate release…in order to give the public or groups the opportunity to express an opinion."[35]

C. LACK OF SCIENTIFIC KNOWLEDGE OR CONSENSUS DOES NOT INDICATE LEVEL OR ABSENCE OF RISK

Directive 2001/18/EC states, "The precautionary principle […] must be taken into account when implementing (the Directive)"[36] and references that principle elsewhere in the document;[37] however, we were unable to find explicit reference to precaution within the German regulations reviewed. The idea that absence of scientific knowledge is not indicative of absence of risk may be implicitly incorporated into some aspects of the German approach to LMOs. For example, in the case of deliberately released GMOs, the BVL adheres to the criteria for risk assessment that are set out in the Directive (see II.D,

30 Gesetz zur Regelung der Gentechnik (Gentechnikgesetz – GenTG). Translated as "Act regulating the gene (Gene Technology Act - GenTG)". http://bundesrecht.juris.de/bundesrecht/gentg/gesamt.pdf (accessed 14 Oct. 2009). §10.7.

31 Gesetz zur Regelung der Gentechnik (Gentechnikgesetz – GenTG). Translated as "Act regulating the gene (Gene Technology Act - GenTG)". http://bundesrecht.juris.de/bundesrecht/gentg/gesamt.pdf (accessed 14 Oct. 2009). §15.

32 Gesetz zur Regelung der Gentechnik (Gentechnikgesetz – GenTG). Translated as "Act regulating the gene (Gene Technology Act - GenTG)". http://bundesrecht.juris.de/bundesrecht/gentg/gesamt.pdf (accessed 14 Oct. 2009). §4.1.2.

33 Verordnung über Anhörungsverfahren nach dem Gentechnikgesetz (Gentechnik-Anhörungsverordnung - GenTAnhV). Translated as "Regulation on the consultation process according to the Gene Technology Act (Genetic engineering consulting regulation - GenTAnhV)". http://bundesrecht.juris.de/bundesrecht/gentanhv/gesamt.pdf (accessed 23 Oct. 2009). §2.

34 Verordnung über Anhörungsverfahren nach dem Gentechnikgesetz (Gentechnik-Anhörungsverordnung - GenTAnhV). Translated as "Regulation on the consultation process according to the Gene Technology Act (Genetic engineering consulting regulation - GenTAnhV)". http://bundesrecht.juris.de/bundesrecht/gentanhv/gesamt.pdf (accessed 23 Oct. 2009). §3.1.2.

35 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Article 9.1.

36 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Preamble (8).

37 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Article 1, Article 4, Annex II.B.

above). Another example is the assignment of proposed genetic engineering work (i.e., contained-use GMOs) to the "security levels" ("Sicherheitsstufe") described in section II.D. above. Level 1 work is assumed to pose no risk to human or environmental health; Level 4 work is high-risk or can be reasonably assumed to be such.[38] If doubt exists regarding the appropriate level of security, the work is assigned the next-higher security rating.[39]

D. RISK CONSIDERED IN THE CONTEXT OF RISK POSED BY NON-MODIFIED RECIPIENTS OR PARENTAL ORGANISMS

Within the German national legal and regulatory documents reviewed, we were unable to find reference to the context of risk. Directive 2001/18/EC explicitly states that the characteristics of the GMO that could potentially cause adverse effects, given its intended use, should be compared to "the non-modified organism from which it is derived and its use under corresponding situations".[27] Additionally, a risk assessment for hybrid crosses of herbicide-tolerant and insect-resistant strains of maize (i.e., stacked traits) considered the risk of the occurrence of adverse effects such as gene flow within the context of conventional maize and previously-approved single-trait GM parental lines.[40,41] Specifically, the outcrossing distances of conventional, hybrid, and hybrid-cross varieties were compared in the risk assessment.

E. CASE-BY-CASE BASIS

Within the national legal and regulatory documents reviewed, we were unable to find explicit reference to whether the German approach to risk analysis for GMOs is "case-by-case". However, the BVL's policy on deliberate releases of GMOs into the environment is that risk assessments are required, must be performed on a case-by-case basis, and that any necessary risk management measures shall be determined specifically for every single application.[16] We were unable to determine how "case" is defined, although the risk assessment for maize expressing stacked traits (see III.D., above) provided some indirect evidence. A single application was submitted to the BVL for five genetically modified lines or "events" - three varieties of GM maize (NK603, MON 89034, and MON88017) and 2 hybrid strains resulting from crosses between MON 89034 and the other two GM parental lines.[41] Although this single application requested approval for the deliberate release of several different GM events at the same location(s), the risk assessment considered the properties of each event separately. In such cases, the BVL evaluates each event individually based on its properties and issues a single consent document if approval is granted.

> the BVL's policy on deliberate releases of GMOs into the environment is that risk assessments are required, must be performed on a case-by-case basis, and that any necessary risk management measures shall be determined specifically for every single application

Directive 2001/18/EC states that a "case-by-case environmental risk assessment should always be carried out prior to a (deliberate) release" of a GMO.[42] "Case-by-case" means that the information required in a risk assessment "may vary depending on the type of the GMOs concerned, their intended use and the potential receiving environment, taking into account, *i.a.*, GMOs already in the environment."[27]

38 Gesetz zur Regelung der Gentechnik (Gentechnikgesetz – GenTG). Translated as "Act regulating the gene (Gene Technology Act - GenTG)". http://bundesrecht.juris.de/bundesrecht/gentg/gesamt.pdf (accessed 14 Oct. 2009). §7.1.1 - §7.1.4.

39 Gesetz zur Regelung der Gentechnik (Gentechnikgesetz – GenTG). Translated as "Act regulating the gene (Gene Technology Act - GenTG)". http://bundesrecht.juris.de/bundesrecht/gentg/gesamt.pdf (accessed 14 Oct. 2009). §7.1a.

40 B/DE/06/185. Notification according to Directive 2001/18/EC, Part B, for the deliberate release of MON 89034 x MON 88017, MON 89034 x NK603 maize and their parental lines, MON 89034, MON 88017 and NK603, for the use in field trials in Germany. Monsanto Agrar Deutschland GmbH, on behalf of Monsanto Company. 15 Nov. 2006. http://gmoinfo.jrc.ec.europa.eu/gmp_report.aspx?CurNot=B/DE/06/185 (accessed 17 Oct. 2009).

41 Notification 6786-01-0185 (B/DE/06/185). Summary of the risk assessment of the German Competent Authority regarding LMO NK603, MON89034, MON88017, MON89034 x MON88017, MON89034 x NK603 (Courtesy translation, only the German text is official). Section III.1.2 only. Available at http://bch.cbd.int/database/record-v4.shtml?documentid=46345 (accessed 16 Oct. 2009).

42 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Preamble (19).

IV. Methodology

A. IDENTIFICATION OF NOVEL GENOTYPIC/ PHENOTYPIC CHARACTERISTICS ASSOCIATED WITH LMO, THAT MAY HAVE ADVERSE EFFECTS ON BIOLOGICAL DIVERSITY IN THE LIKELY POTENTIAL RECEIVING ENVIRONMENT, ALSO TAKING INTO ACCOUNT RISKS TO HUMAN HEALTH

1. Recipient/Parental Organisms

In the case of contained use, the properties ("die Eigenschaften") of the recipient organism must be provided in the risk assessment submitted with the application for approval of genetic work.[43] We were unable to find a specific list of these properties within the German legal and regulatory documents reviewed. In the case of deliberate environmental releases, the BVL adheres to Directive 2001/18/EC, which requires that specific information be included in deliberate-release applications. With regards to higher plants, the required information includes taxonomy, characteristics relating to reproduction, dispersal, and survivorship, geographic distribution, natural habitat, and ecological interactions.[44]

Both of the risk assessments reviewed included some properties of the recipient organism. In one assessment, the recipient organism was conventional wheat. Its history of cultivation, preference for ruderal habitats, weak competitive abilities, short duration of seed viability (2 years), and short period of pollen fertility (3 hours) were stated.[45] The other risk assessment, which as discussed above was for hybrids of three GM varieties of maize, stated certain properties of both conventional maize and the GM parental strains. Conventional maize was characterized as not being hardy and not being prone to escape cultivation in central Europe: "The establishment of volunteer maize has not been observed in the flora of Central Europe, even in the case of grain maize, which is harvested when fully mature."[41] The competitiveness of the GM parental strains – considered recipient organisms within this risk assessment – was thought to be unaltered by the presence of herbicide-tolerance and insect-resistance genes, based on the assumption that the insertion would not affect persistence characteristics.[41]

With regards to higher plants, the required information includes taxonomy, characteristics relating to reproduction, dispersal, and survivorship, geographic distribution, natural habitat, and ecological interactions.

2. Donor Organism

As with the recipient organisms, the properties ("die Eigenschaften") of the donor organism(s) must be provided in the risk assessment that is submitted with the application for approval of genetic engineering work.[43] With respect to contained use, we were unable to find specifics regarding those properties within the German legal and regulatory documents reviewed. For the donor organisms involved in deliberately released GMOs, Directive 2001/18/EC provides a list of required information both for the donor organism and the vector.[46]

Examples of the required properties also appear within the summary risk assessments. In the risk assessment for GM wheat mentioned above, the donor organism is a RNA virus found in some fungal strains of corn smut (*Ustilago maydis*).[45] The risk assessment details the mode of action of the virus when exposed to various types of fungal and mammalian cells. For example, in *U. maydis*, the virus inhibits the growth of hyphae but it does not appear to inhibit the viability of cells derived from tobacco plants, hamsters, or human kidneys.[45]

43 Gesetz zur Regelung der Gentechnik (Gentechnikgesetz – GenTG). Translated as "Act regulating the gene (Gene Technology Act - GenTG)". http://bundesrecht.juris.de/bundesrecht/gentg/gesamt.pdf (accessed 14 Oct. 2009). §10.2.5.

44 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Annex III B, part B.1-7.

45 Notification 6786-01-0195. Summary of the risk assessment of the genetically modified organisms wheat (Triticum aestivum) KP4 Greina 16 and KP4 Golin 5 within the framework of a proposed deliberate release carried out by the German competent authority. Berlin, 13 Mai 2008. Section III.1.2 only. Available at http://bch.cbd.int/database/record-v4.shtml?documentid=48070 (accessed 20 Oct. 2009).

46 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Annex III A.II.A, Annex III A.II.B, Annex III B.C.

In the risk assessment for GM maize, the donor organisms include *Agrobacterium* species, and subspecies of *Bacillus thuringiensis* (Bt). The properties given are those of the proteins expressed by the genes obtained from the donor organisms, rather than properties of the donor organisms themselves. These properties generally include glyphosate tolerance and formation of the Bt toxin.[41]

3. LMO Characteristics

The properties ("die Eigenschaften") of contained-use GMOs relating both to the level of security required (see III.C above) and their implications for the lives, health and safety of humans, plants, animals, the environment, and material goods must be provided in the risk assessment that is submitted with the application.[43] In the case of deliberately-released GMOs, an application must provide current and relevant data on safety-related characteristics of the organism and must describe circumstances under which the GMO could survive, reproduce, and disseminate.[47] Directive 2001/18/EC includes a list of additional required information.[48]

The novel properties of the GMOs in question were discussed in the context of particular adverse effects, which were not limited to those on biological diversity. In the risk assessments for both GM wheat and maize, the adverse effects considered included toxic effects on humans or animals consuming the plant tissues, allergenicity, weediness or invasiveness, gene flow via pollen transfer, and horizontal gene transfer to soil micro-organisms. The risk assessment for GM maize also mentioned effects on the targeted insect pests and non-target organisms such as soil microbes.[40]

The risk assessment for GM wheat considered several novel LMO characteristics and their potential adverse effects. These included the toxicity of the inserted viral DNA, measured as its impact on the viability of cultured plant, hamster, and human cells; the lack of properties such as heat stability that are typically found in allergenic proteins in food; and the propagation mode and rate, dispersal distance, fertility, and vitality in the GM wheat as tested in contained trials.[45] The risk assessment for GM maize considered many of the same novel LMO characteristics as the risk assessment for GM wheat. In addition, it considered Bt protein toxicity as measured in toxicity studies.[41]

> In the case of deliberately-released GMOs, an application must provide current and relevant data on safety-related characteristics of the organism and must describe circumstances under which the GMO could survive, reproduce, and disseminate.

4. Receiving Environment

Within the national regulatory and legal documents reviewed, we were unable to find stipulations that the receiving environment be considered when identifying the novel LMO characteristics that could adversely affect biological diversity. However, approvals for deliberate introduction into the environment are made for "temporally and spatially limited experimental releases"[7] within Germany. Directive 2001/18/EC requires that risk assessments for deliberate environmental releases, whether experimental or commercial, must include descriptions of the receiving ecosystem, including climate, flora, and fauna; whether sexually compatible wild relatives or domesticated species are present; and proximity to protected areas that could be affected.[49]

Examples of characteristics of the receiving environments that were found in the risk assessments reviewed included the specific geographic locations for those field trials (e.g., Oberboihingen, Baden-Württemberg)[40] and the climate of central Europe.[41]

47 Gesetz zur Regelung der Gentechnik (Gentechnikgesetz – GenTG). Translated as "Act regulating the gene (Gene Technology Act - GenTG)". http://bundesrecht.juris.de/bundesrecht/gentg/gesamt.pdf (accessed 14 Oct. 2009). §15.1.3.

48 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Annex III A.II.C, Annex III B.D.

49 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Annex III B.E.

B. EVALUATION OF THE LIKELIHOOD OF THESE ADVERSE EFFECTS BEING REALIZED, TAKING INTO ACCOUNT THE LEVEL AND KIND OF EXPOSURE OF THE LIKELY POTENTIAL RECEIVING ENVIRONMENT TO THE LMO

1. Intended use of LMO compared to recipient or parental organism

Within the German legal and regulatory documents reviewed, we were unable to find any indication of how the likelihood of adverse effects should be evaluated relative to the intended use. Directive 2001/18/EC states that a GMO's potential to cause adverse effects should be compared to that of the "non-modified organism from which it is derived and its use under corresponding situations."[27] In both of the reviewed risk assessments, the intended use of the GMO is experimental release to determine the safety, efficacy, and agronomic performance of the GMO.[41, 45]

2. Characteristics of relevant potential receiving environment

As mentioned above, the primary adverse effects considered in the context of the receiving environment were the development of invasive or weedy traits or unintended gene flow via pollen transfer. In the case of Bt maize, the likelihood that the GMO would escape cultivation was considered low, given that "maize can not persist in Central European climate conditions."[41] The risk assessment did not indicate whether that evaluation was informed by quantitative data (e.g., germination trials). Similarly, the likelihood of gene flow to wild relatives was considered low given the "lack of a crossing partner."[41] Because the experimental release was for an agricultural setting in Germany, and given the possible proximity of other maize fields, the possibility of gene flow between the GM maize and other maize crops was considered. Maize pollen is sensitive to ultraviolet radiation, humidity, and heat, so the possibility of unintended gene flow to other maize plants was considered low.

3. How incidental exposure to the environment could occur

Although we were unable to find this information in the German legal or regulatory documents reviewed, both risk assessments considered the primary pathways for incidental exposure to be either escape of the GMO from the experimental release area or unintended gene flow.[41,45] In both cases, incidental exposure was considered in the context of the receiving environment. From the documents reviewed, we were unable to determine how the likelihood of the occurrence of adverse effects was evaluated.

4. Conclusion of evaluation of likelihood of exposure

Although we were unable to locate this information within the German legal and regulatory documents reviewed, Directive 2001/18/EC indicates that the likelihood of adverse effects should be evaluated during a risk assessment. The Directive states that the characteristics of the receiving environment and the "manner of the release" are important factors in this evaluation[50] and that risk assessments should take direct, indirect, immediate and delayed effects of release of a GMO into the environment into account.[51] Such consideration could occur during the evaluation of likelihood of exposure.

> The Directive states that the characteristics of the receiving environment and the "manner of the release" are important factors in this evaluation[50] and that risk assessments should take direct, indirect, immediate and delayed effects of release of a GMO into the environment into account

Examples of the evaluation of exposure likelihood were given in the reviewed risk assessments.

50 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Annex II C.2.3.

51 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Annex II Objective.

One adverse effect, gene flow via pollen transfer, was evaluated qualitatively by considering the presence or absence of wild relatives[41,45] and evaluated quantitatively using previously-published studies on out-crossing rates and maximum distances among various species and varieties of wheat.[45] The likelihood of unintended gene flow between the GM wheat and other wheat crops was considered possible based on the "numerous studies (which) have been conducted on out-crossing in wheat."[45] In contrast, "the risk of spontaneous hybridization occurring under field conditions was considered to be extremely low"[45] due to factors such as the necessity of synchronous flowering and genetic incompatibility. It was not clear how this evaluation of "extremely low" was reached, although the use of previously published studies was suggested, given citation of these studies in other sections of the risk assessment. Another adverse effect, allergenicity, was considered unlikely even assuming eventual use of the GMO as food, feed, or for processing. This evaluation was based on previously-published acute toxicity studies in which the Bt protein was administered via feed or by gavage and no differences in body weight, weight gain, or pathology were found between the control and study groups.[41]

C. EVALUATION OF THE CONSEQUENCES SHOULD THESE ADVERSE EFFECTS BE REALIZED

Although we were unable to find reference to the evaluation of the consequences of adverse effects within the German regulatory and legal documents reviewed, Directive 2001/18/EC states that a risk assessment should gauge the magnitude of the consequences, which will be strongly influenced by the receiving environment and the "manner of release."[552]The Directive also provides a list of examples of adverse effects: disease, toxicity, and allergenic effects in humans, plants and animals; "altered susceptibility to pathogens"; "compromising…therapeutic effects in medical, veterinary, or plant protection treatments"; effects on species populations (including genetic diversity) in the receiving environment; and effects on soil biogeochemistry.[53] The Directive provides additional details for some of these effects, especially in the case of GMOs that are not higher plants. For example, effects on species populations should take into account any "competitive advantage of the GMOs in relation to the unmodified recipient or parental organism(s)."[54]

In the reviewed risk assessment of GM maize, the consequences of the adverse effects that GM plant tissues might have on non-target organisms were quantified using toxicity studies.[41] The consequence of the escape and naturalization of GM wheat may be implied by the following statement given in the risk assessment, that "…wheat is not known to establish in natural, intact plant communities."[45] This conclusion was apparently based on previous trials, which found no difference between the GM and conventional varieties in persistence, dispersal, or ability to establish outside of cultivation. The assessment states that, given this lack of difference, "the possibility that the genetically modified wheat might persist in the open field or that plants might establish in this way is extremely slight."[45] However, we were unable to find explicit statements linking possible escape with invasiveness or biological diversity.

Statements such as the following appear within the reviewed risk assessments: "In view of the selective mechanisms of action of Bt toxins due, amongst other things, to receptor-specific binding in the intestinal tract of sensitive insects, no adverse effects on the environment are expected".[41] We were unable to locate the data supporting these statements in the reviewed risk assessments.

52 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Annex II C.2.2.

53 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Annex II C.2.1.

54 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Annex III A.IV.B.9.

D. ESTIMATION OF THE OVERALL RISK POSED BY THE LMO BASED ON THE EVALUATION OF THE LIKELIHOOD AND CONSEQUENCES OF THE IDENTIFIED ADVERSE EFFECT BEING REALIZED

Within the documents reviewed, we were unable to find specific information on how the overall risk posed by the GMO is estimated. Directive 2001/18/EC states that the estimation of risk should be made by combining the likelihood of an adverse effect with the magnitude of the consequences should the effect occur, taking proposed risk management strategies into account.[55] In the notification report for experimental release (i.e., field trials) of GM maize, the estimation of overall risk was stated qualitatively: "The environmental risk assessment has indicated that the environmental risks of this maize are negligible."[40] We were not able to determine whether this estimation is made by the BVL or by the EU.

E. RECOMMENDATION AS TO WHETHER THE RISKS ARE MANAGEABLE, INCLUDING, WHERE NECESSARY, IDENTIFICATION OF STRATEGIES TO MANAGE THESE RISKS

Management of risks associated with the contained use of GMOs in Germany begins with the assignment of a security level to genetic engineering work for which an application has been made. The security levels ("Der Sicherheitsstufe"),[56] elsewhere referred to as "safety assessments" ("sicherheitstechnischen Einstufung"),[57] are assigned to the genetic engineering work based on its level of risk to human health and the environment. Level 1 is assigned to work that is assumed to pose no risk; Level 4 is assigned to work that poses or is reasonably suspected to pose a high risk. If uncertainty exists about the level of risk posed by the proposed work, a higher security level may be assigned. It is not clear from the translated documents under review whether only GMOs assigned to specific security levels may be approved for deliberate release. The Central Commission reviews applications and issues an opinion both on the safety assessment of the proposed work and on the necessary safety measures.[58] In addition, the application must describe monitoring techniques and emergency plans.[59]

In the risk assessments reviewed, the adverse effect identified as possibly occurring, although still having a low likelihood, was unintended gene flow. In both cases, risk management strategies were identified. These included minimum isolation distances, use of a border strip planted with non-GM individuals, and small rather than large experimental plots.

F. WHERE THERE IS UNCERTAINTY REGARDING THE LEVEL OF RISK, IT MAY BE ADDRESSED BY REQUESTING FURTHER INFORMATION ON THE SPECIFIC ISSUES OF CONCERN OR BY IMPLEMENTING APPROPRIATE RISK MANAGEMENT STRATEGIES AND/OR MONITORING THE LMO IN THE RECEIVING ENVIRONMENT

We were unable to find explicit reference to uncertainty in the national regulatory or legal documents reviewed. Directive 2001/18/EC partially addresses uncertainty by acknowledging the need to incorporate new information. The following is one of the Directive's General principles of environmental risk assessment: "if new information on the GMO and its effects on human health or the environment becomes available, the e.r.a. (environmental risk assessment) may need to be readdressed in order to: determine whether the risk has changed; (or) determine whether there is a need for amending the risk management accordingly."[27]

55 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Annex II C.2.4, II C.2.6.

56 Gesetz zur Regelung der Gentechnik (Gentechnikgesetz – GenTG). Translated as "Act regulating the gene (Gene Technology Act - GenTG)". http://bundesrecht.juris.de/bundesrecht/gentg/gesamt.pdf (accessed 14 Oct. 2009). §7.1.

57 Gesetz zur Regelung der Gentechnik (Gentechnikgesetz – GenTG). Translated as "Act regulating the gene (Gene Technology Act - GenTG)". http://bundesrecht.juris.de/bundesrecht/gentg/gesamt.pdf (accessed 14 Oct. 2009). §12.5.

58 Gesetz zur Regelung der Gentechnik (Gentechnikgesetz – GenTG). Translated as "Act regulating the gene (Gene Technology Act - GenTG)". http://bundesrecht.juris.de/bundesrecht/gentg/gesamt.pdf (accessed 14 Oct. 2009). §5.

59 Gesetz zur Regelung der Gentechnik (Gentechnikgesetz – GenTG). Translated as "Act regulating the gene (Gene Technology Act - GenTG)". http://bundesrecht.juris.de/bundesrecht/gentg/gesamt.pdf (accessed 14 Oct. 2009). §15.1.5.

German law[60] and Directive 2001/18/EC[7] both require post-release monitoring of GMOs. The holder of the approved application is expected to submit their monitoring plans to the BVL and report their monitoring results annually. An amendment to the Directive lists the objectives, General principles, and design of monitoring plans that should be implemented for deliberate releases into the environment of commercialized GMOs.[61]

V. Discussion

The German approach to risk analysis for LMOs distinguishes between contained use and deliberate release and includes a harmonized legal and bureaucratic framework, broad representation, and public participation. The contained use of GMOs (i.e. in a containment facility such as a laboratory) are regulated primarily by one document (GenTG). Deliberate experimental (e.g., isolated field trials) and commercial releases of GMOs into the environment are mainly regulated by Directive 2001/18/EC, which requires that particular information be included in risk assessments and adheres to General principles of scientific soundness, transparency, assessment on a case-by-case basis using the non-modified parent organism as a comparator, and the incorporation of new scientific knowledge.

The Central Commission's role in providing the authorities of the German federal states with opinions on the risk class of contained-use GMOs helps to balance bureaucracy with external expert opinion. The requirement that the Central Commission be comprised of representatives from environmental conservation groups, industry and agriculture, and consumer protection organizations further enhances this balance. Public comments are a part of the approval process for deliberate releases of GMOs, with particular attention paid to stakeholders local to the proposed experimental release sites. In addition, there is an emphasis on post-release monitoring that pre-dates Directive 2001/18/EC, which suggests a precautionary approach.

Deliberate experimental (e.g., isolated field trials) and commercial releases of GMOs into the environment are mainly regulated by Directive 2001/18/EC, which requires that particular information be included in risk assessments and adheres to General principles of scientific soundness, transparency, assessment on a case-by-case basis using the non-modified parent organism as a comparator, and the incorporation of new scientific knowledge.

One notable feature of the GenTG is its objective of safeguarding goods against potential hazards related to genetic engineering. A related objective is to ensure the coexistence and marketability of food and feed, whether produced conventionally, organically, or by genetic engineering. These provisions not only enlarge the legislative scope beyond human and environmental health, but also may allow consideration of economic impacts and consumer concerns. The GenTG does not specify how adverse effects are to be identified, how exposure and effects or the likelihood of their occurrence are to be evaluated, or how overall risk should be estimated. Directive 2001/18/EC provides some guidance by listing the "Steps in the e.r.a." which includes a list of possible adverse effects.[62] Based on the reviewed risk assessments, quantitative measures of exposure likelihood are combined into a qualitative estimate of overall risk. Uncertainty appears to be addressed largely through risk management strategies and post-release monitoring.

60 Gesetz zur Regelung der Gentechnik (Gentechnikgesetz – GenTG). Translated as "Act regulating the gene (Gene Technology Act - GenTG)". http://bundesrecht.juris.de/bundesrecht/gentg/gesamt.pdf (accessed 14 Oct. 2009). §16c.2.

61 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Annex VII.

62 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities 17.4.2001. Annex II C.2.

Chapter 9. Japan: Elements of risk assessment for LMOs

I. Abstract

Regulation of living modified organisms in Japan is primarily based on a national law (Act 97/2003) and a risk-assessment guidance document, both of which are harmonized with the Cartagena Protocol on Biosafety. The Act stipulates that risk assessment requirements are determined first by whether the intended use is uncontained (Type 1) or contained (Type 2), then by the broad taxonomy of the living modified organism (LMO) (plant, animal, or micro-organism), followed by the combination of recipient organism, donor nucleic acid, vector, and transformation method. Approval of applications for Type 1 use are made by the appropriate competent minister in consultation with scientific experts.

The Japanese approach to risk assessment for LMOs is data-driven and requires specific consideration of "assessment items", which are properties of LMOs that could cause adverse effects on biological diversity. Estimation of the risk posed by these items may be based on experimental data or on characteristics of the receiving environment (e.g., lack of sexually compatible wild relatives). The overall estimate of risk posed by the proposed Type 1 use is qualitative. Based on the findings of the risk assessment, the competent minister may require implementation of risk management measures and post-release monitoring.

II. Overview of legislative & regulatory framework

Regulation of living modified organisms (LMOs) in Japan is authorized through several laws, ordinances, and regulations (Appendix 9.A). The *Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003)* (hereinafter Act 97/2003) was passed in Japan to ensure the "precise and smooth implementation of the Cartagena Protocol on Biosafety".[1] A condensed version of the Act is given in *An Outline of Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms*.[2] These documents deal with two primary types of LMO usage. Type 1 uses do not utilize measures to prevent the dispersal of the LMO into the environment.[3] Type 2 uses are "undertaken with the intention of preventing the dispersal of living modified organisms into the air, water or soil outside facilities, equipment or other structures".[4]

1 Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003). http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009). Article 1.

2 An Outline of Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009).

3 Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act 97/2003). Article 2(5).

4 Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003).Article 2(6).

Other pertinent regulatory documents include *Basic Matters under the Provisions of Article 3 of the Law Concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms* (hereinafter *Basic Matters*)[5] and *The Guidance of Implementation of Assessment of Adverse Effect on Biological Diversity of Type 1 Use of Living Modified Organisms* (hereinafter *Guidance*).[6] The *Basic Matters* document, which was an enlargement of Article 3 of Act 97/2003, provides for the implementation of the Cartagena Protocol. The Guidance provides clarification on the preparation of Biological Diversity Risk Assessment Reports, pursuant to Article 4 of Act 97/2003. These are a required component of the application for approval of a Type 1 use of LMOs and must be "…consistent with Annex III of the Cartagena Protocol."[7] The primary steps are outlined under the Procedure of Assessment of Adverse Effect on Biological Diversity[8] (Appendix 9.B) and organized by the taxonomic kingdom of the LMO (Appendix 9.C).[9]

The role of the competent national ministries are presented in the *Regulations related to the Enforcement of the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms.*[10] Two specific categories of LMOs - plants and vaccines - fall within the jurisdiction of the Minister of Agriculture, Forestry and Fisheries and applications for Type 1 uses of these LMOs are additionally regulated.[11], [12] Living modified organisms may also fall under other regulations based on the intended use, such as for food and feed, or if the LMO expresses characteristics which are regulated under other laws (e.g., plants with insecticidal characteristics).

> When deciding whether to accept, amend, or reject applications for Type 1 use, the competent minister consults both with experts knowledgeable about the characteristics of the LMO in question and with experts on the organisms or ecosystems that could be impacted by the proposed use.

Act 97/2003 states that the competent minister responsible for approving applications for Type 1 and Type 2 uses shall be the Minister of Finance, the Minister of Education, Culture, Sports, Science and Technology, the Minister of Health, Labor and Welfare, the Minister of Agriculture, Forestry and Fisheries, the Minister of Economy, Trade and Industry, or the Minister of the Environment.[13] We were unable to determine whether these Ministries are responsible for assessing different types of applications, with the exception of applications for imports of LMOs, which are reviewed by the Minster of the Environment.[14] The competent authorities listed on the Biosafety Clearinghouse are the Ministers of the Environment and of Agriculture, Forestry and Fisheries.

5 Basic Matters under the Provisions of Article 3 of the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009).

6 The Guidance of Implementation of Assessment of Adverse Effect on Biological Diversity of Type 1 Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009).

7 Regulations related to the Enforcement of the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009). Form 11.

8 The Guidance of Implementation of Assessment of Adverse Effect on Biological Diversity of Type 1 Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009). Table 3.

9 The Guidance of Implementation of Assessment of Adverse Effect on Biological Diversity of Type 1 Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009). Table 2.

10 Regulations related to the Enforcement of the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009). Article 40.

11 Concerning the Application for Approval of Type 1 Use Regulations with regard to the genetically modified plants, the production or circulation of which falls within the jurisdiction of the Minister of Agriculture, Forestry and Fisheries. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009).

12 Concerning the Application for Approval of Type 1 Use Regulations with regard to the genetically modified live vaccines, the production or circulation of which falls within the jurisdiction of the Minister of Agriculture, Forestry and Fisheries. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009).

13 Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003).Article 36

14 Basic Matters under the Provisions of Article 3 of the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009).I.3(1)A

When deciding whether to accept, amend, or reject applications for Type 1 use, the competent minister consults both with experts knowledgeable about the characteristics of the LMO in question and with experts on the organisms or ecosystems that could be impacted by the proposed use.[15,16]

III. General principles

A. SCIENTIFICALLY SOUND

There are several ways in which scientific soundness is incorporated into the Japanese approach to risk assessment. First, *Basic Matters* stipulates that the most recent scientific knowledge pertinent to an application is to be used in the risk assessment[17] and that the government shall attempt to collect and analyze data "(i)n order to promote the amplification of scientific knowledge."[18] Experts are consulted during the process of deciding whether to approve an application for Type 1 use. In addition, the *Guidance* document "shall be reviewed as occasion demands" to incorporate advances in scientific knowledge on the adverse effects of LMOs on biological diversity and to take into account "international trends" in LMO risk assessment.[19]

B. TRANSPARENCY

The Japanese risk assessment framework incorporates transparency both procedurally and through public notification. Approval of Type 1 Use of LMOs is contingent on provision of information specified in the publicly-available *Guidance* document, such as the ecology of the recipient organism, the composition of the inserted sequence, and the properties of the vector.[20] The criteria for approval of an application for Type 1 use are clearly specified in *Basic Matters*[21], which is also publicly available. Further, Act 97/2003 states that the Japanese government must increase scientific knowledge about LMOs and the adverse effects their use could have on biological diversity.[22] One specific activity is the preparation of a biosafety information database in which data generated by the various government ministries is compiled and made publicly available.[23]

Transparency through public notification also takes several forms. First, the roster of experts consulted by the competent minister must be published.[24] The competent minister must also publicly announce applications for Type 1 LMO use and take into account public opinions on those applications [25] although the government may not disclose confidential technical or research information.[26]

15 Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003). Article 4(4).

16 Basic Matters under the Provisions of Article 3 of the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009).I.1(2)A.

17 Basic Matters under the Provisions of Article 3 of the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009).I.1(1)A(ii).

18 Basic Matters under the Provisions of Article 3 of the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009).III.1.

19 The Guidance of Implementation of Assessment of Adverse Effect on Biological Diversity of Type 1 Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009). [1].

20 The Guidance of Implementation of Assessment of Adverse Effect on Biological Diversity of Type 1 Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009). [4]1, [4]2.

21 Basic Matters under the Provisions of Article 3 of the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009).I.1(2)B.

22 Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003).Article 34.

23 Basic Matters under the Provisions of Article 3 of the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009).III.2.

24 Regulations related to the Enforcement of the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009). Article 10.

25 Basic Matters under the Provisions of Article 3 of the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009).I.1(2)C.

26 Basic Matters under the Provisions of Article 3 of the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009).III.3.

After approval, the applicant is expected to maintain records on "the conditions of the Use" and information relating to the LMO.[27]

C. LACK OF SCIENTIFIC KNOWLEDGE OR CONSENSUS DOES NOT INDICATE LEVEL OR ABSENCE OF RISK

Within the documents reviewed, we were unable to find explicit reference to the principle that lack of scientific knowledge does not indicate the absence of risk. However, this principle may be implicit within the Japanese approach to LMOs. For example, if unforeseen environmental changes lead to a risk of potential adverse effects on biological diversity due to an previously-approved Type 1 use, the competent minister must amend or rescind that use so as to prevent the adverse effect.[28] Additionally, the risk assessment must include methods of detecting and identifying the LMO and indicate the reliability and sensitivity of those methods[29] as well as emergency measures that should be taken to avoid adverse effects on biological diversity.[30] Also, if a Type 1 use is proposed for a LMO and the only substantial data available are based on laboratory studies or on field studies in natural conditions different from those in Japan, the Type 1 use must be preceded by isolated field trials in Japan.[31]

D. RISK CONSIDERED IN THE CONTEXT OF RISK POSED BY NON-MODIFIED RECIPIENTS OR PARENTAL ORGANISMS

Japanese regulations state that if the recipient organism is one with which "Japan has experience in (its) long-term use", then the risk of adverse effect is determined by comparison between the LMO and the non-modified recipient organism.[32] If the risk assessment, as reviewed by an expert panel, determines that there is no difference between the properties of the LMO and the non-modified recipient, then the risk assessment does not need to specify which "wildlife" are likely to be affected.[33,]

> the risk assessment must include methods of detecting and identifying the LMO and indicate the reliability and sensitivity of those methods[29] as well as emergency measures that should be taken to avoid adverse effects on biological diversity

E. CASE-BY-CASE BASIS

We were unable to find the term "case-by-case basis" within the legal and regulatory documents reviewed for this chapter. However, the information required in Biological Diversity Risk Assessment Reports (risk assessments) includes the taxonomy of the recipient organism, the composition and origins of the donor nucleic acid, the name and origin of the vector, and the method of transferring the donor nucleic acid.[34] This suggests that the basis for a new risk assessment is a combination of intended use (Type 1 or 2) and transformation event.

27 Basic Matters under the Provisions of Article 3 of the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009).II.4.

28 Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003).Article 7(1).

29 The Guidance of Implementation of Assessment of Adverse Effect on Biological Diversity of Type 1 Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009). Section [4]2(5).

30 The Guidance of Implementation of Assessment of Adverse Effect on Biological Diversity of Type 1 Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009). Section [4]3(4).

31 Concerning the Application for Approval of Type 1 Use Regulations with regard to the genetically modified plants, the production or circulation of which falls within the jurisdiction of the Minister of Agriculture, Forestry and Fisheries. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009)III.1(6).

32 The Guidance of Implementation of Assessment of Adverse Effect on Biological Diversity of Type 1 Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009). Table 3.4.

33 The Guidance of Implementation of Assessment of Adverse Effect on Biological Diversity of Type 1 Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009). Table 3.1.

34 The Guidance of Implementation of Assessment of Adverse Effect on Biological Diversity of Type 1 Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009). [4]1, [4]2.

IV. Methodology

A. IDENTIFICATION OF NOVEL GENOTYPIC AND PHENOTYPIC CHARACTERISTICS ASSOCIATED WITH LMO, THAT MAY HAVE ADVERSE EFFECTS ON BIOLOGICAL DIVERSITY IN THE LIKELY POTENTIAL RECEIVING ENVIRONMENT, ALSO TAKING INTO ACCOUNT RISKS TO HUMAN HEALTH

1. Recipient/Parental Organism

As part of the risk assessment the "(h)istory and present state of Use"[35] of the recipient organism must be indicated along with a set of physiological and ecological properties. These include its distribution, reproductive mode, and the environmental conditions required for the species to persist in a given area.[36] Additionally, when exporting to another party to the Cartagena Protocol, the characteristics, taxonomic status, origin, center(s) of diversity, and center(s) of origin of the recipient organism should be indicated.[7]

2. Donor Organism

Japanese regulations state that the name of a LMO must include the species name of the LMO or parental (i.e., donor) organism from which the nucleic acid is obtained.[37] The risk assessment must include the origin, composition, and function of the component elements of the inserted nucleic acid as well as the name, origin, and properties of the vector used.[38]

When exporting to another party to the Cartagena Protocol, the taxonomic status, common name, point of acquisition or collection, and the characteristics of the donor organism must be provided.[7]

> The risk assessment must include the origin, composition, and function of the component elements of the inserted nucleic acid as well as the name, origin, and properties of the vector used.

3. LMO Characteristics

Within the Japanese risk assessment framework, LMO characteristics must be specified in several ways. The name of the LMO must clearly distinguish it from other LMOs and include the species names of the recipient & donor organisms as well as the characteristics of the LMO[37]. The risk assessment must include the name, origin and properties of the vector[38] as well as the structure of the "entire nucleic acid" inserted into the recipient organism, the insertion method, and must indicate the stability of the traits expressed by the inserted sequence.[39] Applications for living modified plants must also include the function of the inserted nucleic acid and the expressed protein.[40] Finally, a description of how the LMO differs "from the recipient organism or the species to which the recipient organism belongs"[41] must be given.

35 The Guidance of Implementation of Assessment of Adverse Effect on Biological Diversity of Type 1 Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009). Table 1.1(2).

36 The Guidance of Implementation of Assessment of Adverse Effect on Biological Diversity of Type 1 Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009). Table 1.1(1).

37 Regulations related to the Enforcement of the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009). Article 8.i.

38 The Guidance of Implementation of Assessment of Adverse Effect on Biological Diversity of Type 1 Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009). Table 1.2(1), 1.2(2).

39 The Guidance of Implementation of Assessment of Adverse Effect on Biological Diversity of Type 1 Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009). Table 1.2(3), 1.2(4).

40 Concerning the Application for Approval of Type 1 Use Regulations with regard to the genetically modified plants, the production or circulation of which falls within the jurisdiction of the Minister of Agriculture, Forestry and Fisheries. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009)Table 1.2(1)(b).

41 The Guidance of Implementation of Assessment of Adverse Effect on Biological Diversity of Type 1 Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009). Table 1.2(6).

The risk assessment that we reviewed provided examples of these LMO characteristics.[42] The assessment was part of an application for Type 1 use submitted for a stacked LMO - a hybrid line developed through conventional crossbreeding of four previously developed recombinant maize lines (MON-88017-3, MON-89034-3, DAS-01507-1, and DAS-59122-7). The LMO name, as listed on the Japan Biosafety Clearing House, identified the recipient organism to subspecies, gives an abbreviation of the donor organism species name (Bt), included the inserted genes (e.g., *cry1A.105*), and listed the expressed characteristics of the LMO that differ from the non-modified recipient organism ("resistant to Lepidoptera and Coleoptera and tolerant to glufosinate and glyphosate herbicides"[42]).

The names and origins of the vectors used to produce the four parent lines were listed (e.g., pBR322, derived from *E. coli* and pSB1 derived from *A. tumefaciens*). The vector properties listed in the risk assessment included the number of base pairs in the vectors, the presence or absence of sequences with specific functions, a description of those functions (e.g., antibiotic resistance used as selectable markers), whether the vector was infectious and if so, its host range.[42]

The risk assessment provided the structure of entire inserted nucleic acids through gene maps and tables that listed the component elements of the plasmids used in the various transformation events. Component elements included borders, promoters, leaders, introns, coding sequences, and termination sequences. Insertion methods used in producing each of the four parental lines were also provided (e.g., *Agrobacterium* method). The stability of the expressed trait was tested in multiple generations of the parental lines using Southern blotting analysis.[42]

The LMO characteristics considered in the risk assessment included the target characteristics (insect resistance and herbicide tolerance), as experimentally determined by comparison of plant tissue damage and plant mortality, respectively, in the parental lines and in non-recombinant maize exposed to target insect species and glyphosate. Other characteristics considered were morphology, growth rates, early-stage cold- and heat-tolerance, pollen size and fertility, and dormancy. Potential for hybridization was not tested due to lack of wild relatives in Japan.[42] We were not able to determine from the documents reviewed whether or not risks of contamination (of conventional maize) or coexistence (between modified and conventional maize) were assessed.

> The Japanese risk assessment framework indicates that adverse effects on biological diversity of living modified plants must be considered under "similar natural conditions to Japan", whenever possible.

4. Receiving Environment

The Japanese risk assessment framework indicates that adverse effects on biological diversity of living modified plants must be considered under "similar natural conditions to Japan", whenever possible.[43] Additionally environmental conditions under which the plant can grow must be indicated.[44] In the risk assessment reviewed, references were made to the "natural environment" and to the "natural environment in Japan".[42] We were unable to determine the characteristics of this environment except that it is probably distinct from agricultural environments, as indicated by the statement: "…it is considered unlikely that these characteristics cause maize,

42 Maize resistant to Lepidoptera and Coleoptera and tolerant to glufosinate and glyphosate herbicides(cry1A.105, modified cry2Ab2, cry1F, pat, modified cp4 epsps, modified cry3Bb1, cry34Ab1, cry35Ab1, Zea mays subsp. mays (L.) Iltis)(MON 89034× B.t. Cry1F maize line 1507×MON 88017× B.t. Cry34/35Ab1 Event DAS-59122-7, OECD UI: MON-89034-3×DAS-01507-1×MON-88017-3×DAS-59122-7) [including the progeny lines isolated from the maize lines, MON 89034, B.t. Cry1F maize line 1507, MON 88017 and B.t. Cry34/35Ab1 Event DAS-59122-7, that contain a combination of any of the transferred genes in the individual maize lines (except those already granted an approval regarding Type I Use Regulation)]. Dow Chemical Japan Ltd. and Monsanto Japan Limited. http://www.bch.biodic.go.jp/english/lmo.html (accessed 5 Nov 2009).

43 Concerning the Application for Approval of Type 1 Use Regulations with regard to the genetically modified plants, the production or circulation of which falls within the jurisdiction of the Minister of Agriculture, Forestry and Fisheries. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009)Table 1.1(3).

44 Concerning the Application for Approval of Type 1 Use Regulations with regard to the genetically modified plants, the production or circulation of which falls within the jurisdiction of the Minister of Agriculture, Forestry and Fisheries. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009)Table 1.1(3)(b).

a *crop* plant, to become self-seeding in the *natural environment*…."[42] (emphasis added). Insofar as resident wildlife species are understood to be part of the receiving environment, the *Guidance* document indicates that they should be evaluated for relatedness to the LMO and for their susceptibility to any toxic substances that it produces.[33]

B. EVALUATION OF THE LIKELIHOOD OF THESE ADVERSE EFFECTS BEING REALIZED, TAKING INTO ACCOUNT THE LEVEL AND KIND OF EXPOSURE OF THE LIKELY POTENTIAL RECEIVING ENVIRONMENT TO THE LIVING MODIFIED ORGANISM

1. Intended use of LMO compared to recipient or parental organism

Japanese regulations state that the proposed use of the LMO, including the insertion method, results in the laboratory or similar environment, and relevant information obtained abroad must be included in the risk assessment.[45] Further, the *Guidance* document indicates that the evaluation of the likelihood of adverse effect is data-driven, based on the statement that the "likelihood of adverse effect on wildlife…shall be evaluated while collecting information" on the habitat and growing season of the species in question.[46]

In the risk assessment reviewed, the intended Type 1 uses are food, feed, cultivation, processing, storage, disposal, and acts incidental to those uses.[42] The expert reviewers of the assessment considered two categories of adverse effects relative to intended use. First, they examined whether the stacked LMO would exhibit any synergism or interactions among the proteins expressed in the various parental lines.[42] Second, they examined three specific adverse effects on biological diversity - competitiveness, productivity of harmful substances, and potential for hybridization.[42,47]

When considering protein interactions, the expert review compared the stacked LMO to the various parental lines, although the risk assessment itself included data from experiments testing the stacked LMO both against the parental lines and against a non-recombinant control. The reviewers opted not to assess risks in comparison to non-recombinant maize because the parental lines had been previously considered to have no adverse impacts on biological diversity under the same uncontained use as the stacked LMO in question.[42] In this context, evaluation of the likelihood of adverse effects occurring was qualitative, as in, "it is considered unlikely that the proteins expressed in this stack maize line from individual parent lines would interact with each other… and it is considered unlikely that notable changes in traits have occurred in (the LMO) except for the traits it received from the parent lines."[42]

The expert reviewers considered adverse effects on biological diversity both in the context of the non-modified recipient species and in terms of the recombinant parental lines. For example, the reviewers stated that maize has a long history of use in Japan and there are no reports of self-seeding, so potential hybridization was not a risk. Although the parental lines are statistically significantly different from non-modified maize in some aspects, none of those differences were considered large enough to increase competitiveness.[42] When considering whether the LMO would produce harmful substances, the reviewers considered allergenicity, root exudates and tissue leachates, and possible effects on non-target insects. In the first instance, the proteins expressed in the LMO were examined directly for structural homology with known allergens. The effects of root exudates and compounds leached from decomposing plant tissues on other plants and on soil microorganisms were compared between the parental lines and non-recombinant controls. Although significant differences were found, the reviewers determined that "these differences did not suggest that the productivity of harmful substances has been increased in

45 The Guidance of Implementation of Assessment of Adverse Effect on Biological Diversity of Type 1 Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009). Table 1.3.

46 The Guidance of Implementation of Assessment of Adverse Effect on Biological Diversity of Type 1 Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009). Table 3.3.

47 The Guidance of Implementation of Assessment of Adverse Effect on Biological Diversity of Type 1 Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009). Table 2.

any of the parent maize line (*sic*)."[42] The stated likelihood of adverse effects on non-target insects at the population level was "extremely low" [42] because the assessors considered the occurrence of non-target Lepidopteran species to be unlikely near the fields in which the LMO was to be cultivated.[42]

2. Characteristics of relevant potential receiving environment

Other than the above-mentioned references to "natural environment" and to the "natural environment in Japan"[42], we were unable to locate this information within the legal and regulatory documents reviewed. Within the reviewed risk assessment, the receiving environments appeared to be those relevant to small-scale experiments. For example, the plants used in Lepidoptera resistance trials were in pots and tests of overwintering ability were conducted in isolated field trials. We were able to locate two other references to the characteristics of the receiving environment: agricultural conditions, that were mentioned in the context of the unlikeliness of non-target Lepidopteran populations inhabiting fields used for LMO cultivation, and Japan generally, which was discussed vis-à-vis the absence of evidence of maize self-seeding in Japan.[42]

3. How incidental exposure to the environment could occur

We were unable to find explicit reference to incidental exposure within the legal and regulatory documents reviewed. The *Guidance* document may implicitly consider incidental exposure for plant LMOs, in that it requires the risk assessment to consider their competitiveness and potential for hybridization as well as their production of "harmful substances".[47] These "assessment items" suggest that the Japanese approach to risk assessment may consider escape from cultivation, unintended gene flow, and release of plant exudates or materials to be pathways of incidental exposure.

4. Conclusion of evaluation of likelihood of exposure

Within the documents reviewed, we were unable to locate information directly stating how the likelihood of exposure was to be evaluated. The *Guidance* document states that the likelihood of adverse effect, which may include likelihood of exposure, was to be evaluated through collecting field data on the distribution and life cycles of wildlife assumed to be affected by LMO properties such as competitiveness and hybridization potential.[42]

C. EVALUATION OF THE CONSEQUENCES SHOULD THESE ADVERSE EFFECTS BE REALIZED

The *Guidance* document contains several implicit references to the evaluation of consequences. First, the document indicates that a data-driven approach should be used to determine the "(c)oncrete details of adverse effect"[48] that LMOs could have on wildlife", suggesting that applicants gather experimental data.[48] One example of the experiments described in the reviewed risk assessment was a toxicity study. The applicants stated that artificial feed containing the Bt protein *cry1A.105* was fed to 15 insect species, including five lepidopteran species. No insecticidal activity was found against honeybees, ladybugs, or other non-lepidopteran taxa.[42]

The *Guidance* document also provides a list of "assessment items", defined as being properties of LMOs which could cause adverse effects on biological diversity.[47] These assessment items imply the consequences of their realization; for example, "competitiveness" is defined as the "property of competing against wild plants for resources…and interfering with their growth,"[47] which suggests that the consequence of increased competitiveness is reduction or loss of biological diversity in wild plant populations.

D. ESTIMATION OF THE OVERALL RISK POSED BY THE LMO BASED ON THE EVALUATION OF THE LIKELIHOOD AND CONSEQUENCES OF THE IDENTIFIED ADVERSE EFFECT BEING REALIZED

For a proposed Type 1 use to be approved, the competent minister must determine that the use would not create any adverse effect "that could pose an unacceptable risk of impairment to the preservation of species or populations of wild fauna or

48 The Guidance of Implementation of Assessment of Adverse Effect on Biological Diversity of Type 1 Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009). Table 3.2.

flora…."[49] This estimation of overall risk is based on each assessment item required for the particular type of LMO. These include the potential for hybridization in plants, predation or parasitism in animals and pathogenicity in micro-organisms.[9] A subsequent estimation of overall risk compares the "degree of adverse effect" found for the LMO to that found for the non-modified recipient species.[32] In the risk assessment reviewed, the expert reviewers qualitatively summarized the pertinent assessment items of competitiveness, hybridization potential, and the productivity of harmful substances and came to determinations of risk such as, "the use of such maize poses no risk of Adverse Effect on Biological Diversity that is attributable to (the assessment item)."[42] The panel then presented an overall qualitative conclusion stating that there was no risk that use of the stacked LMO in question would cause adverse effects on biological diversity in Japan.[42]

> For a proposed Type 1 use to be approved, the competent minister must determine that the use would not create any adverse effect "that could pose an unacceptable risk of impairment to the preservation of species or populations of wild fauna or flora…."

E. RECOMMENDATION AS TO WHETHER THE RISKS ARE MANAGEABLE, INCLUDING, WHERE NECESSARY, IDENTIFICATION OF STRATEGIES TO MANAGE THESE RISKS

As part of the risk assessment, the applicant must collect information on the LMO after initiation of the Type 1 use. Further, the applicant must take necessary measures to prevent adverse effects of the LMO on biological diversity, should such effects be indicated by the risk assessment.[50]

This process includes the submission of a prevention plan[51] and reporting to the pertinent government agency.[52] In addition, the Japanese government may also monitor for adverse effects caused by Type 1 uses of LMOs.[53] To facilitate ongoing monitoring of LMOs, the pertinent risk assessment must include LMO detection and identification methods and must indicate "sensitivity and reliability" of those methods.[54]

F. WHERE THERE IS UNCERTAINTY REGARDING THE LEVEL OF RISK, IT MAY ADDRESSED BY REQUESTING FURTHER INFORMATION ON THE SPECIFIC ISSUES OF CONCERN OR BY IMPLEMENTING APPROPRIATE RISK MANAGEMENT STRATEGIES AND/OR MONITORING THE LMO IN THE RECEIVING ENVIRONMENT

Uncertainty regarding the level of risk appears to be primarily addressed by requiring Type 2 (contained) use for some LMOs. Risk management strategies must be indicated in the application and the competent minister may make approval contingent on their implementation or on amendment of the proposed Type 1 use.[55] Post-release monitoring may be required.[51,56]

49 Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003).. Article 4[5].

50 Basic Matters under the Provisions of Article 3 of the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009).I.1(3)A.

51 Basic Matters under the Provisions of Article 3 of the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009).I.1(1)B.

52 Basic Matters under the Provisions of Article 3 of the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009).I.1(3)C.

53 Basic Matters under the Provisions of Article 3 of the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009).III.1.

54 The Guidance of Implementation of Assessment of Adverse Effect on Biological Diversity of Type 1 Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009). Table 1 2(5).

55 Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003).. Article 5(1).

56 Basic Matters under the Provisions of Article 3 of the Law concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms. http://www.bch.biodic.go.jp/english/law.html (accessed 25 Sept. 2009).I.1(1)A.iv.

V. Discussion

Japan's regulation is primarily based on the Cartagena Protocol on Biosafety and its risk assessment framework follows Annex III of the Protocol. The risk assessment guidance document, which is organized by broad taxonomic category (Appendix 9.C) goes beyond Annex III and outlines additional considerations that relate to exposure pathways such as potential hybridization. The overall estimate of risk must be such that no "unacceptable risk of impairment to the preservation of species or populations of wild fauna or flora" could arise from the approved Type 1 use.[50] This statutory requirement suggests a population-level emphasis on biological diversity.

The Japanese approach to risk assessment appears to combine an emphasis on experimental data with a qualitative estimate of overall risk. We were unable to find explicit reference to whether the lack of scientific knowledge or consensus indicates the level or absence of risk. However, risk management strategies must be indicated for all LMOs and the competent minister may require post-release monitoring of LMOs. These requirements may suggest a precautionary stance. .

Within the Japanese risk assessment framework, uncertainty is addressed in several notable ways. First, the reviewed regulations clearly specify that Japan must have long-term experience in using the non-modified recipient; that experience forms a baseline from which to judge the severity of adverse effects potentially caused by a LMO. If long-term experience is lacking, then the absence of the non-modified recipient forms the baseline. Second, if unforeseen environmental changes lead to a risk of potential adverse effects on biological diversity due to a previously-approved Type 1 use, the competent minister must amend or rescind the approved use so as to prevent the adverse effect.[57] Because the competent minister apparently does not have to prove that an adverse effect will occur, this may indicate a more precautionary approach than is found in frameworks where such proof would be required before the LMO use could be amended or rescinded.

57 Regulations Related to Cartagena Law. http://www.bch.biodic.go.jp/english/law.html (accessed 27 Sept. 2009).

APPENDIX

APPENDIX 9.A: Flowchart of Japanese regulations related to the Cartagena Protocol on Biosafety[57]

APPENDIX 9.B: Guidance document: assessment procedure and implementation methods[4]

Procedure of Assessment of Adverse Effect on Biological Diversity	Method of Implementing the Assessment
1. Identification of wildlife likely to be affected	Types of wildlife assumed to be affected by the properties of living modified organisms mentioned under assessment items in the right-hand column of Table 2 shall be identified by taxonomical categories and other genetic characters. If the species of pertinent wildlife are large in number, some species of wildlife deemed to be appropriate as the subject in carrying out the assessment shown in Procedure 2-4 may be selected in consideration of the growth and living environment of those species, their sensitivity to harmful substances produced by living modified organisms for Type 1 Use, relatedness to living modified organisms, etc. Nevertheless, if Japan has experience in the long-term use of the recipient organism of the living modified organism or the species to which the recipient organism belongs, and if there is no difference between the properties of the living modified organism mentioned under the assessment item in the right-hand column of Table 1 and those of the host or the species to which the host belongs, the wildlife likely to be affected need not be specified.
2. Evaluation of concrete details of adverse effect	Concrete details of adverse effect of living modified organism on wildlife identified or selected in Procedure 1 shall be evaluated, for example, by conducting experiments on reaction of individuals of the wildlife and collecting relevant information.
3. Evaluation of likelihood of adverse effect	The likelihood of adverse effect on wildlife identified or selected in Procedure 1 caused by living modified organism in carrying out Type 1 Use in accordance with Type 1 Use regulations shall be evaluated while collecting information on the places or periods of time of living or growth of said wildlife and other pertinent matters.
4. Judgment of existence of Adverse Effect on Biological Diversity	Whether the preservations of the species or population of the wildlife might be impaired or not shall be judged. If Japan has experience in the long-term use of the recipient organism of living modified organisms or the species to which the recipient organism belongs, judgment may be based on whether the degree of adverse effect is higher compared to that of the recipient organism or the species to which the recipient organism belongs.

4 Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003).Article 2(6).

APPENDIX 9.C: Guidance document: assessment items[4]

Category of Living Modified Organisms	Assessment Items (Property of living modified organisms which might cause Adverse Effect on Biological Diversity)
Plants (living organisms belonging to Plantae and mushroom belonging to Fungi)	Competitiveness (Property of competing against wild plants for resources such as nutrients, sunshine, habitat, etc. and interfering with their growth)
	Productivity of harmful substances (Property of producing substances interfering with the living and growth of wild plants or animals, or microorganisms (hereinafter "wildlife")
	Crossability (Property of hybridizing with related wild plants and transmitting nucleic acid transferred by the technologies regulated by the Law to them)
	Other properties (Properties other than those mentioned above, such as one which indirectly affects wildlife by changing the base of the ecosystem, which are considered to require an assessment of Adverse Effect on Biological Diversity)
Animals (living organisms belonging to Animalia)	Competitiveness (Property of competing against wild animals for resources such as food, nesting places and habitats, etc. and interfering with their living)
	Predacity or parasitism (Property of interfering with living or growth of wildlife by preying upon them or by being parasitic on them)
	Productivity of harmful substances (Property of producing substances interfering with living or growth of wildlife)
	Crossability (Property of hybridizing with related wild animals and transmitting nucleic acid transferred by the technologies regulated by the Law to them)
	Other properties (Properties other than those mentioned above, such as one which indirectly affects wildlife by changing the base of the ecosystem, which are considered to require an assessment of Adverse Effect on Biological Diversity)
Microorganisms (living organisms belonging to Fungi [excluding mushroom], those belonging to the Protista, viruses and viroids)	Property of reducing other microorganisms (Property of reducing other microorganisms by competition, productivity of harmful substances, etc.)
	Pathogenicity (Property of interfering with living or growth of wild plants or animals by infecting them)
	Productivity of harmful substances (Property of producing substances interfering with living or growth of wild plants or animals)
	Property of transmitting nucleic acid horizontally (Property of transmitting nucleic acid being transferred by the technologies regulated by the Law to wild plants and animals and other microorganisms)
	Other properties (Properties other than those mentioned above, such as one which indirectly affects wildlife by changing the base of the ecosystem, which are considered to require an assessment of Adverse Effect on Biological Diversity)

4 Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Act No. 97 of 2003).Article 2(6).

Chapter 10. South Africa: Elements of risk assessment for LMOs

I. Abstract

The Genetically Modified Organisms Act, 1997[1] (Act No. 15 of 1997), administered by the Department of Agriculture, Forestry, and Fisheries of South Africa, regulates LMO activity in South Africa. South Africa takes a qualitative approach to the risk assessment (RA) of LMOs, and decisions surrounding LMOs in South Africa are made by a set of experts on the Executive Council. Two guideline documents exist to make the LMO risk assessment process more transparent, and are designed to help identify adverse effects related to LMO crops. These documents are designed to guide applicants of LMO activities as well as the Advisory Committee for providing a complete RA application document. In South Africa, LMO regulation is triggered by genetic modification. In conducting a risk assessment, the South African framework differentiates between the information required for LMO plants or microorganisms (fungi, viruses, etc). South Africa's RA guideline documents are primarily focused on herbicide resistant crops (HRC) and insect resistant crops (IRC), although general guidelines are also provided for microorganisms (fungi, viruses, etc) as well as LMOs used as food and feed.

II. Overview of legislative & regulatory framework

The Genetically Modified Organisms Act (GMO), 1997[1] regulates South Africa's framework for LMO risk assessments, and this Act is in turn administered by the Department of Agriculture, Forestry, and Fisheries of South Africa. The Register is responsible for administration of the GMO Act, and two regulatory bodies, the Advisory Committee and the Executive Council, oversee all activity surrounding LMO releases in South Africa.[2] The Advisory Committee evaluates the risk assessment data within each LMO application while the Executive Committee is responsible for approving applications for LMO activities. Two guideline documents exist that facilitate and detail the LMO risk assessment process in South Africa, and these two documents are the primary sources of information for this summary. The first guideline document entitled "Guideline Document for Work with Genetically Modified Organisms" [3] provides general information for LMO applicants on the GMO Act and describes the type of information to be included in a LMO risk assessment (RA) application and focuses mainly on requirements for LMO crops. The second document

1 Genetically Modified Organisms Act, 1997 (Act 15 of 1997). South Africa.

2 Processing of handling GMO applications. Guideline Document for Use by the Advisory Committee When Considering Proposals/ Applications for Activities with Genetically Modified Organisms (May 2004). 2004. Department of Agriculture, South Africa. Accessed 20 October 2009. http://www.daff.gov.za/ Figure 1.

3 Guideline Document for Work with Genetically Modified Organisms (May 2004). 2004. Department of Agriculture, South Africa. Accessed 20 October 2009. http://www.nda.agric.za/doaDev/sideMenu/biosafety/doc/GUIDELINE4WORKwithGOM.pdf.

entitled "Guideline Document for Use by the Advisory Committee When Considering Proposals/Applications for Activities with Genetically Modified Organisms"[4] provides guidance for the Advisory Committee on completing an application for LMO crops that can in turn also be used by the Executive Council for RA decision-making. The South Africa framework differentiates between the requirements for small-scale experimental release into the environment and large-scale commercial releases of LMO crops. Within South Africa's RA framework, specifications for required information are made based on the receiving organisms (plants, micro-organisms, and food/feed).

> two regulatory bodies, the Advisory Committee and the Executive Council, oversee all activity surrounding LMO releases in South Africa.[2] The Advisory Committee evaluates the risk assessment data within each LMO application while the Executive Committee is responsible for approving applications for LMO activities

Within South Africa's framework documents, LMOs are referred to as GMOs. We were unable to obtain a completed RA for South Africa to use for further discussion.

III. General principles

A. SCIENTIFICALLY SOUND

To incorporate scientific soundness in the RA process of LMOs in South Africa, the members of the regulatory bodies regarding LMOs in South Africa must collectively be knowledgeable in the development and application of LMOs and ecology as related to LMOs.[5] If the necessary expertise is lacking to complete a review of a LMO application, additional committee member(s) may be added to the necessary regulatory body.[6] In the event that new or additional scientific information becomes available regarding a LMO, previous RAs should be reviewed regarding that LMO.[7]

B. TRANSPARENCY

South Africa attempts to make their LMO RA process transparent through several guideline documents that detail the application process, risk decision-making process, LMO status certification process, as well as the public notification process involved with LMOs.[8] These documents, created as a result of the GMO Act, 1997, clearly define the regulatory bodies involved with RAs and the decision-making process regarding LMOs in South Africa. In addition, South Africa also has their own Biosafety Clearing-House website.

C. LACK OF SCIENTIFIC KNOWLEDGE OR CONSENSUS DOES NOT INDICATE LEVEL OR ABSENCE OF RISK

South Africa explicitly states the use of the precautionary principle for all risk assessments of LMOs.[9] They advocate a conservative approach in managing uncertain levels of risk by recommending control measures applicable to the higher risk level.[10]

D. RISK CONSIDERED IN THE CONTEXT OR RISK POSED BY NON-MODIFIED RECIPIENTS OR PARENTAL ORGANISMS

No information was found regarding this topic within the documents reviewed.

4 Guideline Document for Use by the Advisory Committee When Considering Proposals/Applications for Activities with Genetically Modified Organisms (May 2004). Department of Agriculture, South Africa.

5 Guideline Document for Use by the Advisory Committee When Considering Proposals/Applications for Activities with Genetically Modified Organisms (May 2004). Section 1.2 Genetically Modified Organisms Act, 1997 (Act No. 15 of 1997) Department of Agriculture, South Africa.

6 Guideline Document for Use by the Advisory Committee When Considering Proposals/Applications for Activities with Genetically Modified Organisms (May 2004). Department of Agriculture, South Africa. Section 3.2.1.

7 Guideline Document for Work with Genetically Modified Organisms (May 2004). Department of Agriculture, South Africa. Section 5v.

8 Biosafety. Department of Agriculture, Forestry and Fisheries, South Africa. Accessed 20 October 2009. http://www.daff.gov.za/

9 Guideline Document for Work with Genetically Modified Organisms (May 2004). Department of Agriculture, South Africa. Section 1.4.

10 Guideline Document for Work with Genetically Modified Organisms (May 2004). Department of Agriculture, South Africa. Section 5iv.

E. CASE-BY-CASE BASIS

South Africa requires that all LMO applications be addressed on a case-by-case basis, although the documents do not explicitly define a "case". Based on the guideline documents for South Africa RA applications, LMO RAs are divided by categories of the receiving organisms (plants, micro-organisms, and food/feed) and local conditions as well as agricultural practices assessed for each LMO case.[11] The amount of information required to consider and complete a RA may vary, however, depending on whether the LMO being addressed is a well-studied and understood organism versus a "dangerous organism about which there is a lot of uncertainty."[12] Finally, the South Africa framework makes a clear distinction between the risks and management practices associated with the specific LMOs of HRC and IRC.[13]

LMO RAs are divided by categories of the receiving organisms (plants, micro-organisms, and food/feed) and local conditions as well as agricultural practices assessed for each LMO case.

IV. Methodology

A. IDENTIFICATION OF NOVEL GENOTYPIC AND PHENOTYPIC CHARACTERISTICS ASSOCIATED WITH LMO, THAT MAY HAVE ADVERSE EFFECTS ON BIOLOGICAL DIVERSITY IN THE LIKELY POTENTIAL RECEIVING ENVIRONMENT, ALSO TAKING INTO ACCOUNT RISKS TO HUMAN HEALTH

1. Recipient/Parental Organism

No information was found regarding this topic within the documents reviewed.

2. Donor Organism

No information was found regarding this topic within the documents reviewed.

3. LMO Characteristics

Within the documents reviewed for South Africa, the guideline document lists desirable LMO characteristics that should be included in the LMO RA. The desired information mainly focuses on the insert(s) and/or characteristics of modification for the LMO such as sequence, function, and location of inserts as well as methods of modification. The documents also request information on the identity of the LMO such as taxonomic description, scientific name, and cultivar name for any genetically modified plants as well as a description of the vector's construction.[14]

The South Africa framework identifies a number of intended and unintended ecological and human health/welfare effects that could occur as a result of phenotypic changes in the LMO. This information is provided in Appendix 10.A.[15] These effects are categorized by the type of phenotypic change that may be incurred, such as a metabolic vs. behavioral change or a morphological alteration vs. an evolutionary change. These identified effects range from altered feeding rates in the LMO to changes in biological diversity.

4. Receiving Environment

The South African guidelines specifically request "Information on the receiving environment" be included in the LMO RA. This request includes information on the geographical location, size of release area, method(s) of release, proximity to protected areas and related/compatible species for hybridization, climatic considerations, target/non-target ecosystems, planned land developments in the region, and the distance to human settlements.[16]

11 Guideline Document for Work with Genetically Modified Organisms (May 2004). Department of Agriculture, South Africa. Section 5.3.1.
12 Guideline Document for Work with Genetically Modified Organisms (May 2004). Department of Agriculture, South Africa. Section 5iii.
13 Guideline Document for Use by the Advisory Committee When Considering Proposals/Applications for Activities with Genetically Modified Organisms (May 2004). Department of Agriculture, South Africa. Section 8.2.
14 Guideline Document for Work with Genetically Modified Organisms (May 2004). Department of Agriculture, South Africa. Section 5.3.3.i.
15 Guideline Document for Work with Genetically Modified Organisms (May 2004). Department of Agriculture, South Africa. Table 1.
16 Guideline Document for Work with Genetically Modified Organisms (May 2004). Department of Agriculture, South Africa. Section 5.3.3.iii.

Information available on previous releases of the relevant LMO is also considered. Specifically addressing LMO plants, the framework documents request information on hybridization potential with other plants, resistance development, spatial and temporal dispersal, and gene transfer potential. Much of the information requested on the receiving environment focused on ecological characteristics; this information is important because it is necessary to utilize the Keys provided in the Advisory Committee guideline document to estimate the likelihood of risk for LMO crops. (See Appendix 10.B)

B. EVALUATION OF THE LIKELIHOOD OF THESE ADVERSE EFFECTS BEING REALIZED, TAKING INTO ACCOUNT THE LEVEL AND KIND OF EXPOSURE OF THE LIKELY POTENTIAL RECEIVING ENVIRONMENT TO THE LIVING MODIFIED ORGANISM

1. Intended use of LMO compared to recipient or parental organism

The South Africa RA framework provides different guidelines for compiling a risk assessment depending on the intended use of the LMO. For the plant LMO guidelines, no specific mention was made to compare the LMO to a recipient/parental organism.

2. Characteristics of relevant potential receiving environment

This information was covered previously. (See previous section IVA4.)

3. How incidental exposure to the environment could occur

The South Africa framework documents identify a number of potential dispersal routes of LMOs into the environment. The routes of exposure are categorized as either natural or human-mediated dispersal routes. The natural routes are primarily water-related methods (flowing water, floods, currents, etc), but mention is also made for wind, insects, animals, and extreme weather being capable of causing dispersal. Human-caused routes cover a wide range of possibilities including different types of transportation (boats/ships, planes, etc), the transfer of water (ex. canals), trash/sewage, and seeds/stock.[17]

4. Conclusion of evaluation of likelihood of exposure

A qualitative method of determining the likelihood of adverse effects is provided in the Advisory Committee guideline document. A set of five dichotomous keys is provided to determine the likelihood of an adverse effect from planting HRC and/or IRC in an area or country (see Appendix 10.B). These keys utilize the scientific information requested in the other guideline document. The Keys attempt to facilitate the use of scientific information into the RA decision-making process, but they are only provided for the LMOs of HRC/IRC.[18]

C. EVALUATION OF THE CONSEQUENCES SHOULD THESE ADVERSE EFFECTS BE REALIZED

The South Africa framework documents reviewed address consequences of adverse effects in acknowledging that risk characterization must take into consideration both the magnitude and likelihood of adverse effects.[19] This indicates that consequences are likely qualitatively evaluated, although further evaluation criteria were not discussed within the documents reviewed.

D. ESTIMATION OF THE OVERALL RISK POSED BY THE LMO BASED ON THE EVALUATION OF THE LIKELIHOOD AND CONSEQUENCES OF THE IDENTIFIED ADVERSE EFFECT BEING REALIZED

Risk estimation is determined through a qualitative process in South Africa. The estimation of risk from LMOs is conducted by a group of experts on the Executive Council. The reviewed documents mention that in risk estimation, these experts should take into consideration the results of the

17 Guideline Document for Work with Genetically Modified Organisms (May 2004). Section 4.

18 Guideline Document for Use by the Advisory Committee When Considering Proposals/Applications for Activities with Genetically Modified Organisms (May 2004). Department of Agriculture, South Africa. Section 8.

19 Guideline Document for Work with Genetically Modified Organisms (May 2004). Department of Agriculture, South Africa. Section 7.1.

dichotomous keys for HRC/IRC and the lists of potential ecological effects and the magnitude and likelihood of adverse effects (Appendix 10.A and 10.B). In addition to the information provided in the LMO application, the risk estimate should also consider "expert opinions and, sometimes, public hearings of scientific institutions, consumer organizations, NGOs and the general public".[19] Regarding HRC/IRC release, "cropping practices, local environmental conditions and characteristics can affect the risks and how they are assessed or perceived."[18] No further guidelines were provided in the documents reviewed regarding the estimation of overall risk.

E. RECOMMENDATION AS TO WHETHER THE RISKS ARE MANAGEABLE, INCLUDING, WHERE NECESSARY, IDENTIFICATION OF STRATEGIES TO MANAGE THESE RISKS

The South Africa framework documents list a number of risk mitigation measures, and these measures are differentiated between management practices for plants, animals, and microorganisms.[3] Risk mitigation measures are further delineated for HRC and IRC, although it is clearly noted that the measures provided are not exhaustive. The documents mention the use of isolation distances, crop rotation, barriers, and monitoring for risk management during the deliberate release of a LMO into the environment. Four types of barriers are identified relevant to LMO crop risk management: physical/chemical, mechanical, biological, and the scale of the release.[18] Finally, South Africa approaches risk management for LMOs on a case-by-case basis, and the results from the RA should have a strong influence on determining an appropriate risk management plan.

> Four types of barriers are identified relevant to LMO crop risk management: physical/chemical, mechanical, biological, and the scale of the release.

F. WHERE THERE IS UNCERTAINTY REGARDING THE LEVEL OF RISK, IT MAY BE ADDRESSED BY REQUESTING FURTHER INFORMATION ON THE SPECIFIC ISSUES OF CONCERN OR BY IMPLEMENTING APPROPRIATE RISK MANAGEMENT STRATEGIES AND/OR MONITORING THE LMO IN THE RECEIVING ENVIRONMENT

Although no information was found specifically addressing this topic within the documents reviewed, South Africa does adopt the precautionary principle when dealing with LMOs.

V. Discussion

South Africa is transparent in their RA process regarding LMOs, by providing guideline documents associated with the LMO RA process. These guidance documents clarify a decision process for all associated parties, from someone applying for LMO release or use to members of the Advisory committee responsible for making decisions regarding a LMO RA. South Africa also has its own Biosafety Clearing-House to post the country's decisions regarding LMOs, although the website is not currently up-to-date. The guideline documents also provide Keys for estimating the likelihood of effects occurring, but final estimation of risk is left to the Advisory Council.

South Africa takes a case-by-case approach in assessing risks from LMOs. The RA approach is differentiated early on in the guideline documents between plants, microorganisms, and viruses/viral vectors. With these categories, they also consider the intended use of the LMO (ex. experimental containment vs. open release), and the RA guidelines differ according to the LMO product category. South Africa's RA framework relies heavily on the use of examples (Appendix 10.A) to exemplify the potential adverse effects that may be associated with LMOs, particularly with the risks surrounding HRC/IRC.

Some similarities as well as differences exist in the information requested by the South Africa RA guideline documents and Annex III of the Cartagena Protocol. Similarities include characterization of the LMO based on vector information, the type of modification involved, detailed information on the receiving environment, as well as clearly stating the identity of the LMO. Within the documents reviewed, we could not find requests for information on the parental/recipient organism, the donor organism, or the centers of origin, which are included in Annex III. The South Africa framework asks for more detailed information on the LMO than that requested in Annex III, such as the stability of traits, the rate and expression of the new material inserted, and the effects of more than one insert (ex. stacking). The South Africa framework also desires further details on the receiving environment such as potential land-use changes and distance to human settlements. Regarding risk management, South Africa lists in detail several management methods for HRC/IRC risk mitigation including herbicide rotation, cultural weed control methods, and economic thresholds.

APPENDIX

APPENDIX 10.A: The relationship between the potential and intended phenotypic modifications, unintended or intended ecological effects, and effects on human health and welfare in South Africa. The following table is provided in the GMO Act, 1997.[15]

Type of Effect	Examples of potential/intended phenotypic changes	Examples of intended/ unintended ecological effects	Examples of effects on human health and welfare
Metabolism	• Individual growth rates • Energy metabolism, pathways and rates • Photosynthetic and chemosynthetic pathway structures and rates • Rates of nutrient uptake and cycling • Amounts and types of nutrients used • Use of pollutants as nutrients, and pollution degradation • Nitrogen fixing pathways and rates • Carbon dioxide consumption • Tolerance of elevated CO2 • Expression of novel proteins or metabolites, and increased metabolic wastes • Production of antibiotics, or biological toxins such as that from Bacillus thuringiensis (Bt toxin) • Antibiotic or pesticide resistance	• Altered feeding rates and efficiencies • Altered rates of nutrient cycling and biological energy transfers • Altered rates of photosynthesis and carbon fixation and plant productivity • Modified rates and patterns of nitrogen fixing • Shifts in competitive abilities among species • Changes in the degree of pesticide and antibiotic resistance among target and naturally occurring species, and spread of antibiotic resistance genes by lateral transfer • Release of antibiotics, toxins, or increased concentration of novel metabolites • Decrease or increase of biological diversity	Changes in agricultural productivity Changes in forest production and timing of tree harvesting cycles Changes in stock composition and productivity of fisheries Increased dependence on aquaculture Increased intensity and variety of food allergies due to novel proteins, hormones or other metabolites, or altered levels of normal proteins and hormones and other metabolites

Type of Effect	Examples of potential/intended phenotypic changes	Examples of intended/ unintended ecological effects	Examples of effects on human health and welfare
Tolerance of physical factors	• Temperature • Humidity or moisture • Soil chemical and physical properties, including nutrients and water potential • Light intensity • Salinity • pH (acid/base) • Water chemistry • Pressure • Oxygen, carbon dioxide, and other gases such as those of anaerobic environments • Toxic chemicals/pesticides/ antibiotics • Heavy metals (e.g. mercury	• Geographical relocation, expansion or concentration of preferred habitats for species and ecological communities • Changed species/population phenology (seasonal timing of life cycles), including patters of growth, development, and breeding • Altered geographical ranges of species • Altered patterns of dispersal and migration • Increased and change in routes and extent of biomagnification (concentration) of toxic substances, including heavy metals • Changed composition and diversity of ecological communities	• Change in geographical or local constraints on crop production • Changes in geographical or local constraints on disease vectors, pathogens, pests or pollinators • New threats or persistence and abundance of terrestrial and aquatic wildlife • Increased invasiveness of noxious or weedy species • Loss of genetic diversity in natural populations
Morphology or architecture of organisms	• Animal shape, size, colour • Internal and surface geometry of unicellular algae and protozoa • Antigenicity of disease organisms and parasites • Skeletons and appendages • Leaf shape, pattern of plant nodal extension and branching, flower structure, branching and frond geometry of macrophytic algae • Spines, hairs, trichomes and other protective devices • Bacteria cell-wall characteristics • Mosaic segments of virus • Cell structure, organs, organ systems • Unicellularity, multicellularity	• Altered species interaction: predator/prey, herbivory, competition • Mate recognition • Changes in bacterial cell walls and some antibiotic resistances • Altered virus/host interaction • Changed crop plant architecture • Increase or decrease in plant protection against pathogens and herbivores	• Increase or decrease in virulence of pathogens • Gains or losses in plant yields through changes of architecture (e.g. dwarf varieties of rice and wheat) • New problems in conservation • New opportunities for horticultural innovation

Type of Effect	Examples of potential/intended phenotypic changes	Examples of intended/ unintended ecological effects	Examples of effects on human health and welfare
Behaviour	• Reproduction • Territoriality • Migration, navigation or orientation • Chemosensory abilities, including pheromones and allelochemicals • Motility/locomotion • Animal communication • New kinds and levels of plant secondary compounds • Colonisation • Pathogenicity of bacteria, virus and fungi • Mutualisms/coevolution • Pollination • Photoperiodism • Foraging patterns and feeding specialisation and rates • Social behaviour, communicable and co-operative living, "altruism"	• Altered breeding patterns and cycles, and mate-recognition systems • Change in population abundance and species assemblages • Altered population dynamics and phenology • Changes in self-compatibility and incompatibility of plants • Changes in rates, plant species spectrum, and effectiveness of pollination • Increases and decreases in pathogenicities and patterns of disease transmission	• Changes in local and geographical patterns of abundance of wildlife, game and commercially harvested species • Alterations in agricultural productivity • Increase or decrease in human, animal and plant health as behaviours of pathogens, disease vectors and pollinators change
Factors controlling regulating natural populations	• Novel disease resistance • Reduced predation or parasitism • Habitat preferences, extensiveness of preferred and secondary habitats • Antibiotic or biocide sensitivity and resistance • Extinction, local or global • Increases or decreases in fitness	• Altered population and community dynamics • Release from pre-existing ecological limits or establishment of new limits • Changed disease transmission • Lateral transfer of antibiotic and toxin resistances among bacteria • Changed tropic interactions • Increase or decrease in pest and pathogen populations and the attendant problems	• Decline or loss of therapeutic effectiveness of antibiotics • Origin of new pests, weeds and pathogens (especially plant virus modification)

Type of Effect	Examples of potential/intended phenotypic changes	Examples of intended/ unintended ecological effects	Examples of effects on human health and welfare
Demography, life history, population genetics and evolution	• Population fitness • Average life cycle patterns (simple or complex) • Mode of reproduction: sexual, asexual, or alternating between these two • Frequency of reproduction • Average rates and patterns of embryonic and larval development • Patterns of metamorphosis • Age of reproductive maturity and age of last reproduction • Fertility and fecundity • Survival rates with age (survivorship), average longevity • Net and intrinsic rates of change in population size and density • Age-structure of population • Social organisation, kin selection and inclusive fitness • Substratum affinities • Patterns of dormancy, diapause, aestivation, hibernation, and spore and seed banks • Sex, sex ratios, mating types • Population genetic structure, genetic recombination within populations • Genotype-environment interactions and correlation • Pathogens host ranges • Vector host ranges and competence • Geographical arrays of conspecific populations (metapopulations) • Specialised genetic exchange (sexual) mechanisms of bacteria (transduction, transformation, conjugation, retrotransposons, conjugative, transposons, other mobile elements) • Gene flow among conspecific populations • Genetic exchange between species and phylogenetic lineage	• Altered population and community dynamics • Shifts in the composition of ecological communities and local biological diversity • Increased or decreased fitness of populations • Increased or decreased population sizes and densities • Increased or decreased populations fluctuations, population stability • Altered age-structure in populations Micro-evolutionary changes set in motion in the GMO population or surrounding natural populations • Changes in spatial and temporal distribution of population and species • Altered genetic structure of the GMO population and their parental populations, if the two are sympatric (conspecific introgression) • Increase interspecies hybridisation • GMO evolution due to mutation, genetic exchange and natural selection	• New problems in pest and pathogen control • Epidemiological problems • Commercially harvested and/or game species yield change • Conservation and wildlife management practices require adjustment • Design of wildlife refuges and nature preserves require reconsideration and possibly change • Mitigation procedures become necessary to protect biological diversity and the genetic diversity of natural populations

APPENDIX 10.B: Keys utilized in South Africa to determine likelihood of risks from living modified organism. 18

When using a key, if you reach a point where you cannot continue any further or there is an indication of "stop", it means that you need to make a decision about a particular risk.

Key 1: Likelihood that the competitive abilities of wild relatives occurring in undisturbed wild-lands will be altered by hybridization with transgenic crops

1. Is the crop only self-pollinating?

If no: Go to No. 2 If yes: Stop, and go to key 3.

2. Can viable hybrids form between the crop and wild relatives?

If yes: Go to No. 3 If no: Stop, and go to key 2.

3. *Do these wild relatives occur in the proximity of the crop?*

If yes: Go to No. 4 If no: Stop, and go to key 2.

4. *Do the crop and the wild relatives overlap in flowering periods?*

If yes: Go to No. 5 If no: Stop, and go to key 2.

5. *Do hybrids survive and reproduce in the native habitat*

If yes: Go to No. 6 If no: Stop, and go to key 2.

6. *Does HR/IR trait give hybrids or introgressants a fitness advantage in wild habitats?*

If yes: Go to No. 7 If no: Stop, and go to key 2.

7. *Is the resistance trait maternally inherited?*

If yes: Likelihood of producing If no: Likelihood of producing new, more competitive native new, more competitive native species rapidly.

Key 2: Likelihood that a new type of arable weed will be produced by gene flow between the transgenic crop and its relatives:

1. *Do hybrids occur between the crop and any weedy/ wild relative?*

If yes: Go to No. 2 If no: Stop, and go to key 3.

2. *Do these weedy/wild relatives occur in the proximity of the crop?*

If yes: Go to No. 3 If no: Stop, and go to key 3.

3. Do the crop and the weedy/wild relatives overlap in flowering periods?

If yes: Go to No. 4 If no: Stop, and go to key 3.

4. *Are the hybrids and/or introgressants highly competitive in arable environments?*

If yes: Go to No. 5 If no: Stop, and go to key 3.

5. *Are hybrids or introgressants herbicide resistant or insect resistant?*

If HR: Go to No. 6 If IR: Go to No. 8.

6. *Can HR hybrids or introgressants easily be controlled by other means besides the herbicides associated with the HRC?*

If yes: Likelihood of losing If no: Go to No. 7 one herbicide.

7. *Is the same herbicide used in succeeding crops?*

If yes: Likelihood of losing If no: Stop and go to key 3. the only weed control option.

8. *Does the IR trait confer an increased fitness in the wild/weedy relative compared to non- IR relative?*

If yes: Likelihood of increased If no: Stop and go to key 3. weed problems

Key 3: Likelihood that the transgenic crop will become a volunteer problem on arable land or wild areas:

1. *Is the crop known to leave volunteers in succeeding crops?*

If yes: Go to No. 2 If no: Stop. There should not be a volunteer problem. Assess hazard of evolution of herbicide or insecticide resistance (keys 4 and 5).

2. *Does the crop have weedy traits?*

If yes: Go to No. 3 If no: Stop, and go to key 4.

3. *Is the volunteer plant expected to be herbicide resistant or insect resistant?*

If HR: Go to No. 4 If IR: Go to No. 6.

4. *Can the HR-volunteer easily be controlled by other means but the herbicides associated with HRC?*

If yes: likelihood of losing If no: Go to No. 5 use of a herbicide.

5. *Is the herbicide used for control of non-transgenic volunteers in succeeding crops?*

If yes: likelihood of losing If no: Stop, and go to key 4 the weed control option (herbicide)

6. *Is the IR-volunteer crop able to establish itself in the wild?*

If yes: likelihood of escapes If no: Go to No. 7 into wild habitats

7. *Can the IR volunteer easily be controlled in succeeding crops?*

If no: Go to No. 8 If yes: Stop, and go to key 5

8. *Does the IR trait confer an increased fitness in the volunteer compared to non-transgenic volunteers?*

If yes: Likelihood of increased If no: Stop, and go to key 5 weed problems

Key 4: Likelihood of build-up of HR-resistant weeds:

1. *Are resistance cases to the herbicide that the HRC withstands or herbicides belonging to the same chemical family or having the same mode of action (MOA) or degradation known to occur, or is gene flow possible from HRC to related weedy species, or is the herbicide a new chemical?*

If yes: Go to No. 2 If no: Stop. There should be a low hazard of evolution of herbicide resistant weeds, especially if integrated weed management is used.

2. *Is the cropping system primarily a monoculture or the HRC is or will be fully rotated with other crops?*

If monoculture: Go to No. 5 If fully rotated: Go to No. 3.

3. *Is weed management primarily based on an integrated strategy or on chemical control?*

If chemical control: Go to No. 4. If integrated strategy: Stop. Very limited hazard of herbicide resistance evolution.

4. *Is the MOA of the herbicide used in HRC crop similar or different to that used in the other rotational crops?*

If same: consider likelihood If other: Stop. Very limited of selection for resistant hazard of herbicide weed resistance evolution.

5. *Is weed management under the monoculture system primarily dependent on herbicides?*

If yes: Go to No. 6 If no: Stop. Very limited hazard of herbicide resistance evolution.

6. *Is the herbicide to be used in the HRC a new persistent compound or a chemical to be used twice or more in cropping cycle?*

If yes: consider the likelihood If no: Go to No. 7 of selecting new resistant weeds.

7. *Does the herbicide used in HRC share MOA with others in use?*

If yes: Risk of aggravating or If no: Stop. Limited speeding resistance problems hazard of herbicide resistance evolution.

Key 5: Likelihood of build-up of resistant insects:

1. *Does the IRC comprise a major proportion of the local area planted with non-transgenic varieties of that crop?*

If yes: Go to No. 2 If no: Stop. Limited hazard of insecticide resistance evolution.

2. *Does the IRC express only a single or few insecticidal-toxin(s) active against the harmful insect?*

If yes: Go to No. 3 If no: Stop. Limited hazard of insecticide resistance evolution.

3. *Is expression of the IR trait confined to a short lasting selected growth stage of the crop?*

If no: Go to No. 4 If yes: Stop. Limited hazard of insecticide resistance evolution.

4. *If resistance in insects occurs, is expression of the IR trait associated with a significant fitness penalty for the resistant insect?*

If no: Go to No. 5 If yes: Stop.

5. *Are resistant insects easily controlled by other control measures?* If yes: likelihood of losing If no: likelihood of effect of the IR trait losing the IR trait and specific-toxin based biological pesticides.

Chapter 11. United States: Elements of risk assessment for LMOs

I. Abstract

The United States' (U.S.) framework for the regulation of living modified organisms (LMOs) is complex, with three agencies providing complementary and sometimes overlapping regulation of LMOs depending on their intended use. A salient feature of this "coordinated framework" is that while it originally called for a product-based approach to LMO oversight, the trigger for regulation and risk assessment actually varies in practice among agencies. For example, the Animal and Plant Health Inspection Service (APHIS) regulates plants and plant pests produced by modern biotechnology while the Environmental Protection Agency's (EPA) trigger for regulation is based on pesticidal traits of the LMO. The risk assessments conducted by APHIS assessments are usually qualitative, based on literature reviews, theory, and results from field testing. The EPA risk assessments often include quantitative data, including results of toxicity tests and information generated from mathematical modeling. Nonetheless, the U.S. agencies generally follow similar overarching principles, (e.g. level of transparency and a case-by-case approach) despite some differences in specific regulatory procedures.

II. Overview of legislative & regulatory framework

The regulation of LMOs in the United States falls under the oversight of three agencies that collectively function within the Coordinated Framework for the Regulation of Biotechnology (hereafter, coordinated framework).[1] The types of LMOs that each agency regulates, the legislation administered by each agency, and the type of risk assessment conducted, are summarized in Table 11.1. The coordinated framework grants complementary and sometimes overlapping regulatory responsibility, depending on the type of LMO, to the U.S. Department of Agriculture – Animal and Plant Health Inspection Service (APHIS; plants, plant pests, and veterinary biologics), the U.S. Food and Drug Administration (FDA; food, feed, additives, and drugs), and the U.S. Environmental Protection Agency (EPA; microbial and plant pesticides, referred to by EPA as plant-incorporated protectants – PIPs, also virus-resistance LMOs). A LMO falling into categories regulated by more than one agency requires approval from each applicable agency. Our focus here is on risk assessment frameworks used for the environmental release of LMOs, and not for food, feed, and processing uses.

1 "Coordinated framework for regulation of biotechnology; announcement of policy; notice for public comment," 51 U.S. Federal Register 123 (26 June 1986), pp. 23302-23350.

The FDA does provide guidance for food crops used for pharmaceuticals and industrial compounds; however, in most cases, LMOs released into the environment are only subject to APHIS and EPA guidelines. Therefore, our focus for the remainder of this summary is on APHIS and EPA regulations.

> The coordinated framework grants complementary and sometimes overlapping regulatory responsibility, depending on the type of LMO, to the U.S. Department of Agriculture – Animal and Plant Health Inspection Service (plants, plant pests, and veterinary biologics), the U.S. Food and Drug Administration (food, feed, additives, and drugs), and the U.S. Environmental Protection Agency (microbial and plant pesticides

Unlike many countries that have drafted new legislation specifically for regulation of LMOs, all U.S. regulations under the coordinated framework are interpreted within existing legislation. For example, APHIS guidelines[2] are outlined under the Plant Protection Act,[3] while EPA guidelines[4] fall under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)[5] and the Toxic Substances Control Act (TSCA).[6] Since most EPA authority falls under FIFRA, we do not cover policies under TSCA in this chapter. Developers of LMO technology must submit two types of application to APHIS before a LMO can be considered for "non-regulated" status (i.e. not subject to APHIS biotechnology regulations; Figure 11.1). First, a notification or permit application is submitted to APHIS to seek permission for use of the LMO for field testing. Second, a developer wishing to transport a LMO across state boundaries without needing to notify or request a permit from APHIS submits a petition to seek a determination of non-regulated status from APHIS. The petitioning process requires information detailed enough for APHIS to conduct an "environmental assessment," a type of risk assessment.

TABLE 11.1: Summary of U.S. oversight of LMOs, including types of LMOs regulated, legislation invoked for regulation, and risk assessment procedure.

Federal Agency	Types of LMOs regulated	Legislation Invoked for Regulation	Risk Assessment Procedure
U.S. Dept. of Agriculture – Animal and Plant Health Inspection Service (APHIS)	Plants and plant pests	Plant Protection Act	Environmental assessment & FONSI (finding of no significant impact)
Environmental Protection Agency (EPA)	Microbial and plant pesticides, novel microbes	• Federal Insecticide, Fungicide, and Rodenticide, Act • Toxic Substances Control Act (Section 5); *not examined in this chapter	Environmental assessment
Food and Drug Administration (FDA)	Food, feed, additives, drugs	Federal Food, Drug, and Cosmetic Act	-Industry "consultation" with FDA

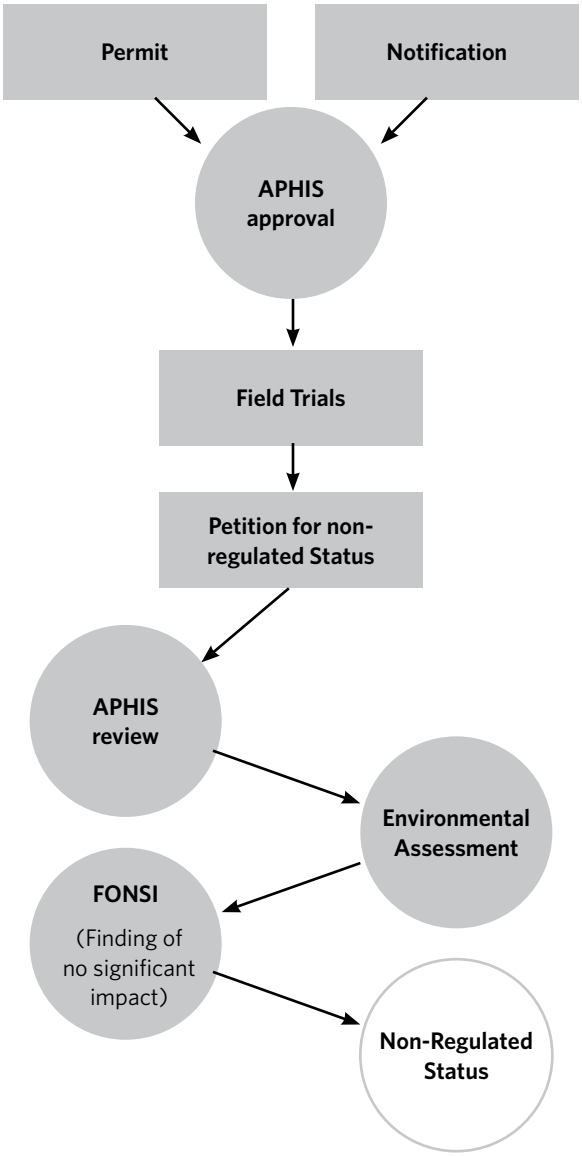
2 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," Title 7 Code of Federal Regulations, Part 340. 2008 Edition.
3 U.S. Plant Protection Act. June 2000.
4 "Regulations under the Federal Insecticide, Fungicide, and Rodenticide Act for plant-incorporated protectants (formerly plant pesticides)," Title 40 Code of Federal Regulations, Parts 152, 174. 2001 edition.
5 U.S. Federal Fungicide, Insecticide, and Rodenticide Act (FIFRA). 1996.
6 U.S. Toxic Substances Control Act (TSCA). 2008.

If there is determined to be minimal risk associated with non-regulated release of a LMO, APHIS issues a finding of no-significant impact (FONSI). In the remainder of this chapter, "deregulated" is used to indicate that the LMO has received a determination of non-regulated status from APHIS.

The process for receiving approval for a LMO from the EPA is as follows. Developers of LMO-PIP technologies must submit applications to the EPA for any environmental release, including experimental field trials. The EPA regulates these initial field releases under an experimental use permit, which restricts the size of the release and may require certain management practices to avoid potential adverse environmental effects during testing. The developer can then apply for a commercial registration. The EPA may grant temporary or permanent registrations, and may require certain risk management measures as a stipulation of granting a registration.

The remainder of this summary focuses on the above APHIS and EPA guidelines, as well as individual APHIS environmental assessments and FONSIs for determinations of non-regulated status. Specifically, we examined three environmental assessments, with one case (*Bt* Cry1F corn line 1507) used to illustrate examples in several of the following sections.

FIGURE 11.1: Steps followed under APHIS regulations for a LMO to reach non-regulated status. Rectangles represent actions taken by an applicant seeking LMO deregulation and circles represent investigation and approval steps conducted by APHIS.



III. General principles

A. SCIENTIFICALLY SOUND

Both the APHIS and EPA approaches to regulating LMOs contain aspects that address the issue of scientific soundness. The Plant Protection Act, under which APHIS regulates LMOs, repeatedly states that consideration of requests and determinations should be based on "sound science."[3] We were unable to find explicit reference to scientific soundness or expert knowledge in the APHIS and EPA guideline documents we reviewed; however, APHIS guidelines imply the need for field tests to be conducted in a scientific manner. For example, reports on results of field tests must include methods of observation, resulting data, and methods of analysis for adverse effects.[7] Likewise, EPA regulations require that studies are conducted using "Good Laboratory Practices,"[8] an extensive set of guidelines outlining standards (e.g. personnel, facilities, equipment, and protocols) required for studies that are submitted in support of applications for pesticide registration.[9] A review of APHIS environmental assessments also indicates that determinations of non-regulated status are based on review of scientific literature, including personal communication for technical information; however, the documents reviewed for this report did not state requirements for the level of scientific expertise of these consultants.

B. TRANSPARENCY

Both the APHIS and EPA approaches to regulating LMOs contain aspects that address the issue of transparency. For example, the Plant Protection Act (PPA) states that regulations and policies developed under the act should be "transparent and accessible"[10] and that "public input will be sought in advance of promulgating regulations necessitating a risk assessment."[11] Specific details required for environmental assessments (APHIS) and risk assessments (EPA) are included in the regulatory guidelines which are publicly accessible in the U.S. Code of Federal Regulations.[12,13,14,15,16,17] Likewise, risk assessments and decisions for specific cases are accessible on agency websites and searchable databases (e.g. http://www.aphis.usda.gov/brs/biotech_ea_permits.html and http://www.isb.vt.edu/), and the public is notified through the federal register when APHIS releases environmental assessments and FONSIs. The EPA provided an example of transparency when it held public hearings regarding the re-registration of Bt corn.

Specific details required for environmental assessments (APHIS) and risk assessments (EPA) are included in the regulatory guidelines which are publicly accessible in the U.S. Code of Federal Regulations.[12,13,14,15,16,17] Likewise, risk assessments and decisions for specific cases are accessible on agency websites and searchable databases

C. LACK OF SCIENTIFIC KNOWLEDGE OR CONSENSUS DOES NOT INDICATE LEVEL OR ABSENCE OF RISK

We were unable to locate this specific information, including reference to the precautionary principle, within the reviewed legislation and guidance documents. However, with regard to regulation of LMOs,

7 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," Title 7 Code of Federal Regulations, Part 340.3. 2008 Edition.
8 "Regulations under the Federal Insecticide, Fungicide, and Rodenticide Act for plant-incorporated protectants (formerly plant pesticides)," Title 40 Code of Federal Regulations, Part 152.50. 2001 Edition.
9 "Good laboratory practice standards," Title 40 Code of Federal Regulations, Part 160. 2001 Edition.
10 U.S. Plant Protection Act. June 2000. Section 411(a).
11 U.S. Plant Protection Act. June 2000. Section 412(d)1.
12 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," Title 7 Code of Federal Regulations, Part 340.3(d)2. 2008 Edition.
13 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," Title 7 Code of Federal Regulations, Part 340.6(c)1-5. 2008 Edition.
14 "Reporting requirements and review processes for microorganisms," 40 Code of Federal Regulations, Part 725.155. 2003 Edition.
15 "Reporting requirements and review processes for microorganisms," 40 Code of Federal Regulations, Part 725.160. 2003 Edition.
16 "Reporting requirements and review processes for microorganisms," 40 Code of Federal Regulations, Part 725.255. 2003 Edition.
17 "Reporting requirements and review processes for microorganisms," 40 Code of Federal Regulations, Part 725.260. 2003 Edition.

it is generally well known that the U.S. does not ascribe to a precautionary approach.[18]

D. RISK CONSIDERED IN THE CONTEXT OF RISK POSED BY NON-MODIFIED RECIPIENTS OR PARENTAL ORGANISMS

Comparison of risks between the LMO and non-modified recipients is a key feature of the APHIS approach. For example, regulatory guidelines issued by APHIS require that applicants describe the "biology of the non-modified recipient plant"[19] and genotypic and phenotypic differences between recipient and modified plants, including morphological, structural, and physiological traits, the number of inserted copies of genetic material, and the state of the genetic material inside the recipient organism.[20] Furthermore, evidence for the risk of adverse effects must be provided to substantiate the likelihood of the LMO becoming a plant pest relative to the non-modified organism.[21] In establishing EPA's plant-incorporated protectant rules, microbial plant pesticides and conventionally bred plants were considered for comparison for pest protected plants.[22]

E. CASE-BY-CASE BASIS

In accord with the requirements of the coordinated framework,[1] a case-by-case approach to risk assessment is taken by APHIS, such that regulation is triggered for each transformation event. Likewise, EPA uses a case-by-case approach to regulate PIPs, focusing regulation on both novel pesticidal traits and novel uses.[23] However, there is an exception to the APHIS case-by-case oversight: when two deregulated LMOs are combined, the offspring of such a crossing are not subject to regulation by APHIS. In contrast, EPA retains regulatory authority over a LMO with two approved PIPs.

a case-by-case approach to risk assessment is taken by APHIS, such that regulation is triggered for each transformation event. Likewise, EPA uses a case-by-case approach to regulate PIPs, focusing regulation on both novel pesticidal traits and novel uses

IV. Methodology

A. IDENTIFICATION OF NOVEL GENOTYPIC AND PHENOTYPIC CHARACTERISTICS ASSOCIATED WITH LMO THAT MAY HAVE ADVERSE EFFECTS ON BIOLOGICAL DIVERSITY IN THE LIKELY RECEIVING ENVIRONMENT, ALSO TAKING INTO ACCOUNT RISKS TO HUMAN HEALTH.

1. Recipient/Parental Organism

Both APHIS and EPA require detailed information about recipient organisms in their respective risk assessment guidelines. The APHIS notification/permitting process for field tests of LMO plants requires classification information, including scientific, common, and trade names.[12,24] The APHIS petition process for seeking non-regulated status of a LMO further clarifies that the above information should be provided to allow the recipient plant to be classified to the "narrowest taxonomic grouping possible."[25] In addition, APHIS requests a description of the biology, phenotype, genotype, and location where the recipient organism is collected,

18 Peck, A. 2008. The new imperialism: Toward an advocacy strategy for GMO accountability. The Georgetown International Environmental Law Review 21:37-32.

19 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," Title 7 Code of Federal Regulations, Part 340.6(1). 2008 Edition.

20 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," Title 7 Code of Federal Regulations, Part 340.4(5). 2008 Edition.

21 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," Title 7 Code of Federal Regulations, Part 340.6(4). 2008 Edition.

22 National Research Council. 2000. Genetically-modified pest-protected plants: science and regulation. National Academy Press, Washington, D.C.

23 McHughen, A., Smyth, S. 2008. US regulatory system for genetically modified [genetically modified organism (GMO), rDNA or transgenic] crop cultivars. Plant Biotechnology Journal 6: 2-12.

24 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," Title 7 Code of Federal Regulations, Part 340.4(b). 2008 Edition.

25 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," Title 7 Code of Federal Regulations, Part 340.6(c)1. 2008 Edition.

developed, and produced.[26] A review of APHIS environmental assessments verified that such information is indeed considered when reaching decisions. For example, an environmental assessment of an insect-resistant and glufosinate-tolerant corn line (Bt Cry1F corn, line 1507) assessed results of laboratory testing for molecular genetic characterization and phenotypic characterization of the LMO and the non-modified counterpart[27] (see Table 11.2 for details). The EPA information requirements are similar to those of APHIS, including a description of taxonomic classification (to strain), habitat, geographical distribution, and source.[28]

TABLE 11.2: Examples of data submitted in support of nonregulated status for Bt Cry1F corn line 1507 (Adapted from [27]).

Molecular Genetic Characterization
Southern analysis of the cry1F gene in TC1507, the ubiquitin promoter for Cry1F gene, the pat gene, and the CaMV promoter for pat gene
Mendelian segregation of B. Cry1F maize line for glufosinate tolerance
Cry1F protein characterization in tissues from line 1507 hybrids
Phenotypic Characterization
Agronomic Performance Traits between a line 1507 hybrid and a hybrid control
Seed Germination
Compositional and Nutritional Analysis

2. Donor Organism

APHIS guidelines outline that taxonomic information, including scientific, common, and trade names of donor organisms must be included in notifications and permits for field tests[12,24] and in petitions for determination of non-regulated status.[25] EPA regulations also require data allowing for determination of the donor organism to the level of strain.[29]

3. LMO Characteristics

Both APHIS and EPA require detailed information regarding LMO traits and potential adverse effects associated with those traits. For example, petitions to APHIS for determination of non-regulated status require description of how the LMO genotype differs from the recipient organism, including the "nature of the transformation system, the inserted genetic material and its product(s), and the regulated article."[30] Furthermore, the phenotype of the LMO must be described in relation to the non-modified analog with reference to weediness, pest characteristics, disease and pest susceptibilities, gene expression, new enzymes, changes to plant metabolism, effects to non-target organisms, and gene transfer to sexually compatible species.[26] The issues discussed in "potential environmental impacts" sections of APHIS environmental assessments closely match the above LMO considerations.[27,31,32] For example, in an environmental assessment of an herbicide and lepidopteran-resistant corn line (BtCry1 corn line 1507), APHIS' consideration of traits that may cause non-target impacts included among other things, the potential impacts of the LMO on other lepidopterans, beneficial organisms, non-lepidopteran pests, and threatened and endangered arthropods[27] (see Table 11.3 for further examples).

26 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," Title 7 Code of Federal Regulations, Part 340.6(c)3-4. 2008 Edition.

27 USDA-APHIS. 2001. USDA/APHIS decision on mycogen seeds c/o Dow AgroSciences LLC and Pioneer Hi-Bred International, Inc. Petition 00-136-01P seeking a determination of nonregulated status for BtCry1F insect resistant glufosinate tolerant corn line 1507 – Environmental assessment and finding of no significant impact. Website: http://www.aphis.usda.gov/brs/aphisdocs2/00_13601p_com.pdf.

28 "Reporting requirements and review processes for microorganisms," 40 Code of Federal Regulations, Part 725.155(d)2. 2003 Edition.

29 "Reporting requirements and review processes for microorganisms," 40 Code of Federal Regulations, Part 725.155(d)1. 2003 Edition.

30 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," Title 7 Code of Federal Regulations, Part 340.6(c)3. 2008 Edition.

31 USDA-APHIS. 1998. USDA/APHIS response to Monsanto petition 98-216-01 for determination of nonregulated status for glyphosate tolerant canola line RT73 – Environmental assessment and finding of no significant impact. Website: http://www.aphis.usda.gov/brs/aphisdocs2/98_21601p_com.pdf.

32 USDA-APHIS. 2004. USDA/APHIS environmental assessment – Monsanto Company and Forage Genetics international petition 04-110-00P for determination of non-regulated status for Round-up Ready Alfalfa events J101 and J163 – Environmental assessment and finding of no significant impact. Website: http://www.aphis.usda.gov/brs/aphisdocs2/04_11001p_com.pdf.

The EPA information requirements for characteristics of the LMO largely overlap those outlined by APHIS,[4,33] although, some unique information is required. For example, applicants must include a description about how introduced genetic material may affect the recipient's behavior, as well as the genetic material's stability, expression, and alteration, and maps of introduced sequences.[28] The EPA also requires information on the LMO's host range as well as potential non-target effects including interactions with predators, prey (for animals), competitors, symbionts, parasites, and pathogens.[34] Information is also required regarding the LMO's expected role in biogeochemical and biological processes, expected byproducts of its use and total production volume.[34]

TABLE 11.3: Examples of test results used by APHIS for assessing presence of non-target effects of Bt Cry1F corn line 1507 (adapted from source[27]).

Comparison of maize-derived Cry1F protein and microbially-derived Cry1F protein
Environmental fate of Cry1F in soil
Honeybee – dietary effects on larvae mortality and development
Collembola – 28 day chronic exposure study
Green Lacewing larvae, parasitic Hymenoptera, Ladybird Beetle, Earthworm, Bobwhite Quail – dietary toxicity tests
Monarch Butterfly (and other Lepidopterans) – non-target exposure and risk assessment for dispersal of Cry1F pollen
Beneficial arthropod predator – field study
Allergenicity profile – comparison of amino acid sequence similarity of Cry1F and PAT proteins to known allergen proteins

4. Receiving Environment

The information APHIS requires about the receiving environment is less extensive than that required for the characteristics of the recipient, donor, and LMOs. However, applicants must provide information about the location of release and the size of introduction when notifying APHIS of field tests.[35] Petitions for a determination of non-regulated status also require a description of field test results indicating negative impacts of the LMO on "plants, non-target organisms, and the environment."[36] Although we were unable to find specific reference to consideration of the receiving environment in the EPA documents we reviewed, such consideration is implicit in the diverse array of tests required prior to the release of a LMO. For example, the EPA requires that a diversity of non-target toxicity tests are conducted for a broad array of taxa, including plants, birds, mammals, fish, marine species, and soil invertebrates[37] (see section IV C and Appendix 11.A for more details).

Although we were unable to find specific reference to consideration of the receiving environment in the EPA documents we reviewed, such consideration is implicit in the diverse array of tests required prior to the release of a LMO. For example, the EPA requires that a diversity of non-target toxicity tests are conducted for a broad array of taxa, including plants, birds, mammals, fish, marine species, and soil invertebrates

33 "Protection of Environment". Title 40 Code of Federal Regulations, Part 154. 2012 Edition.

34 "Reporting requirements and review processes for microorganisms," 40 Code of Federal Regulations, Part 725.155(d)3. 2003 Edition.

35 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," Title 7 Code of Federal Regulations, Part 340.3(d)c. 2008 Edition.

36 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," Title 7 Code of Federal Regulations, Part 340.6(c)5. 2008 Edition.

37 "Data requirements for pesticides," Title 40 Code of Federal Regulations, Part 158.63. 2008 Edition.

B. EVALUATION OF THE LIKELIHOOD OF THESE ADVERSE EFFECTS BEING REALIZED, TAKING INTO ACCOUNT THE LEVEL AND KIND OF EXPOSURE OF THE LIKELY POTENTIAL RECEIVING ENVIRONMENT TO THE LIVING MODIFIED ORGANISM.

1. Intended use of the LMO compared to recipient or parental organism

The approach of the U.S. coordinated framework reflects how different sets of regulations apply to LMOs with different intended uses (e.g. plants, pesticides, or food products – see section II for further discussion). For plants and plant pests, APHIS field test permitting guidelines require a description of the "intended uses and/or distribution of the intended article.[38] In the "summary" and "background" sections of individual APHIS environmental assessments, the unique traits and expected benefits of the LMO are described in depth. For example, in the environmental assessment of Bt Cry1F corn (line 1507), APHIS states that "…Corn line 1507 has been developed to provide farmers an alternative option for the control of larvae of certain lepidopteran insects which are significant pests in corn," and that "…herbicide tolerance provides an alternative weed management tool."[27] An environmental assessment for roundup-ready alfalfa (events J101 and J163) summarizes the intended uses concisely, stating that the modified alfalfa would be a cheaper option to weed control compared to non-modified alfalfa and would further allow for the option of "applying herbicide after weeds have germinated and only in the areas of the field where there are weeds."[32]

We were unable to find information in any of the EPA guidance documents reviewed regarding the intended use of plants containing PIPs compared to their non-modified counterparts. However, under FIFRA, all registered products with the EPA must have their use clearly specified. For a PIP, this means the crop and the target pests must be specified.[22]

2. Characteristics of relevant potential receiving environment

The APHIS risk assessment for *Bt* Cry1F corn line 1507 provides examples of how the receiving environment is considered with regard to evaluation of the likelihood of adverse effects being realized[27] (Table 11.3). For example, this risk assessment included analysis of the environmental fate of Cry1F in the soil, non-target exposure of monarch butterflies (and other lepidopterans) due to dispersal of Cry1F pollen, and a field study of the potential for beneficial arthropod predators to be exposed to Cry1F pollen.

3. How incidental exposure to the environment could occur

Guidelines for both APHIS and EPA consider how LMOs could be incidentally exposed to the environment; however, the requested categories of exposure lack requirements for detail about potential mechanistic routes. For example, APHIS requires a description of potential non-target effects, such as gene flow to sexually non-compatible organisms, in general terms only.[39] No specific requirements exist for a description of the mechanism for how gene flow would be expected to occur.

EPA guidelines refer to the potential for non-target gene flow via interactions with predators, prey, competitors, symbionts, parasites, and pathogens,[34] and for toxicity impacts to animals,[37] but we were unable to find specific mention in the documents reviewed about how LMO genetic material might be physiologically incorporated into these other groups of organisms in the documents reviewed. The most specific example of EPA guidelines referring to mechanistic routes of exposure is found in their discussion of risk management practices. Here the guidelines list procedures for minimizing the likelihood that the organism will be dispersed into the environment by "people, machinery, or equipment."[40]

38 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," Title 7 Code of Federal Regulations, Part 340.4(b)11. 2008 Edition.

39 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," Title 7 Code of Federal Regulations, Part 340.6(c)4. 2008 Edition.

40 "Reporting requirements and review processes for microorganisms," 40 Code of Federal Regulations, Part 725.255(e)2. 2003 Edition.

4. Conclusion of evaluation of likelihood of exposure

APHIS guideline documents indicate that the evaluation of likelihood of the above exposure routes is generally conducted in a qualitative manner. From an in depth examination of three environmental assessment documents,[27,31,32] and through cursory examination of several additional assessments, it appears that APHIS arrives at its likelihood conclusions based on both field test results submitted by the petitioner and reviews of current scientific literature. For example, in an assessment of *Bt* Cry1F corn (line 1507), APHIS used field test results to reach a determination of non-regulated status. The types of results assessed included analysis of environmental fate of the LMO in the soil, toxicity studies, and a non-target exposure and risk assessment for dispersal of LMO pollen to monarch butterflies[27] (See also Table 11.3). These results were combined to reach a final qualitative determination of no significant risk: "From this analysis, we are reasonably certain that no significant cumulative impact would result if [deregulation] is taken."[27]

The EPA typically bases its conclusions for likelihood of exposure (pesticides, including PIPs) on literature reviews.[4,41] In addition, a combination of product analysis data and information generated from mathematical models results in an overall estimate of exposure.

C. EVALUATION OF THE CONSEQUENCES SHOULD THESE ADVERSE EFFECTS BE REALIZED

APHIS requires field test reports of LMOs regarding adverse effects on "plants, non-target organisms, or the environment."[36] However, since APHIS bases all evaluation on whether the GMO is a potential plant pest, effects that do not have the potential to result in a change of plant pest status are not considered. Thus, the effects on non-targets described below are only relevant if such effects can result in higher plant pest risk.

Guidelines by APHIS require that applicants consider the likelihood that a LMO becomes a plant pest, an agricultural weed, or has negative effects to non-target organisms relative to the non-modified counterpart. Examples of specific field tests used to determine adverse effects come from the *Bt* Cry1F corn environmental assessment, and include dietary toxicity tests for numerous non-target species (e.g. lacewings, parasitic hymenoptera, earthworms, and bobwhite quail), and a comparison of the allergenicity profile of *Bt* Cry1F to known allergen proteins[27] (Table 11.3).

The EPA regulations require information on potential adverse effects to "human health and the environment."[42] Specific adverse effects to consider include interactions with predators and prey, competitors, symbionts, parasites, and pathogens.[34] Furthermore, EPA also requires information about the LMO's expected role in biogeochemical and biological processes, as well as expected byproducts of its use.[34] The procedure for registration of pesticides (including PIPs) requires a broad array of laboratory tests on animal models to determine the potential for toxicity to animals. Tests required for all LMOs used for environmental release include LD_{50} (i.e. **dose** of the pesticide that kills 50% of organisms when administered) and LC_{50} (i.e. **concentration** of the pesticide that kills 50% of organisms when administered) tests for birds, mammals, fish, invertebrates, and marine organism.[37] (See Appendix 11.A for detailed list of tests.) Furthermore, EPA guidelines outline numerous tests that aid in determination of possible consequences of non-target effects to native plants[43] (Table 11.4). Examples of results gathered from these tests include seedling emergence and vegetative vigor of non-target plants in terrestrial, aquatic, forestry, and residential settings. Finally, the EPA requires a variety of tests to determine consequences associated with the environmental fate of the pesticide[44] (Appendix 11.B).

41 "Data requirements for pesticides," Title 40 Code of Federal Regulations, Part 158. 2008 Edition.

42 "Reporting requirements and review processes for microorganisms," 40 Code of Federal Regulations, Part 725. 2008 Edition.

43 "Data requirements for pesticides," Title 40 Code of Federal Regulations, Part 158.66. 2008 Edition.

44 "Data requirements for pesticides," Title 40 Code of Federal Regulations, Part 158.1300. 2008 Edition.

TABLE 11.4: Testing for non-target effects to plants required by U.S. Environmental Protection Agency for registration of pesticides, including plant-incorporated protectants (PIPs). Abbreviations: R = Required, CR = Conditionally required, NR = Not required, TGEP = Technical Grade of the active ingredient, TEP = Typical end-use product, PAI = Pure active ingredient, EP = End-use product.[43]

Guideline Number	Data Requirement	Use Pattern			Test Substance	Test Note No.
		Terrestrial	Aquatic	Forestry and Residential Outdoor		
Nontarget Area Phytotoxicity – Tier I						
850.4100	Seedling emergence	R	R	R	TEP	1, 2, 7
850.4150	Vegetative vigor	R	R	R	TEP	1, 2, 3, 7
850.4400 850.5400	Aquatic plant growth (algal and aquatic vascular plant toxicity)	R	R	R	TEP of TGAI	1, 2, 7
Nontarget Area Phytotoxicity – Tier II						
850.4100	Seedling emergence	CR	CR	CR	TEP	1, 4, 5, 7
850.4150	Vegetative vigor	CR	CR	CR	TEP	1, 3, 4, 5, 7
850.4400 850.5400	Aquatic plant growth (algal and aquatic vascular plant toxicity)	CR	CR	CR	TEP or TGAI	1, 4, 6, 7
Nontarget Area Phytotoxicity – Tier III						
850.4300	Terrestrial field	CR	CR	CR	TEP	1, 7, 8, 10
850.4450	Aquatic field	CR	CR	CR	TEP	1, 7, 8, 10
Target Area Phytotoxicity						
850.4025	Target area phytotoxicity	CR	CR	CR	TEP	1, 7, 9, 10

D. ESTIMATION OF THE OVERALL RISK POSED BY THE LMO BASED ON THE EVALUATION OF THE LIKELIHOOD AND CONSEQUENCES OF THE IDENTIFIED ADVERSE EFFECT BEING REALIZED.

In the primary APHIS guideline documents reviewed, we were unable to find explicit mention of how overall LMO risk is estimated based on the information submitted by the petitioner. However, the approach of APHIS is to issue a qualitative estimation of the overall risk in consultation with the industry and based on the tests conducted by the industry.

A detailed investigation of three environmental assessment documents[27,31,32] and a brief examination of several additional assessments suggest that APHIS arrives at a characterization of risk based on: 1) field test results submitted by the petitioner, and 2) reviews of current scientific literature. In environmental assessments, each potential risk is addressed using a combination of the above information. A final overall determination (stated as a "finding of no significant impact" when risk is determined to be low) is made based on a combination of these separate risk determinations; however, it is not clear how the relative weight of separate risk determinations is formulated into the final risk designation.

The EPA typically bases its conclusions of overall risk on a combination of laboratory testing of toxicity in animal models, testing of impacts to non-target native plants, and environmental fate testing (see section IV C for details), as well as literature reviews. An example comes from the EPA's environmental assessment of *Bt* Cry1F corn line 1507: "the reviewed publications, recent research data, and information submitted as a result of the data call…indicate no unreasonable adverse effects of *Bt* Cry proteins expressed in plants to non-target wildlife or beneficial invertebrates."[45]

> The EPA typically bases its conclusions of overall risk on a combination of laboratory testing of toxicity in animal models, testing of impacts to non-target native plants, and environmental fate testing as well as literature reviews

E. RECOMMENDATION AS TO WHETHER THE RISKS ARE MANAGEABLE, INCLUDING, WHERE NECESSARY, IDENTIFICATION OF STRATEGIES TO MANAGE THESE RISKS

The APHIS guidelines list several risk management standards for the use of regulated LMOs in field tests under the notification and permitting processes (i.e. for field testing of LMOs prior to environmental release).

For example, risk management steps during field trials include prevention of persistence in the environment, prevention of LMO reproduction, and elimination of all viable genetic material from test sites after tests are completed.[46] We were unable to find any recommendations for risk management strategies when APHIS considered petitions for state to state transport of a LMO (i.e. after deregulation), and indeed it is well known that APHIS has no post-market control for LMOs.[22]

> The EPA has also issued guidelines for management of insect pest-resistance following the market release of LMOs, including limitations on the geographical use of some LMOs and development of insect pest-resistance management plans that include the provision of refugia fields.[22] For pesticides that have already been released, EPA also requires reporting of any adverse effects observed after release

EPA guidelines also include several standards that relate to risk management. For example, experimental release applications for small-acreage release of PIPs require applicants to include information on "monitoring, confinement, mitigation, and emergency termination procedures "[40] as well as means to detect and control adverse effects and procedures to minimize the likelihood that the organism will be dispersed into the environment by "people, machinery, or equipment."[40] The EPA has also issued guidelines for management of insect pest-resistance following the market release of LMOs, including limitations on the geographical use of some LMOs and development of insect pest-resistance management plans that include the provision of refugia fields.[22] For pesticides that have already been released, EPA also requires reporting of any adverse effects observed after release.[47,48] Finally, in an effort to mitigate risks

45 Environmental Protection Agency. 2001. Biopesticides Registration Action Document - Bacillus thuringiensis Plant-Incorporated Protectants.

46 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," Title 7 Code of Federal Regulations, Part 340.3(c)6. 2008 Edition.

47 National Research Council. 2000. Genetically-modified pest-protected plants: science and regulation. National Academy Press, Washington, D.C. p. 154.

48 U.S. Federal Fungicide, Insecticide, and Rodenticide Act (FIFRA). 1996, Part 6(a)2.

associated with older pesticides, the EPA requires that LMOs be re-registered within five years. Thus, the EPA has not granted any LMO a permanent registration. All temporary registrations granted by EPA have an expiration date with a requirement for additional information from the registrant.

F. WHERE THERE IS UNCERTAINTY REGARDING THE LEVEL OF RISK, IT MAY BE ADDRESSED BY REQUESTING FURTHER INFORMATION ON THE SPECIFIC ISSUES OF CONCERN OR BY IMPLEMENTING APPROPRIATE RISK MANAGEMENT STRATEGIES AND/OR MONITORING THE LMO IN THE RECEIVING ENVIRONMENT

The APHIS regulations address uncertainty (as related to incomplete information in decision-making) by stating that applications that do not fully meet the information requirements will be requested to provide additional information.[49,50] There are no provisions by APHIS for specification of risk management strategies or monitoring programs for the LMO once it has achieved non-regulated status in order to address uncertainty.

The EPA guidelines go one step farther in reducing uncertainty associated with incomplete information and decision-making. In addition to the temporary registrations mentioned above (section E), EPA requires that after an application has been submitted for review, applicants must submit any new information regarding potential impacts of PIPs to human health, non-target organisms or the environment,[51,52,53] as required under FIFRA.[48]

V. Discussion

To summarize, the scope of oversight associated with the U.S. regulatory framework for biosafety is broad. The three agencies responsible for regulating LMOs (APHIS, EPA, and FDA) jointly cover plants, plant pests, veterinary biologics, foods, drugs, and pesticides. Furthermore, regulatory guidelines produced by APHIS and EPA include separate but sometimes overlapping regulatory processes and risk assessment requirements for contained use of LMOs in laboratories,[7] for field testing,[54] and for environmental release.[55] Despite this relatively comprehensive coverage, APHIS exempts some LMOs from the oversight and risk assessment process. For example, assuming certain safeguarding conditions are met, any plant pests contained within the genetic material of certain bacteria species (some strains of *Escherichia coli*, *Saccharomyces cerevisiae*, or *Bacillus subtilis*) or in the genetic material of the plant *Arabidopsis thaliana* are exempt from regulations.[56] Moreover, plants that are produced as a result of crossing two deregulated plants are not subject to APHIS biosafety regulations.[23]

Despite this relatively comprehensive approach to regulating LMOs, differences between the agencies arise with regard to finer details. The most fundamental difference between APHIS and the EPA is in their definition of a LMO. Neither agency refers to "LMOs," *per se*. Instead, APHIS focuses on a "regulated article," which is defined as an organism produced by genetic engineering that is not currently classified as "non-regulated" and also has the potential to become a plant pest.[57]

49 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," Title 7 Code of Federal Regulations, Part 340.4(c). 2008 Edition.

50 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," Title 7 Code of Federal Regulations, Part 340.4(c). 2008 Edition.

51 "Regulations under the Federal Insecticide, Fungicide, and Rodenticide Act for plant-incorporated protectants (formerly plant pesticides)," Title 40 Code of Federal Regulations, Part 152.125. 2001 Edition.

52 "Regulations under the Federal Insecticide, Fungicide, and Rodenticide Act for plant-incorporated protectants (formerly plant pesticides)," Title 40 Code of Federal Regulations, Parts 174.71(d). 2001 Edition.

53 "Reporting requirements and review processes for microorganisms," 40 Code of Federal Regulations, Part 725.36. 2003 Edition.

54 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," Title 7 Code of Federal Regulations, Part 340.4. 2008 Edition.

55 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," Title 7 Code of Federal Regulations, Part 340.6. 2008 Edition.

56 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," Title 7 Code of Federal Regulations, Part 340.2(b). 2008 Edition.

57 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," Title 7 Code of Federal Regulations, Part 340.1. 2008 Edition."

The focus for EPA is on "plant-incorporated protectants," or more specifically, the genetic material and resulting protein that act as a plant pesticide.[58]

> APHIS exempts some LMOs from the oversight and risk assessment process. For example, assuming certain safeguarding conditions are met, any plant pests contained within the genetic material of certain bacteria species (some strains of Escherichia coli, Saccharomyces cerevisiae, or Bacillus subtilis) or in the genetic material of the plant Arabidopsis thaliana are exempt from regulations.[56] Moreover, plants that are produced as a result of crossing two deregulated plants are not subject to APHIS biosafety regulations

Procedural differences also exist between APHIS and EPA. Despite the original directive of the coordinated framework for a product-based approach to regulation, APHIS bases its regulatory trigger on whether or not an organism has been genetically modified (i.e. process-based approach).[23,57] The EPA risk assessment trigger is focused on pesticidal traits of plants (PIPs). Analytical techniques also differ between APHIS and the EPA. The environmental assessments and decisions of APHIS are based on a qualitative assessment of field testing results and literature, while EPA risk assessments sometimes incorporate quantitative data collection and consideration of information generated from mathematical models in addition to qualitative information.

As an update to the original LMO guidelines, APHIS has drafted proposed revisions to the LMO regulatory framework. However, it is important to note that these revisions have yet to be enacted. A key directive of the proposed revisions is to eliminate the notification procedure, which was previously used by LMO developers to alert APHIS of introduction of a LMO for field testing.[7] The new approach for this procedure includes a permitting process that categorizes a LMO *a priori* into one of four risk categories (Table 11.5), based on 1) the risk of it persisting in the environment, and 2) the risk of harm or damage from the engineered trait. Subsequent risk assessment requirements would then be based on this preliminary categorization. The proposed revisions also include an increased attention to the potential for a LMO to become a noxious weed[59] and allowance for revocation of non-regulated status of a LMO given new information.[60] Finally, the APHIS proposal clearly stresses a move towards product-based assessment of LMOs, with future assessment being based on "known plant pest and noxious weed risks…or traits of the organism" rather than "the mere act of genetic engineering."[59]

TABLE 11.5: Proposed method for initial definition of risk categories (A-D) for LMOs used for environmental release. Ranking based on persistence risk of the recipient plant species and potential harm or damage of engineered trait. Risk category A corresponds to the lowest initial risk designation while risk category D corresponds to the highest initial risk designation.[61]

	Potential harm or damage of engineered trait			
Persistence*	Low	Moderate	High	Severe
Low	A	A	C	D
Moderate	A	B	C	D
High	B	B	C	D
Severe	D	D	D	D

*Persistence risk of the recipient plant species

58 U.S. Environmental Protection Agency. Plant Incorporated Protectants. Online [url]: http://www.epa.gov/pesticides/biopesticides/pips/index.htm. Accessed 3-30-2012.

59 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," 73 U.S. Federal Register 197 (9 October 2008) p. 60012.

60 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," 73 U.S. Federal Register 197 (9 October 2008) p. 60023.

61 "Introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests," 73 U.S. Federal Register 197 (9 October 2008) p. 60019.

APPENDIX

APPENDIX 11.A: Laboratory testing required by U.S. Environmental Protection Agency for registration of pesticides, including plant-incorporated protectants (PIPs). Abbreviations: R = Required, CR = Conditionally required, NR = Not required, TGEP = Technical Grade of the active ingredient, TEP = Typical end-use product, PAI = Pure active ingredient, EP = End-use product.[37]

Guideline Number	Data requirement	Use Pattern						Test Substance
		Terrestrial	Aquatic	Forestry	Residential Outdoor	Greenhouse	Indoor	
Avian and Mammalian Testing								
850.2100	Avian oral toxicity	R	R	R	R	CR	CR	TGAI
850.2200	Avian dietary toxicity	R	R	R	R	NR	NR	TGAI
850.2400	Wild mammal toxicity	CR	CR	CR	CR	NR	NR	TGAI
850.2300	Avian reproduction	R	R	R	R	NR	NR	TGAI
850.2500	Simulated or actual field testing	CR	CR	CR	CR	NR	NR	
Aquatic Organisms Testing								
850.1075	Freshwater fish toxicity	R	R	R	R	CR	CR	TGAI, TEP
850.1010	Acute toxicity freshwater invertebrates	R	R	R	R	CR	CR	TGAI, TEP
850.1025 850.1035 850.1045 850.1055 850.1075	Acute toxicity estuarine and marine organisms	R	R	R	R	NR	NR	TGAI, TEP
850.1300	Aquatic invertebrate life cycle (freshwater)	R	R	R	R	NR	NR	TGAI
850.1350	Aquatic invertebrate life cycle (saltwater)	CR	CR	CR	CR	NR	NR	TGAI
850.1400	Fish early-life stage freshwater)	R	R	R	R	NR	NR	TGAI

Guideline Number	Data requirement	Use Pattern						Test Substance
		Terrestrial	Aquatic	Forestry	Residential Outdoor	Greenhouse	Indoor	
850.1400	Fish early-life stage (saltwater)	CR	CR	CR	CR	NR	NR	TGAI
850.1500	Fish life cycle	CR	CR	CR	CR	NR	NR	TGAI
850.1710 850.1730 850.1850	Aquatic organisms bio-availability, bio-magnification toxicity	CR	CR	CR	CR	NR	NR	TGAI, PAI, degradate
850.1950	Simulated or actual field testing for aquatic organisms	CR	CR	CR	CR	NR	NR	TEP
Sediment Testing								
850.1735	Whole sediment: acute freshwater invertebrates	CR	CR	CR	CR	NR	NR	TGAI
850.1740	Whole sediment: acute marine invertebrates	CR	CR	CR	CR	NR	NR	TGAI
	Whole sediment: chronic invertebrates freshwater and marine	CR	CR	CR	CR	NR	NR	TGAI
Insect Pollinator Testing								
850.3020	Honeybee acute contact toxicity	R	CR	R	R	NR	NR	TGAI
850.3030	Honey bee toxicity of residues on foliage	CR	CR	CR	CR	NR	NR	TEP
850.3040	Field testing for pollinators	CR	CR	CR	CR	NR	NR	TEP

APPENDIX 11.B: Testing for environmental fate required by U.S. Environmental Protection Agency for registration of pesticides, including plant-incorporated protectants (PIPs). Abbreviations: R = Required, CR = Conditionally required, NR = Not required, TGEP = Technical Grade of the active ingredient, TEP = Typical end-use product, PAI = Pure active ingredient, EP = End-use product.[44]

Guideline Number	Data Requirement	Use Pattern						Test Substance
		Terrestrial	Aquatic	Green-house	Indoor	Forestry	Residential Outdoor	
Degradation Studies – Laboratory								
835.2120	Hydrolysis	R	R	R	CR	R	R	TGAI or PAIRA
835.2240	Photo-degradation in water	R	R	NR	NR	R	NR	TGAI or PAIRA
835.2410	Photo-degradation on soil	R	NR	NR	NR	R	NR	TGAI or PAIRA
835.2370	Photo-degradation in air	CR	NR	CR	NR	CR	CR	TGAI or PAIRA
Metabolism Studies – Laboratory								
835.4100	Aerobic soil	R	CR	R	NR	R	R	TGAI or PAIRA
835.4200	Anaerobic soil	R	NR	NR	NR	NR	NR	TGAI or PAIRA
835.4300	Aerobic aquatic	R	R	NR	NR	R	NR	TGAI or PAIRA
835.4400	Anaerobic aquatic	R	R	NR	NR	R	NR	TGAI or PAIRA
Mobility Studies								
835.1230 835.1240	Leaching and adsorption/ desorption	R	R	R	NR	R	R	TGAI or PAIRA
835.1410	Volatility - laboratory	CR	NR	CR	NR	NR	NR	TEP
835.8100	Volatility - field	CR	NR	CR	NR	NR	NR	TEP
Dissipation Studies – Field								
835.6100	Terrestrial	R	CR	NR	NR	CR	R	TEP
835.6200	Aquatic (sediment)	CR	R	NR	NR	NR	NR	TEP
835.6300	Forestry	NR	NR	NR	NR		NR	TEP
835.6400	Combination and tank mixes	CR	CR	NR	NR	NR	NR	TEP
Ground Water Monitoring								
835.7100	Ground water monitoring	CR	NR	NR	NR	CR	CR	TEP

Chapter 12. Comparisons among risk assessment frameworks[1]

I. Overview

This chapter discusses commonalities among and noteworthy features of the reviewed risk assessment frameworks. Each of the three main subsections of this chapter (Regulatory landscape, General principles, and Methodology) includes one or more matrices that provide information in a summary format. As stated in Chapter 2 (Methods), all information provided in this Comparison chapter was based on our interpretation of publicly available documents.

Lack of mention of a particular country in reference to a given risk assessment practice may indicate that we were unable to find evidence of such within the documents reviewed. It should not be construed as a finding that the country did not or does not engage in the practice. Information presented in this Comparison was obtained from laws, regulations, guidance documents, decision documents, risk assessments, and/or risk assessment summaries. For clarity, we have not attempted to distinguish among those sources in this Comparison chapter. Instead, we have referred to them collectively as "risk assessment frameworks" or simply "frameworks". We have used the term "legal frameworks" when evidence for a point of discussion was obtained primarily or exclusively from laws and regulations rather than risk assessment documents. When describing or discussing specific national risk assessment frameworks, the following abbreviations are used: Australia (AU), Brazil (BR), Canada (CA), China (CH), Cuba (CU), Germany (GE), Japan (JN), South Africa (SA), United States (US). For consistency with Annex III of the Convention on Biological Diversity, the term "living modified organism" (LMO) is used throughout this comparison chapter despite the use of "genetically modified organism" or similar terms in some national risk assessment frameworks.

1 Citations within the text of this Comparison chapter generally reference the corresponding section and subsection within the previous chapter(s) summarizing the pertinent framework(s). For example, the citation (AU, CH) appearing within this chapter's subsection IV.B.1 "Intended use of the LMO" references the subsections of the same number and name appearing within the chapters on the Australian and Chinese frameworks. However, citations appearing within the following subsections of this Comparison chapter correspond to categories within the accompanying summary matrices but do not appear as discrete subsections within Chapters 3 – 11: (i) Regulatory landscape: Trigger for conducting new risk assessment, (ii) Regulatory landscape: Number and nature of regulatory frameworks, (iii) Regulatory landscape: Presence and type(s) of guidance documents, (iv) Methodology (A): Types of potential adverse effects identified, (v) Methodology (B): Extrapolation from data, (vi) Methodology (C): Genetic effects, (vii) Methodology (C): Effects on species and populations, (viii) Methodology (C): Effects on ecosystem processes, (ix) Methodology (C): Conclusion of consequences of adverse effects, (x) Methodology (D): Approach used to combine consequences and likelihood, (xi) Methodology (D): Who makes final decision of overall risk?, (xii) Methodology (D): Type of risk estimate produced, (xiii) Methodology (D): Uncertainty analysis conducted, (xiv) Who are the actors that implement policy based on risk decision?

∗ Indicates headings and subheadings that do not readily fall within Annex III.

II. Regulatory landscape

*Trigger for conducting new risk assessment**

Within all the risk assessment frameworks reviewed in this report, new risk assessments were triggered by genetic manipulation. However, national frameworks varied with regards to what specific genetic modifications constituted triggers. Some utilized a broad definition of "gene technology" as a trigger (AU), while others indicated that transformation events (JN) or new combinations of donors or genes were triggers (BR, CH). The Chinese framework in particular recognized that removal of a gene in the context of genetic modification of LMOs may trigger a risk assessment.

Within all the risk assessment frameworks reviewed in this report, new risk assessments were triggered by genetic manipulation. However, national frameworks varied with regards to what specific genetic modifications constituted triggers.

Genetic manipulation was not the sole risk assessment trigger for all frameworks, however. Other triggers included the type of release (contained versus uncontained), the intended use of the LMO, and the receiving environment of the LMO. Unique to Canada was the use of a "novel trait", regardless of the process used to create it, as the trigger for risk assessment.

*Number and nature of regulatory frameworks**

A majority of the countries we reviewed (AU, BR, CH, CU, GE, JN, SA) used one primary framework to regulate activities involving LMOs. Several of these countries (BR, CH, JN, SA) further divided regulation by the type of LMO considered (animal, plant, micro-organism, etc.).

The United States (U.S.) was unique in that separate governmental agencies worked together to provide a coordinated regulatory framework for products of biotechnology, including LMOs. In the case of Canada we found no evidence of an overarching regulatory framework.

A single national law regulated LMOs in a majority of the countries reviewed (AU, BR, CH, CU, GE, JN, SA); in some countries, LMOs were governed by multiple regulations (CA, CH, GE, JN). While a single governmental agency or body was responsible for regulating LMOs in some nations (AU, BR, CH, CU), in the U. S., three agencies were involved. Several countries had unique legal structures governing the use of LMOs. For example, in the U.S., four different national acts were pertinent to LMO regulation. In Germany, LMO use conformed both to national laws and to an international treaty established by the European Union. In Canada, the type of LMO (plant, animal, fish, etc.) determined which regulation applied to a particular LMO.

National guidance documents related to LMO risk assessment generally fell into one of two categories: guidance for preparing LMO applications and risk assessments or guidance for the regulatory bodies responsible for evaluating LMO risk assessments

*Presence and type(s) of guidance documents**

National guidance documents related to LMO risk assessment generally fell into one of two categories: guidance for preparing LMO applications and risk assessments or guidance for the regulatory bodies responsible for evaluating LMO risk assessments. A majority of countries reviewed (AU, BR, CH, CU, JN, SA) had a single primary document guiding the submission of all LMO applications; these documents provided details on the information required for the LMO risk assessment. In contrast, the U.S. had two separate sets of guidelines for LMO risk assessments and each originated in a different governmental agency.

∗ Indicates headings and subheadings that do not readily fall within Annex III.

We found two guideline documents for LMO applications in Canada and the type of LMO (plants with novel trait or veterinary biologics) determined which document was relevant to a particular application. South Africa provided two guidance documents for different audiences: one for applicants and another for the regulatory body responsible for evaluating risk assessments. In Australia, guidance for risk assessments was found within the "Risk Analysis Framework" document. It should be noted, however, that the scope of this document extended beyond guidance for LMO applications as the "Risk Analysis Framework" also explained Australia's approach to LMO risk assessment and risk management.

REGULATORY LANDSCAPE MATRIX

Trigger for conducting new risk assessment*	Number and nature of regulatory frameworks*	Presence and type(s) of guidance documents*
• Type of use (contained or uncontained) (GE, JN, SA) • Intended use of LMO (CH, CU, GE) • Receiving environment of LMO (CU) • Transformation event (BR, CH, JN) • Pesticidal traits (US) **Types of genetic manipulations** • Use of gene technology/genetic modification (AU, GE, SA) • New type of GMO (CU, GE) • New donor/gene recipient combination (BR) • Novel combination of recipient organism species (JN) • Novel combination of recipient and modification (CH) • Genetic engineering work (CH) including recombinant nucleic acid techniques, direct introduction of externally prepared heritable material, and cell fusion (GE) • Novel traits (CA) • Products of modern biotechnology (US)	**Frameworks** • 1 primary framework for all LMOs (AU, BR, CH, CU) • 1 primary framework requiring different information for different kinds of LMOs (animal, plant, micro-organism) (BR, CH, JN, SA); for different types of uses (BR, GE, JN) • 1 coordinated framework for products of biotechnology (US) • No overarching framework (CA) **Regulation** • 1 national law or act on LMOs (AU, BR, CH, CU, GE, JN, SA) • 1 international treaty (GE) • Multiple national regulations (CA, CH, GE, JN) • Different regulations for type of organism (animals, fish, veterinary biologics, plants) (CA) • 1 national agency (CH) • 1 regulatory body for LMOs (AU, BR, CU) • 3 agencies with complementary regulation under 4 main acts (US)	• Country had one primary guidance document for LMO applications (AU, BR, CH, CU, JN, SA) • Two separate sets of guidance documents outlining information needed for LMO risk assessment (US) • Guidance documents for plants with novel traits and veterinary biologics (CA) • Guidance document for decision-making body reviewing LMO applications (AU, SA) • Single document providing specifics on risk assessment (risk classes, risk management, etc.) (BR, CH) or on information required in risk assessments (BR, CH, GE) • Documents describing routine tests for assessment of different kinds of LMOs (e.g. herbicide-resistant maize) (CH)

∗ Indicates headings and subheadings that do not readily fall within Annex III.

III. General principles

A. SCIENTIFICALLY SOUND

The majority of countries reviewed (AU, BR, CH, CU, GE, US) had a law or regulation that explicitly mentioned the need for scientific soundness in risk assessment. All of the reviewed frameworks included some suggestions about the types of data considered appropriate for use in risk assessment; however, frameworks differed with respect to the type(s) of data that were considered scientifically sound. A majority of countries (AU, BR, CA, CU, GE, JN) considered consultation with experts and secondary sources to be appropriate means of gathering data for use in risk assessment. Collection of original data was also mentioned by many countries. Three frameworks explicitly suggested that original data be collected (BR, CA, JN) and others indirectly referred to the collection of original data by stating that field (CA, US) or lab (CH, US) tests must be conducted in a scientifically sound manner. Another common point was that a majority of frameworks (AU, BR, CA, CU, JN, US) indicated that new information could be requested during or after the risk assessment process if knowledge gaps were observed.

Some frameworks took notable steps to ensure the quality of scientific evidence. The Australian approach included a system for weighing evidence based on its reliability and on its appropriateness. For example, widely accepted, peer reviewed literature was considered more reliable than expert opinion and data on the LMO or parental organisms were considered more appropriate than data based on surrogate systems. Both the Cuban and Australian frameworks emphasized ongoing training for risk assessors to ensure high-quality interpretation of data. The Australian risk assessment guidelines were aligned with those developed by internationally recognized organizations such as the World Health Organization, Food and Agriculture Organization, the Organization for Economic Cooperation and Development and the U.S. National Research Council's "Red Book".

B. TRANSPARENT

All reviewed frameworks included procedures for ensuring transparency in risk assessment, though the levels of transparency ranged from public notification to extensive public involvement. For most frameworks, the information required for risk assessment (BR, CA, CH, GE, JN, SA) and/or the necessary requirements for conducting risk assessments (AU, CA, CH, GE, JN, SA, US) were available online. In the event that environmental release of a LMO was approved, a majority of risk assessment frameworks required public notification (AU, BR, CA, CH, CU, GE, JN, US), usually by posting the decision on a public website. In the cases of Australia, Japan and the U.S., risk assessments for approved LMOs were also placed on a public website and other frameworks (BR, CA, CU, GE) included the same for risk assessment summaries.

Some risk assessment frameworks included public involvement. For example, public comment periods were required by the Australian, German and Japanese frameworks. In the case of Australia, public comments were published along with posted risk assessments and stakeholders dialogued with the Regulator responsible for making the final decision on each LMO release. The Japanese framework required that the competent minister charged with approving a LMO must take public opinions into account.

Some frameworks required that the identities of those making risk-related decisions, such as the experts consulted during a risk assessment (JN) be made public. Published Brazilian risk assessments included both the names and opinions of those dissenting with LMO approvals. In addition, members of the Brazilian government body charged with risk assessment were required to disclose their conflicts of interest both prior to becoming members and with regard to any particular LMO approval.

C. LACK OF SCIENTIFIC KNOWLEDGE OR CONSENSUS DOES NOT INDICATE LEVEL OR ABSENCE OF RISK

In situations where risks are uncertain, the precautionary principle assumes that risks could be present, and efforts should be made to protect human health and the environment.[1] In the context of risk assessment for LMOs, this might mean that approval for environmental release may be inadvisable when risks are unknown. The legal frameworks of about half of the countries that we reviewed state that the precautionary principle is accepted (AU, BR, CU, GE, SA). The frameworks of several other countries allow for the reversal of approvals for LMOs that exhibit adverse effects after release (CH, CU, JN).

D. RISK CONSIDERED IN THE CONTEXT OF RISK POSED BY NON-MODIFIED RECIPIENTS OR PARENTAL ORGANISMS

The frameworks of most countries (AU, BR, CA, CH, CU, GE, JN, US) considered LMO risk in comparison to the risk of a non-modified counterpart. Japan's framework uniquely noted that this comparison was necessary only if the parental organism had a history of use in Japan. Comparisons between the LMO and its non-modified counterpart may take into account risks related to the respective production practices of each (AU, BR, CH). Notably, in the case of Australia and Canada, the baseline organism for comparison with the LMO could be a LMO already in use. When risk assessments involved conventionally bred hybrids of LMOs, the German and Japanese frameworks considered both the risks compared to a non-modified counterpart and to the LMO parents of the hybrid.

E. CASE-BY-CASE BASIS

The reviewed frameworks of a majority of countries (BR, CH, CU, GE, SA) specifically stated that risk assessments would be conducted on a case-by-case basis. However, what constituted a "case" differed among frameworks. Characteristics of "cases" that varied among frameworks included the type of genetic modification (BR, CH, CU, GE, JN, US), traits of the LMO (CA, SA, US), the intended use of the LMO (BR, CU, GE, JN, US), the receiving environment (CU, GE), the classification of parental organism (CH, SA) and the scale of the release (AU, BR, CA, CH, JN).

The frameworks of a majority of countries (AU, BR, CA, GE, JN, SA, US) allowed streamlined risk assessment processes for LMOs perceived to be of low risk. The Brazilian framework accepted abbreviated risk assessments for new transformation events that involved previously approved recipient and donor or gene combinations. The South African framework allowed streamlined risk assessments for well-studied LMOs. Other frameworks (AU, JN) allowed risk assessments for LMOs with stacked traits to take into account the risk assessments previously performed for those individual traits. In the case of Brazil, stacked traits resulting from conventional breeding of two approved LMOs were sometimes subjected to risk assessments whereas such LMOs were generally exempt from risk assessment in Canada and the U.S.

In a notable approach to streamlining, the U.S. has proposed in revisions to its LMO regulation framework that LMOs be initially placed in one of four risk classes based on the probability that the organism will persist in the environment and/or become a noxious weed. The subsequent full risk assessment varied according to this initial classification.

1 Kriebel, D., J. Tickner, P. Epstein, J. Lemons, R. Levins, E.L. Loechler, M. Quinn, R. Rudel, T. Schettler, M. Stoto. 2001. The precautionary principle in environmental science. *Environmental Health Perspectives.* 109 (9): 871-876.

GENERAL PRINCIPLES MATRIX

Scientifically sound	Transparent	Absence of scientific information does not indicate lack of risk	Risk considered in context of non-modified counterpart	Case-by-case basis
General • Risk assessments considered direct, indirect, immediate, delayed, and cumulative effects (GE) • Risk assessments considered available scientific and technical data (CA, CH, GE, JN) • Law/regulation explicitly mentioned scientific soundness (AU, BR, CH, CU, GE, US) • Guidelines developed by consultation with internationally recognized organizations (AU) • Quality of scientific evidence should be considered (AU) • Government collected and analyzed LMO information (JN) **Conducting Experiments** • scientifically sound manner (CA, US) • Clear description of test procedures (CA) • Use of secondary sources • Use of peer-reviewed literature (BR, CA, US, AU) • Data or results from previously submitted notifications may be used (GE) • Required studies to use "Good Laboratory Practices" (CH, US) • In all reports and applications, "main indexes and analytic methods used" should be described (CH)	**Clear risk assessment guidelines and policies** • Published government policy documents on specific situations (license variations, stacked events, monitoring) (AU) • Regulations and policies must be "transparent and accessible" (US) • Information required for risk assessment process was explicitly stated (AU, CA, CH, CU, GE, JN, SA) • Required information for applications available on public website (AU, BR, CA, CH) • Risk assessment requirements publicly available online (AU, CA, CH, GE, JN, SA, US) • Risk assessment requirements made publicly available in government newsletter (AU) **Public Notifications** • Public notification of proposed release (CA, GE, JN) • Abstracts of LMO applications available in Federal Gazette before evaluation (BR) • Risk assessment posted on public website (AU, JN, US) • Risk assessment summary posted on public website (BR, CA, CU, GE) • Risk assessment summary published in Federal Gazette (BR)	**General acceptance of precaution** • Law/regulation required that precaution be taken into account (GE, SA) • Observance of precautionary principle listed as a function of regulatory body (BR) • Law declared that lack of scientific information does not indicate the absence or risk or acceptable risk (CU) • Adopt a precautionary approach for preventing environmental degradation (AU) **Monitoring** • Monitoring should be conducted in precautionary manner (BR) • Risk assessment must include LMO detection methods and emergency measures (BR, CH, JN) **Decision Reversal** • Approval may be rescinded if unforeseen environmental changes lead to risk of adverse effect (CU, JN) • Safety certificate may be revoked if the LMO is found to be harmful (CH) • Approval may be reversed if LMO is found to be harmful (CU)	**Established need for comparison** • Law/regulation required comparison with non-modified parental organism (AU, BR, CA, CH, CU, GE, US) • Law/regulation required comparison with non-modified recipient if Japan has long-term experience with recipient (JN) • "Substantial equivalency" should be shown between LMO and counterpart (CU, CA) • "Substantial equivalence" to unmodified counterpart considered (BR) • Risk determined through comparative assessment with a parental baseline organism (AU, JN, CH, BR) **Comparing risk of LMO to counterpart in context of their uses and environment** • Context included similar use, similar environment to non-modified parental organism (GE) • Risk comparison between LMO and kindred organism may include risks of agricultural practices used with each (BR) • Environmental or human risks from parental organism were considered as part of baseline for comparison (AU, BR, CH)	**General** • Law/regulation explicitly required case-by-case approach (BR, CH, CU, GE, SA) **How a risk assessment was triggered/definition of case** • "Case" included GMO type, intended use, receiving environment (CU, GE)A • Genetic modification triggered regulatory process (AU, BR, CH) • Each donor/gene recipient combination required risk assessment (BR) • Each combination of recipient and modification was a case (CH) • Risk assessment needed for each transformation event, including stacked events (US) • Risk assessment needed for each new combination of use and transformation event, including stacked events resulting from conventional breeding of LMOs (JN) • New risk assessment triggered by novel trait (CA) • Risk assessment needed for novel pesticidal traits and novel uses (US) • Intra-specific and inter-specific crosses, trait stacking, re-transformation, or re-mutation generally not considered a new case (CA)

Scientifically sound	Transparent	Absence of scientific information does not indicate lack of risk	Risk considered in context of non-modified counterpart	Case-by-case basis
• Conducting experiments and data collection explicitly suggested (BR, CA, JN) • Field tests needed to be conducted in **Use of experts** • Consultation with scientific experts (AU, BR, CA, CU, GE, JN) • Members of regulatory body must be knowledgeable about LMOs (SA) • Ongoing training of personnel on scientific expertise and best practices in risk analysis (AU, CU) **Handling new information** • Risk assessment can be readdressed as new information is available (AU, GE, SA, US) • More information can be requested during approval process (AU, BR, CA, CU, JN, US) • Monitoring results from other countries taken into account (BR) • Guidance document can be revised to incorporate new knowledge of LMOs or trends in risk assessment (AU, CA, JN) • Safety certificate may be revoked if the LMO is found to be harmful (CH) • Approval may be reversed if LMO is found to be harmful (CU)	• Release of risk assessment published in Federal Register (US) • Portions of risk assessment process were confidential business information (CA, CH, GE) • Dissenting opinions published with decision documents (BR) • Public notifications of approved release (AU, BR, CA, CH, CU, GE, JN) • Community informed about issues relating to safety (BR) • Roster of experts consulted by competent minister is publicly announced (JN) • Decision makers must disclose conflicts of interest (BR) • Government maintained biosafety information database on public website (JN) **Public participation** • Included public comments in RA documents (AU) • Formal procedures in place for requesting to attend hearings on LMO decisions (BR) • Approval process included public comment periods (AU, GE, JN)		**Baseline for comparison can be another LMO** • Baseline may include LMO in cases where the LMO comprises most of the commercial product (AU) • Counterpart was defined as the non-modified parent or the closest isogenic line which can include a previously authorized modified plant with novel traits (CA) • Risks considered both in terms of non-modified recipients and the LMO parents of conventionally bred hybrids (GE, JN)	• Offspring from two approved LMOs exempted from risk assessment process (US) • Stacked events that were the result of conventional breeding required risk assessment at discretion of regulatory body (BR) • Simplified risk assessment for new transformation event (when same donor/gene and recipient) (BR) • Whether LMO was a well-studied or new organism partially determined amount of information needed in RA (GE, SA) • RA guidelines dependent on category of receiving organism (SA, CH) • Differentiated between herbicide-resistant and insecticide-resistant LMOs (SA) • Considered spatial scale (AU, BR, CH) and temporal scale (AU, CH) of release • Considered volume of LMO released (CU) • Different information required based on intended use (BR) • For stacked events, the risk assessments for each previously approved LMO were considered (AU, JN) • Separate applications for limited/controlled release and commercial release (AU, CH) • Applications differed for LMO releases in confined areas and environmental release (AU, CA, JN)

IV. Methodology

A. Identification of novel genotypic and phenotypic characteristics associated with LMO, that may have adverse effects on biological diversity in the likely receiving environment, also taking into account risks to human health.

Types of potential adverse effects identified[*]

The potential adverse effects identified within the reviewed documents covered a broad spectrum but generally fell into one of the following four categories: gene flow, effects on species and populations, effects on ecosystem processes, and adverse effects on humans. A majority of the reviewed risk assessment frameworks identified potential adverse effects within each of these four categories, demonstrating the broad range of adverse effects under consideration. Many frameworks (BR, CA, CH, GE, SA, US) identified gene flow to wild relatives or domestic species as an adverse effect. Examples of effects on ecological processes generally involved changes in biogeochemistry or agricultural practices. Adverse effects on species and populations that were typically considered in the reviewed documents included LMO toxicity (AU, CA, CH, GE), impacts to beneficial (AU, CU, SA, US), or threatened or endangered organisms (CA, CH, CU, US), and increased weediness (AU, CA, CH, GE, SA) or competitive ability (CH, JN) of the LMO. Allergenicity and toxicity of plant materials to humans were two commonly identified adverse effects on humans (AU, BR, CA, CH, GE).

The reviewed risk assessment frameworks varied with regards to the identification of potential adverse effects. Some frameworks provided detailed examples of potential effects to be considered; others made the LMO applicant primarily responsible for identifying adverse effects. To assist LMO applicants with the identification of potential adverse effects, the South African framework took the unique approach of providing numerous and detailed examples of phenotypic changes that can occur in a LMO. South African risk assessors categorized such changes as intended effects, unintended (adverse) effects, or effects on human health and welfare.

∗ Indicates headings and subheadings that do not readily fall within Annex III.

The effects were then further delineated into types of phenotypic changes, such as metabolic and behavioral. In contrast, the Australian risk assessment framework provided very general and broad guidance for identifying adverse effects.

1. Recipient/Parental Organism

Within the nine reviewed national risk assessment frameworks, information regarding novel traits of the recipient/parental organism fell into four general categories: background information, genotypic and phenotypic traits, ecological traits, and toxicity/disease traits. The Canadian framework had a particularly noteworthy approach to the provision of information on recipient organisms. Canada's Plant Biosafety Office provides "biology documents" which outline the characteristics of the plant with novel traits that is proposed for release, in comparison to the non-modified recipient organism. This approach to compiling recipient organism information is relatively formal compared to that of other countries. For instance, many frameworks required applicants to submit such information on a case-by-case basis and did not provide official reference documents for given LMOs. However, Canada's biology documents were produced using subject-matter experts, peer-reviewed literature, and consensus documents developed by the Organization for Economic Cooperation and Development.

> The reviewed risk assessment frameworks varied with regards to the identification of potential adverse effects. Some frameworks provided detailed examples of potential effects to be considered; others made the LMO applicant primarily responsible for identifying adverse effects.

A majority of the risk assessment frameworks that we analyzed required several types of information pertaining to the recipient/parental organism. All of the frameworks required basic background information about the recipient organism, including its taxonomic classification to at least the species level.

Most also required a description of its geographic distribution (BR, CA, CH, CU, GE, JN, SA, US), and a majority required the information on the history and present state of its use (AU, BR, CA, CH, JN). Some countries required information on genotypic and phenotypic traits of the recipient organism, especially with regards to the recipient's sexual compatibility with other species (CA, CH, CU, GE). A majority of frameworks further required a general biological or physiological characterization of the recipient organism (AU, CA, CH, JN, SA), with the degree of required detail varying among countries. Ecological traits, such as predators, competitors, parasites, and the general ecology of the recipient, were likewise required by many risk assessment frameworks (AU, BR, CA, CH, CU, GE, JN). Finally, information about toxicity and disease traits associated with the recipient was commonly required. Examples included human allergenicity (AU, BR, CA, CH, GE, SA) or information about toxicity and pathogenicity that did not specifically refer to humans (AU, BR, CH, CU, GE, JN).

2. Donor Organism

Information requirements for novel traits of the donor organism were generally less extensive than for the parental/recipient organism. Taxonomic identification to at least the species level was the only point included by a majority of the reviewed risk assessment frameworks (AU, CA, CU, JN, US). Other information that appeared in up to three frameworks were the common name and source of the donor and traits of the donor organism, including relevant ecological information, toxicant properties, or traits that could cause disease or injury to other plants or animals.

Transformation Event[*]

The reviewed risk assessment frameworks varied with regards to what information was required regarding LMO transformation events. The mandated information fell into two general categories: vector traits and traits specific to the inserted genetic material. One noteworthy approach was that used by the Japanese risk assessment framework.

Extensive information about the inserted genetic material was required, including the structure of the "entire nucleic acid" inserted into the recipient organism, the insertion method, and the names and origins of the vectors. Furthermore, plasmid maps (i.e. the sequence of the intended insert) were included in one of the reviewed risk assessments submitted to Japanese authorities.

As with the recipient or parental and donor organisms, a majority of the reviewed frameworks (BR, CH, CU, GE, JN) required detailed information about the vector, including name, origin, or source. In some cases, information about the vector host range (BR) and genetic sequence (CA, CU) was also required. With regard to information about the inserted genetic material, various frameworks required a description of the methods used for genetic transformation (CA, CH, CU, GE), the sequence of the inserted genes (BR, CA, CH, CU, SA, US), and the origin or source (CU, GE, JN) or intended function (BR, CA, CU, GE, JN) of the inserted fragment.

3. LMO Characteristics

Collectively, the reviewed national risk assessment frameworks provided numerous examples of the types of information required with regards to LMO traits. This information could be divided into five general categories: background information, traits of the insert within the context of the recipient, genotypic and phenotypic traits, ecological traits, and toxicity, disease, or nutrition traits. All of these general categories were addressed by a majority of frameworks; however, as evidenced by the summary matrix (Methodology Matrix I), this diversity of information meant that relatively few specific points were incorporated by more than a few countries.

In general, the degree of detail required for LMO background information was similar to that required for recipient and donor organisms. A majority of the frameworks required information about previous releases of the LMO in question and descriptions of methods by which it could be detected and identified (CH, CU, GE, JN, SA).

* Indicates headings and subheadings that do not readily fall within Annex III.

In some cases, details were required about the location (CA, CH, CU, GE, SA) and expression (CA, CH, CU, GE, SA, US) of the inserted genetic material within the recipient. Information about the genetic stability of the LMO (CA, CH, GE, SA, US) and a description of its phenotypic properties relative to the non-modified recipient (BR, CA, CU, GE, JN, SA, US) appeared in a majority of the reviewed frameworks. Finally, some frameworks included a description of the ecological traits of the LMO (AU, BR, CH, GE, US), with most of the required information relating to non-target impacts.

4. Receiving Environment

The reviewed risk assessment frameworks provided varying examples of information required about the receiving environment. Examples fell into five general categories: logistic information about the release, abiotic information about the release site, information about biota at the release site, ecosystem considerations, and social or economic considerations related to the release site. The Cuban risk assessment framework had an especially comprehensive information requirement that included genetic and species diversity, expected interactions between the LMO and resident biota, and abiotic information on site geology, geography, and climate. The Brazilian framework was noteworthy for requiring information about social and economic considerations near the proposed release site. For example, applicants had to consider the lands held by indigenous peoples by providing descriptions of cultures located in the vicinity of the proposed release and estimated impacts on those cultures by the LMO in question.

Several types of information regarding the receiving environment are required by a majority of the reviewed frameworks. All of them required information about the release site such as the size (spatial scale) of the intended release (AU, CA, CH, GE, SA, US) or a general description of the recipient environment's climate (AU, CH, CU, GE, JN, SA). Most frameworks (AU, BR, CA, CH, GE, JN, SA, US) required applicants to consider the presence of species that were sexually compatible with the LMO and a majority (CA, CH, CU, GE, SA) also stipulated that information about the biology or ecology of resident species be provided. Generally, the reviewed frameworks varied considerably in their requirements for specific information related to the receiving environment. Many items, such as water temperature (CU), extant pollinators (BR), and planned development (SA), were required only by a few countries.

> The reviewed risk assessment frameworks provided varying examples of information required about the receiving environment. Examples fell into five general categories: logistic information about the release, abiotic information about the release site, information about biota at the release site, ecosystem considerations, and social or economic considerations related to the release site.

METHODOLOGY MATRIX I

Identification of novel traits that may have adverse effect					
Types of potential adverse effects identified*	**Recipient/parental organism**	**Donor organism**	**Transformation event**	**LMO traits**	**Receiving environment**
Human adverse effects: • Allergenicity (AU, BR, CA, CH, GE, SA) • Disease in humans or animals (CU, GE) • Toxicity of plant tissues (AU, CA, CH, GE) **Gene flow** • Gene flow to wild relatives or domestic species (BR, CU, GE, CA, CH, SA, US) • Hybridization with related organisms (AU, CA, CH, JN, SA) • Horizontal gene transfer to soil microbes (BR, GE) **Effects on Ecosystem Processes** • Effects on bio-geochemistry especially in soils (BR, GE) • Expected role of LMO in biogeo-chemical & biologi-cal processes (US) • Changes in management including agricultural practices (GE) • Unintended spread of the GMO in the environment (CH, GE) • Expected byproducts of LMO's use (US) • Degradation of abiotic environment (AU)	**Background information** • Common name (CA, CH, CU, GE) • Taxonomy (AU, CA, JN, SA, US); including to strain/ cultivar (BR, CH, CU, GE) • Geographic distribution (BR, CA, GE, CH, CU, JN, SA,US) • Source (AU, CH, CU), including where collected, developed, & produced (US) • Ecological conditions of native range (CH, CU, GE), environmental conditions allowing persistence or growth (JN) • Information considered from within country & abroad (AU, CH) • Comparison of multiple "baseline" organisms when > 1 is used for comparisons (AU) • History & present state of use (AU, CA, CH, JN), including as it relates to humans (BR, CH), animals & environment (BR) **Genotypic & Phenotypic traits** • Sexual compatibility with other plant species (CA, CH, CU, GE)	**Traits of the donor organism** • Taxonomy of donor organism (AU, CA, CU, JN, US); classified to strain (BR) • Name of donor organism CH, GE, JN) • Source of donor organism (CU) • Relevant ecological information (AU) • Characteristics of the donor organism (CU) • Toxicant properties (CA) • Traits that cause disease or injury to plants & other organisms (CA)	**Traits of the Vector** • Name of vector (BR, CH, GE, JN); "origin" or "source" of vector (CU, GE, JN, CH) • Properties of vector (CH, GE, JN) • Host range of the vector (BR) • Nucleic acid sequence of vector (CA, CU) • Presence of genetic material from vector in final product (CU) • Stability of vector (CU) • Ability of vector to insert itself into other hosts (CU) • Pathogenicity of vector (CH) **Traits specific to the inserted genetic material** • Origin or source of inserted fragment (GE, CU, JN) • Size of inserted fragment (CH, GE) • Method of vector insertion (CA, CH, CU, GE) • Number of copies of inserted gene (BR, CH, CU, GE) • Sequence of inserted genes (CA, CU, CH), including maps (BR, CA, CH, US) & structure of entire transferred nucleic acid (JN)	**Background information; OECD: Organization for Economic Cooperation & Development** • Identity (CA), cul-tivar name (CH, SA) • Unique identifier for each transformation event using OECD standards (CA) • Name must include recipient & donor species names and LMO characteristics (JN) • Origin (CA) • Intended use (AU, CA, CU, US) • Production method (e.g. breeding, propagation, rearing) (AU, JN) • Information about previous releases (CU, CH, GE, JN, SA) • Description of detection & identification methods (CA, CH, CU, GE, JN) **Insert in the context of the recipient** • Location of the insert (CA, CH, CU, GE, SA) • Methods for de-termination of insert location (CH, GE) • Expression of the insert (CA CH, CU, GE, US) • Characteristics of the inserted genes (AU, CA, GE, SA, US) • Pleiotropic or epistatic effects of inserted genes (BR)	**Logistic information about release** • Location of release site (BR, CA, CH, CU, GE, SA, US) • Spatial scale of release (AU, CA, CH, GE, SA, US) • Temporal scale of release (AU, CH, SA) • Geographic characteristics (BR, CH) • Planned control mechanisms (e.g. herbicides) (CH) • Previous releases of LMO in area (SA) • Method of release (GE, SA) • Release site preparation and management methods (GE) **Abiotic information about release site** • Climate (AU, CH, CU, GE, JN, SA) • Geography (CU, CH) • Environmental conditions that affect survival & multiplication of LMO (CU, CH) • Wind direction, speed & seasonal variation (CU) • Geology, including soil & subsoil classification, chemical profile & filtration (CU) • Water temperature, salinity & nutrients (CU)

∗ Indicates headings and subheadings that do not readily fall within Annex III.

Identification of novel traits that may have adverse effect					
Types of potential adverse effects identified*	**Recipient/parental organism**	**Donor organism**	**Transformation event**	**LMO traits**	**Receiving environment**
Effects on species and populations • Non-target effects (CA, CH, GE, JN, US, SA) • Non-target toxicity tests for a broad array of taxa (US) • Allergenicity to animals (GE, US) • Toxicity of LMO (AU, CA, CH) or of plant tissues to animals (CH, GE) • Impacts on populations of species including genetic diversity (AU, GE) • Unintended spread of the GMO in the environment (CH, CU, GE) • Impacts to beneficial plants & animals (AU, CU, SA, US) • Impacts to threatened or endangered organisms (CA, CH, CU, US) • Production of substances interfering with the living or growth of plants, animals, microorganisms (JN) • Competition against wild plants for resources or interfering with their growth (CH, JN) • Selection of tolerant weed species (SA) • Pest aspects (except weediness) of the LMO (CA, AU) • Weediness (AU, CA, CH, GE, SA) or invasiveness (CA, GE)	• Potential to adapt (CU), including into hazardous weed (CH) • Genetic stability (CH) • Biological characteristics of baseline organism (AU, CA, CH); physiological properties (CH, JN, SA) • Phenotype characterization tests (US) • Morphology of baseline organism (AU) • Reproductive mode (CA, CH, CU, GE, JN) • Ability to form dormant structures (BR, GE) & length of dormant period (CH) • Fertility (CH) • Generation time (CA, GE) • How plant disperses & how far (BR, GE) • Tolerance to disease (CU) • Tolerance to different climates (CH, CU) • Characteristics relating to biosafety (CU) **Ecological traits** • Ecology of baseline organism (AU, CH), ecological properties (JN)		• Description of methods used for genetic modification (AU, CA, CH, GE, JN, US) • Intended function of inserted fragment (BR, CA CU, GE, JN) • Size & function of promoter, terminator, marker & reporter genes (CH) • Size and function of deleted regions (CH, GE) • Stability of inserted sequence (CH)	• Mechanism of interaction between LMO & target organism (GE) **Genotypic and Phenotypic traits** • Genetic stability (CA, CH, GE, SA, US), stability of expressed traits (CA, JN) • Genotypic properties (AU, CA) • Gene products (CA, US) • Change in ability to transfer genetic material to other organisms (BR, CH) • Phenotypic properties (AU) relative to non-modified recipient (BR, CA, CU, GE, JN, SA, US) • Phenotypic stability (GE) • Weediness & pest characteristics (CA, CH, US) • New enzymes produced (US) • Reproduction (BR, CA, CH, GE) • Hybridization potential (AU, CA, GE) • Dissemination of LMO (BR, CH, GE) • Resistance to chemical agents (BR) • Rate of degradation (BR) • Changes in behavior (SA, US) • Changes in metabolism, physical tolerance, morphology, & life history (SA)	**Information about organisms at release site** • Presence of sexually compatible relatives (AU, BR, CA, GE, SA, JN, CH, US) • Presence of similar genes (AU) • Genetic diversity of species present (CU) • Biology of plant & animal species present (CH, CU, GE, SA) • Ecology of species present (CA, CU) • List of animals present & if they are threatened or endangered (CH) • Pollinators (BR) • Biodiversity (CU) • Non-target toxicity tests for a broad array of taxa (US) • Pathogen; symbiont or beneficial organism; consumer; Gene transfer (CA) **Ecosystem considerations at release site** • Ecosystems in proximity (CU), including protected areas (BR, GE,SA) • Ecological characteristics (BR) • Possibility of LMO population increase in the environment (CU)

∗ Indicates headings and subheadings that do not readily fall within Annex III.

Identification of novel traits that may have adverse effect					
Types of potential adverse effects identified*	**Recipient/parental organism**	**Donor organism**	**Transformation event**	**LMO traits**	**Receiving environment**
	• Pollination mechanism (CA, CH) • Predators (CA, CH, CU, GE), predacity (JN) • Parasites (CH, GE), parasitism (JN) • Pathogens (CA) • Competitors (CH, CU, GE) • Symbionts (CA, CH, GE) • Possible threats to rare plant species (CH) **Toxicity / Disease traits** • Human allergenicity (AU, BR, CA, CH, GE, SA) • Toxicity (AU, CH, GE) • Pathogenicity (BR, CU, JN) • Production of harmful substances (JN)			• Changes in survivability (GE) • Mechanism of interaction with target organisms (GE) • Pollination mechanisms (SA) **Ecological traits** • Host range of LMO (US) • Impact on associated organisms (BR) • Traits relevant to identifying adverse effects to humans & environment (AU) • Effects on soil composition (BR) • Potential changes in interaction of LMO with non-target organisms (CH, GE) • Potential interactions with abiotic environment (GE) **Toxicity / Disease / Nutrition Traits** • Toxicity to humans (CH, GE) & animals (AU,CA, CH GE, US) • Allergenicity to humans (AU, CH, GE) & animals (AU, CH, GE, US) • Disease & pest susceptibility (US) • Anti-nutritional influence (CH) • Nutritional composition (CH)	• If agricultural system, common diseases of LMO & their severity or prevalence (CH) • Consideration that receiving environment is "not static" (AU) **Social/Economic considerations at release site** • Current production and work practices for the LMO (AU) • Agricultural practices for LMO crops (AU, SA), including primary production areas (CA) • Description of human cultures in vicinity of release (BR), including size (CU) • Planned developments in region (SA)

∗ Indicates headings and subheadings that do not readily fall within Annex III.

B. EVALUATION OF THE LIKELIHOOD OF THESE ADVERSE EFFECTS BEING REALIZED, TAKING INTO ACCOUNT THE LEVEL AND KIND OF EXPOSURE OF THE LIKELY POTENTIAL RECEIVING ENVIRONMENT TO THE LIVING MODIFIED ORGANISM

1. Intended use of the LMO compared to recipient or parental organism

A majority of the frameworks reviewed (CA, CU, GE, JN, US) required that a description of the LMO's intended use, purpose or distribution be included in the risk assessment. A few frameworks also required that a history of the use of the LMO be incorporated into the risk assessment (CH, CU, JN).

Many of the national risk assessment frameworks included comparisons between the LMO and the non-modified recipient organism (AU, BR, CA, CU, GE, JN, US). In most cases, the comparisons were explicitly made in the context of the same or similar uses (BR, CA, CU, GE, JN, US). The Japanese framework was notable for using the LMO parental lines as comparators for conventionally bred hybrid offspring of those lines. Within the frameworks of a few countries (AU, CA, CH), commercial releases into the environment were distinguished from limited or controlled environmental releases (e.g., isolated field trials).

2. Characteristics of relevant potential receiving environment

Most of the reviewed risk assessment frameworks requested that applicants describe characteristics of the receiving environment that could affect the likelihood of an adverse effect occurring (AU, BR, CA, CH, CU, GE, JN, US). Information relating to the location and spatial scale of the LMO introduction was requested by a majority of frameworks (AU, CH, CU, GE, US) and the proximity of indigenous human cultures to the release site was specifically mentioned in the case of Brazil. Several risk assessment frameworks addressed the temporal scale of the release (AU, CH, GE) and a majority required information regarding the presence or proximity of sexually compatible wild or domestic relatives (AU, CA, CH, CU, GE, JN, US). The Cuban approach was noteworthy for requiring substantial and specific documentation of the receiving environment's characteristics in the context of exposure.

3. How incidental exposure to the environment could occur

All nine of the reviewed risk assessment frameworks considered incidental exposure to the environment. Such exposure could occur from three major routes: gene flow, horizontal gene transfer, and via plant parts or exudates. Gene flow was the most commonly addressed route of incidental exposure; explicitly-considered mechanisms included the dispersal of reproductive material by either human-mediated or natural means (AU, BR, CA, CH, CU, SA), outcrossing and related concerns such as pollen viability or the proximity of sexually compatible wild or domestic species (CA, CH, GE, JN, US), gene flow interactions with other organisms in the receiving environment (CA, CH, US), and unintended spread of the LMO population into areas beyond the release site (CU, GE, JN). Horizontal gene transfer to soil microbes was explicitly mentioned in the Brazilian framework. Incidental exposure via plant parts or exudates was considered by a majority of the reviewed frameworks. In one case, this route included consideration of waste products (CU) but was more generally evaluated in terms of toxicity to non-target organisms through ingestion or contact (CA, CH, CU, JN, US).

All nine of the reviewed risk assessment frameworks considered incidental exposure to the environment. Such exposure could occur from three major routes: gene flow, horizontal gene transfer, and via plant parts or exudates

Extrapolation from data[*]

A majority of the reviewed frameworks allowed the use of extrapolated data in LMO risk assessments. In some cases, risk assessments were permitted to reference other assessments that had been performed on the same LMO in other countries (CH, GE,

∗ Indicates headings and subheadings that do not readily fall within Annex III.

JN) or on the genetically modified parental lines of a stacked LMO (GE, JN). Several of the reviewed frameworks allowed the inclusion of data that were generated in other nations, such as monitoring results (BR, CH, CU), the history of use of the LMO (BR, CH, CU), or experimental findings (BR, CH, GE). We observed additional instances of extrapolation within the Brazilian framework. These included estimation of chronic toxicity in one species based on acute-toxicity studies of a surrogate species and the use of one LMO risk assessment to provide a partial basis for estimation of the risks posed by a different recipient organism with the same transgene (BR).

4. Conclusion of evaluation of likelihood of exposure

A majority of the frameworks reviewed used either a qualitative or qualitative-categorical approach to evaluating the likelihood of exposure in the frameworks reviewed. In some cases, a qualitative likelihood estimate was based on laboratory or field trial findings, published literature, or data included in other risk assessments (GE, JN, US). Several other frameworks placed LMOs in likelihood or safety categories based on predetermined qualitative criteria (AU, BR, CH, SA). The U.S. framework was notable for using mathematical modeling and previously published data to quantitatively determine the likelihood of exposure. An additional approach, observed primarily in the Australian framework, involved the explicit description of the process of estimating exposure: all steps in an exposure pathway were identified and each likelihood value was individually assessed. This process simultaneously took into account the baseline organism (AU), the genetic modification (AU, CH), the LMO characteristics (AU, CH), the intended use (AU), the receiving environment (AU, GE) and the scope or manner of the release (AU, CH, GE).

> A majority of the frameworks reviewed used either a qualitative or qualitative-categorical approach to evaluating the likelihood of exposure

METHODOLOGY MATRIX II

Evaluation of likelihood of adverse effects being realized				
Intended use of GMO compared to recipient	**Characteristics of receiving environment**	**How incidental exposure to environment could occur**	**Extrapolation from data (geographical, temporal)***	**Conclusion of evaluation of likelihood of exposure**
• LMO properties with potential for adverse effect compared to non-modified parent under similar use (AU, CA, CU, GE, JN, US) • LMO compared to baseline organism and type of proposed release (AU) • Use of LMO compared to use of unmodified organism in a "conventional production system" (BR) • Baseline for conventional hybrid of LMOs is LMO parental lines under same use (JN) • Description of intended use, purpose, and/or distribution of LMO (AU, CA, CU, GE, JN, US) • History of use of the LMO (CH, CU, JN) • Distinction between limited/controlled releases and commercial releases (AU, CA, CH) • Description of cultivation practices (CA) • Ability of GMO to be cultivated outside area of current cultivation (CA) • Volume or number, scale, & frequency of release (CU) • Unique traits & expected benefits of LMO discussed in risk assessments (US)	**Logistic information about recipient environment** • Location of release (CU, GE, US) • Human cultures in vicinity of release (BR) • Size of introduction (CU, US), area of cultivation (CH) • Size of release sites compared to size of fields of sexually compatible crops (GE) • Spatial scale can affect exposure (AU, CH, GE) • Temporal scale of LMO release is important (AU, CH) • Effects potentially occurring beyond a limited time period for limited/controlled releases must be considered (AU); consider both delayed & immediate effects (GE) **Abiotic information about recipient environment** • Abiotic conditions allowing unintended persistence (CH, GE) • Factors that may affect ability to survive, reproduce, spread, or transfer genes to other organisms (CH) • Description of testing results for impacts on environment (US) **Information about organisms in recipient environment** • Potential competitive advantage of LMO (CA, CH, CU, JN)	**Gene flow** • Dispersal of reproductive structures (BR) • Differentiation between human-mediated & natural dispersal of LMO (CH, SA) • Human-mediated methods such as pollen transfer via clothing (AU, CH); transportation of LMOs (CH, CU) • Movement through water (CU, SA) • Dispersal via extreme weather conditions (SA) • Dispersal via insects and other animals (SA) • Pollen transfer through insect vectors and wind (BR, CA, CH) • Pollen viability (GE, JN) • Outcrossing (AU, CA, GE, JN) • Cross-fertilization frequency (CA, CH) • Non-target gene flow interactions with predators, prey, competitors, symbionts, parasites & pathogens (AU, CA, CH, US) • General description of non-target effects (e.g. gene flow; US) • Sexually compatible species including wild relatives (CA, CH, GE, JN, US) • Unintended spread of LMO to areas beyond release site (CU, GE, JN) • Weediness or becoming plant pest (CA, CH)	**Use of extant risk assessments** • Use of risk assessments performed on same LMO in other countries is allowed (AU, CH, GE, JN) • Use of previously published risk assessments for same LMO is allowed (AU, GE, JN) **Use of other existing data** • Extrapolation from studies conducted in other countries (BR, CH) or for other notifications (GE) is allowed • Results of LMO monitoring in other countries is considered (BR, CH, CU) • LMO history of use in other countries is considered (BR, CH, CU) • Risk assessments on one LMO used to draw conclusions about risk of a different plant with the same transgene (BR) • Gene products produced by other organisms used to test potential effects of LMO (BR) • Acute toxicity in a surrogate species (one dose) used to estimate chronic toxicity in other animals (BR)	**Quantitative** • Exposure estimates from product analysis data & data generated using mathematical models (US) **Qualitative** • Qualitative assessment based on data (experimental, other risk assessments) (GE, JN) • Qualitative assessment of field test results & literature review (US) • Qualitative determination (SA) • Decision for authorization of unconfined release is included qualitatively in the estimation of the overall risk (CA, CH) • A representative of the government body in charge of risk assessment generates an evaluation of likelihood of exposure (BR) **Qualitative/Categorical** • Qualitative process with 4 likelihood categories (AU) • Likelihoods for herbicide-resistant and insecticide-resistant LMO crops rely on a set of qualitative dichotomous keys (SA) • LMO is assigned to risk classes based partly on risk of dissemination (BR) • LMO assigned to a "safety class" based on mode of reproduction and means of dispersal (CH)

∗ Indicates headings and subheadings that do not readily fall within Annex III.

Evaluation of likelihood of adverse effects being realized				
Intended use of GMO compared to recipient	**Characteristics of receiving environment**	**How incidental exposure to environment could occur**	**Extrapolation from data (geographical, temporal)***	**Conclusion of evaluation of likelihood of exposure**
	• Presence of sexually compatible wild or domestic relatives (AU, CA, CH, CU, GE, JN, US) • Description of testing results for impacts on plants & non-target organisms (US) **Ecosystem considerations in recipient environment** • Proximity of release sites to populations of sexually compatible crops (AU, CA, CH, GE) • Natural (versus agricultural) environment (CH, JN) • Anticipated fate of LMO in soil (US)	**Horizontal gene transfer** • Transfer of genes to soil microbiota (BR) **Plant parts & exudates** • Pollinator feeding (presence/absence during confined field trials) (CA) • Seed feeding (secondary or pleiotropic effects via protein, lipids, fiber, others) (CA) • Considers toxicity impacts to non-target animals (US); toxicity (CA, CH) • Production of harmful substances (JN) • Description of harvesting practices (CH) • Escape via waste products (CU)		**Components of the evaluation** • Identifying all steps in an exposure pathway is necessary for a likelihood estimate (AU) • Each likelihood value assessed as an individual case (AU) • Should consider baseline organism (AU, CH) • Should consider the genetic modification (AU, CH) • Should consider the LMO characteristics (AU, CH) • Should consider the use of LMO (AU) • Should consider receiving environment (AU) • Should consider the scope of release (AU, CH)

∗ Indicates headings and subheadings that do not readily fall within Annex III.

C. EVALUATION OF THE CONSEQUENCES SHOULD THESE ADVERSE EFFECTS BE REALIZED

Genetic effects[*]

Adverse effects considered by the reviewed risk assessment frameworks can have two direct genetic consequences. One consequence is gene flow, the uni- or bidirectional exchange of genes among different, sexually compatible populations[2]; the other is the evolution of resistance. Consequences of gene flow to wild relatives were considered in the Canadian and Chinese frameworks. The Canadian guidance documents specified that all risk assessments must identify when gene flow to wild relatives may create hybrid offspring that could become weedy or invasive. The Brazilian risk assessment framework indicated that gene flow and its consequences must also be considered for domesticated relatives. Evolutionary resistance for two types of crops, herbicide-tolerant and insect-resistant, must be considered in assessing the risk consequences in China and Canada. Unique to Canada is the requirement of stewardship management plans to delay the evolutionary resistance of crop pest and weeds.

*Effects on species and populations**

There are four main categories of consequences from adverse effects on species and populations: impacts on plant pests, on non-target species, and on biological diversity, and changes in indicator organisms. Plant pest impacts on native plants must be considered in the United States and Canada but the former requires impact testing. The U.S. framework stipulated that risk assessments must also include field test reports considering the likelihood of the LMO becoming a plant pest or weed. The consequences of non-target species impacts must be included in risk assessments in the U.S., generally via toxicity tests on birds, mammals, fish, invertebrates, and aquatic organisms. Generally, these tests ascertain the doses and concentrations at which 50 percent of the exposed organisms die (i.e., LD50 and LC50 toxicity tests). Among the frameworks reviewed, this requirement was unique to the U.S. The Canadian framework indicated that consequences on pollinators and seed feeders must be identified, including secondary or pleiotropic effects. Further, the consequences of adverse effects on biological diversity must be considered; such effects included those related to metabolism, growth, development, reproduction, physiology and behavior (CA). The Canadian, Chinese, and Cuban frameworks required that threatened or endangered species receive special consideration with regards to the consequences of adverse effects. The Cuban framework, for example, used LMO impact on protected plant species as one factor considered when assigning the LMO to a risk category. The Canadian and Australian frameworks extended special consideration to valued or beneficial organisms. Unique to the Brazilian framework was the consideration of changes in indicator organisms including symbionts, predators, pollinators, parasites, and competitors.

There are four main categories of consequences from adverse effects on species and populations: impacts on plant pests, on non-target species, and on biological diversity, and changes in indicator organisms.

2 Commission for Environmental Cooperation of North America. 2004. Maize and Biodiversity: the Effects of Transgenic Maize in Mexico. Key Findings and Recommendations. Secretariat Article 13 Report, November 8, 2004. North American Agreement on Environmental Cooperation, NAFTA. http://www.cec.org/maize/(accessed 10 March 2012).

∗ Indicates headings and subheadings that do not readily fall within Annex III.

Effects on ecosystem processes[*]

Three of the nine reviewed risk assessment frameworks mentioned specific ecosystem consequences to be considered as part of a risk assessment. This area of risk assessment generally appears to be underdeveloped. The U. S. framework considered the consequences of the environmental fate of pesticides produced by LMOs. Persistent toxic substances must be taken into account under the Canadian framework, which suggested that the persistence of any toxic substance produced by LMOs be determined through residual effects studies using crop rotation. In the case of Australia, two unique ecosystem consequences were considered: disruptive effects on ecosystems and degradation of the abiotic environment.

Conclusion of consequences of adverse effects

There were a variety of ways that each of the reviewed frameworks reached conclusions regarding the consequences of adverse effects. The German, South African, and Australian frameworks considered the magnitude of the consequences. The seriousness of the consequence was combined with the magnitude of consequence to establish four consequence categories in the Australian framework, which additionally considered the scale (spatial and temporal) and potential reversibility of adverse effects. The Japanese framework indicated that concrete details of the consequences of adverse effects were experimentally determined. Specific to the Brazilian and Chinese frameworks was the consideration of experiences in other countries. The Canadian and Chinese frameworks utilized qualitative final conclusions on the consequences of adverse effects and these conclusions were part of the estimations of the overall risks.

∗ Indicates headings and subheadings that do not readily fall within Annex III.

METHODOLOGY MATRIX III

Evaluation of consequences should adverse effects be realized			
Genetic effects*	**Effects on ecosystem processes***	**Effects on species and populations***	**Conclusion of consequences of adverse effects**
Gene flow • Wild relatives (CA, CH, JN) • Invasiveness (CA) • Domesticated relatives (BR) **Evolution of Resistance** • By target insects (CA, CH) • Herbicide tolerance (CA, CH)	• Environmental fate (US) • Persistent toxic substances (CA) • Disruptive effects on ecosystems (AU, GE) • Degradation of abiotic environment (AU) • Effects on biogeochemical cycling especially in soils (BR, GE)	**Plant pest** • To native plants (JN, US) • Invasiveness (CA, CH) • Field tests (US) • LMO becomes novel plant pest (AU, CA) • Weedy in agricultural systems (CA, CH) **Non-target species impact** • Toxicity (CH, GE, JN, US) • Seed feeders (CA) • Pollinators (AU, BR, CA) • Secondary or pleiotropic effects (BR, CA) • Microorganisms (AU) **Loss of biological diversity (animals, plants, or microbes)** • Metabolic, growth, developmental, reproductive, physiological and behavioral effects (CA) • Special consideration for threatened or endangered species (CA, CH, CU) or valued or beneficial species (AU, CA, CU) • Effects on population dynamics and population-scale biological diversity (GE) **Changes in Indicator organisms** • Symbionts, predators, pollinators, parasites, & competitors (BR)	• Magnitude (AU) of consequence combined with likelihood of occurrence (GE) • Seriousness (AU) • Qualitative process with 4 consequence categories (AU) • Each consequence value assessed as an individual case (AU) • Reversibility of potential risk (AU) • Scale (spatial & temporal) (AU) • Qualitative as part of the estimation of the overall risk (CA, CH, CU) • Experimentally determine concrete details (JN) • Experiences in other countries are considered (BR, CH, CU)

∗ Indicates headings and subheadings that do not readily fall within Annex III.

D. ESTIMATION OF THE OVERALL RISK POSED BY THE LMO BASED ON THE EVALUATION OF THE LIKELIHOOD AND CONSEQUENCES OF THE IDENTIFIED ADVERSE EFFECT BEING REALIZED

*Approach used to combine adverse effects and likelihood**

The primary approaches used for combining the likelihood of adverse effects occurring and the consequences if they did occur, were qualitative in nature. A majority of countries combined information sources in various ways to estimate the overall risk. The Australian and Chinese frameworks were unique in that they used a categorical qualitative framework for combining likelihood and consequences. The Australian framework used a risk matrix and combined the likelihood assessment scale and the consequence assessment scale to determine an overall risk estimate. Additionally, uncertainly regarding the level of risk and the manageability of risks were incorporated into the overall estimate (AU). The Chinese framework also used a risk matrix to classify an overall risk estimate. However, this matrix combined the safety classes of the recipient organism with the safety level of the genetic manipulation.

The primary approaches used for combining the likelihood of adverse effects occurring and the consequences if they did occur, were qualitative in nature.

*Who made the final decision of overall risk?**

Based on the documents we reviewed, final decisions regarding the overall risk posed by LMOs fell into one of three categories: a single regulator or minister, a single competent authority (i.e., an organization), or multiple competent authorities. In both the Japanese and Australian frameworks, an individual made the final decision. The Australian framework was unique in that an independent statutory office holder, the Gene Technology Regulator, was responsible for decision-making with regard to release of LMOs. In Japan, a single minister from the national competent authority was charged with the regulation of particular types or uses of LMOs. These frameworks contrasted with the majority of those reviewed, in which a single national competent authority made decisions regarding the overall risk posed by a LMO. In some cases, this entity was a national biosafety authority (committee, council, commission, center) (GE, BR, CH, CU, SA) or a national competent authority charged with regulation of a particular type of organism or use (CA). In the U.S. up to three separate agencies were involved, depending on the use of the LMO. Each agency regulated LMOs based on their respective areas of authority and each would make separate decisions regarding whether to approve environmental release.

*Type of risk estimate produced**

All of the reviewed risk assessment frameworks produced qualitative risk estimates for new LMOs, although the exact form of those estimates varied by country. In the U.S., the estimate of overall risk posed by a LMO was a binary classification of negligible versus non-negligible risk. Other risk assessment frameworks assigned LMOs to one of four or more different risk classes (AU, BR, CA, CH) depending on the relative degree of estimated risk that the LMO posed. In several other cases (CU, GE, JN, SA) we were not able to determine from the available documents the type of risk estimates produced within those frameworks.

*Uncertainty analysis**

Based on the documents reviewed for this report, we found only one example of formal uncertainty analysis utilized during the risk assessment process (AU). Uncertainty inherent to the information or data available was addressed by any of several ways in all countries (see Section 12.G, below), but typically this uncertainty was not explicitly analyzed. This area of risk assessment methodology may merit additional research and development.

∗ Indicates headings and subheadings that do not readily fall within Annex III.

METHODOLOGY MATRIX IV

Evaluation of overall risk based on likelihood and consequences of adverse effects			
Who makes final decision of overall risk?*	**Approach used to combine adverse effects and likelihood***	**Type of risk estimate produced***	**Uncertainty analysis conducted***
Single Person/Regulatory Body • Individual (AU) • Competent minister (JN) or national competent authority (CA), based on use and/or organism • National competent authority (CA, CH, GE) • National Biosafety Committee, Council, Commission, or Center (BR, CH, CU) • One main regulatory body (CU, SA) **Multiple National Competent Authorities** • Depending on use, U1 national agency (US)	**Qualitative Combination of:** • Expert opinion (AU, BR, CA, CH, CU, GE, JN, SA) • Public input (SA) • Field test results (CA, CH, GE, JN, US) • Literature reviews (AU, CA, US) • Lab testing of toxicity (US) • Non-target environmental impacts (CH, US) • Environmental fate testing (US) **Risk Matrix** • Combining likelihood and consequences for each adverse effect (AU) **Safety Class** • Combining safety class and change in safety caused by modification (CH) **Dichotomous Keys** • Use of dichotomous keys (SA) **Other Considerations** • Manageability of risks (AU) • Uncertainty (AU) • Relative difference between modified and non-modified (CA)	• ≥ 4 risk classes (AU, BR, CH) • Risk/no risk (US) • General qualitative (CA, CU, GE, JN, SA)	• Uncertainty is considered in each likelihood, consequence, and risk assessment (AU)

∗ Indicates headings and subheadings that do not readily fall within Annex III.

E. RECOMMENDATION AS TO WHETHER THE RISKS ARE MANAGEABLE, INCLUDING, WHERE NECESSARY, IDENTIFICATION OF STRATEGIES TO MANAGE THESE RISKS

The risk assessment frameworks reviewed generally did not require a statement regarding the manageability of risks. Rather, this decision was largely implicit in the decision to approve or deny an application for environmental release of a LMO. In the case of the Chinese framework, the manageability of risks was considered during the process of assigning recipient organisms to a risk class. Those recipient organisms for which the predicted adverse effects could not be controlled with known technologies were automatically assigned to the highest risk classification (CH). This classification in turn increased the stringency of required risk management practices. Most of the reviewed frameworks (AU, BR, CA, CH, CU, GE, JN, US) addressed risk manageability by requiring applicants to provide a list of appropriate risk management practices that would be employed during LMO testing or production. In one other case, the results of the risk assessment determined what risk management practices must be employed by the applicant (SA). Common risk management strategies generally focused on preventing the spread of LMOs or their genes (CA, CH) and included spatial limitations on LMO use (AU, CA, CH), spatial isolation of LMOs from surrounding ecosystems (AU, CH, CU, US), and temporal isolation to ensure asynchronous flowering (AU, CA).

> The risk assessment frameworks reviewed generally did not require a statement regarding the manageability of risks. Rather, this decision was largely implicit in the decision to approve or deny an application for environmental release of a LMO

In addition to these general risk management practices, several risk assessment frameworks (CH, CU, US) required that an emergency response plan be included with applications.

To facilitate detection of escaped LMOs or LMO genes, most reviewed frameworks also required a description of the molecular technique(s) used to identify the modified or introduced gene (BR, CA, CH, CU, GE, JN).

F. WHO IMPLEMENTS POLICY BASED ON RISK DECISION?*

For the countries under review, we found that government entities were typically responsible for implementing LMO risk policies following a decision to allow environmental release. In a majority of countries (BR, CA, CH, CU, GE, SA) this entity was a government institution or council but in two cases an individual regulator bore this responsibility (AU, JN). In the U.S., policy implementation involved a coordinated effort between multiple government agencies.

> we found that government entities were typically responsible for implementing LMO risk policies following a decision to allow environmental release.

G. WHERE THERE IS UNCERTAINTY REGARDING THE LEVEL OF RISK, IT MAY BE ADDRESSED BY REQUESTING FURTHER INFORMATION ON THE SPECIFIC ISSUES OF CONCERN OR BY IMPLEMENTING APPROPRIATE RISK MANAGEMENT STRATEGIES AND/OR MONITORING THE LMO IN THE RECEIVING ENVIRONMENT

Based on the documents we reviewed, the Australian framework explicitly required identification and description of sources of uncertainty. Many of the other countries addressed uncertainty by requiring that a post-release monitoring plan be presented during the LMO approval application process (BR, CA, CH, CU, GE). In the case of Japan, this kind of plan may be required at the discretion of the regulating body (JN). Some countries test LMOs at sequentially increasing spatial scales (BR, CA, CH).

* Indicates headings and subheadings that do not readily fall within Annex III.

We inferred this to be another form of addressing uncertainty, because it may allow potential problems to be identified when environmental exposures are still relatively low and thereby reduce risk. The German and Chinese frameworks accounted for uncertainty in the degree of LMO-associated risk by generating elevated risk classifications if the effects of the organism on human health or the environment were unknown.

One way novel risks can be identified is through the continued collection of new field data or monitoring of relevant literature. The risk assessment frameworks that we reviewed differed in their utilization of new information. In some cases, the framework documents explicitly required that any new information regarding the LMO be brought to the attention of the regulating authority (CU, US). This new information may be used prior to release so as to supplement application materials and give risk assessors a more complete picture of the risks posed by a new LMO (AU, BR, CU, US). After environmental release has been approved, submission of any new data to the relevant regulatory body may be mandatory, particularly if the data pertain to newly-discovered adverse effects (US). The U.S. further required that LMOs regulated by the Environmental Protection Agency undergo re-registration every five years, at which time recent advances in relevant technologies may be used to re-assess risks. The consequences of newly available information included potential revocation of approval of the LMO (BR, CH) or triggering of another risk assessment (BR, SA).

In many cases the exact risk management practices employed by an applicant varied according to the risks posed by a LMO. For example, to prevent target pests from developing resistance to pesticidal traits, the U.S. required the use of refugia, patches of unmodified crops that separate fields planted with LMOs. Target pests persist in these refugia because they are not subject to the selective pressures of insecticidal proteins. Ideally, gene flow between pest populations in the LMO fields and in the refugia maintains non-pesticide-resistant genes at some frequency in the target population, delaying the evolution of insecticide resistance.

Other examples of risk management techniques include the destruction of LMO materials after testing (US) or harvest (CH), limitation of spatial use of LMOs (US), spatial isolation of LMOs to reduce the risk of gene transfer through wind-borne pollen (CH), and temporal isolation of modified varieties so that they flower asynchronously with neighboring unmodified crops (CH).

METHODOLOGY MATRIX V

Recommendation as to whether risks are manageable including, where necessary, identification of strategies to manage these risks	Who are the actors that implement policy based on risk decision?	Where uncertainty exists, further information may be requested or risk management & monitoring strategies may be implemented
Requirements for a decision • Risk management practices required for approval of LMO (AU, CA, CU, GE, JN, SA, US) • Stewardship plan to prevent insect and herbicide resistance (CA) • Procedures to avoid or reduce LMO dissemination (CU) • Procedures listed for minimizing risk of LMO spread by people (CH, CU, US) by machinery or equipment (US) • Methods of detecting LMOs must be reported (CA, CH, CU, GE, JN); e.g. genetic markers (BR) • Emergency response procedures required for approval (CH, CU, US) **General goals of risk management** • Prevent reproduction of LMO in field tests (CH, US) • Prevent persistence of LMO after field tests (US) • Prevent insect resistance of LMO (CA) • Prevent herbicide resistance of LMO (CA) • Prevent exposure to environment of LMO (CA, CH) • Minimize gene-flow to other organisms (CA, CH) • Protect human health and safety (AU) • Protect the environment (AU) **Risk management strategies** • Destruction of genetic material after field tests (CH, US) • Refugia (US) • Spatial limitations on use (AU, CH, CU, US) • Spatial isolation (AU, CA, CH) • Temporal isolation (AU, CH) **General** • Overall risk classification takes risk manageability into account (AU, CA, CH, CU, GE) • Risk assessment includes risk management measures (AU, CA, CH, CU, GE, JN) • Results of risk assessment influence the type of risk management plan that is developed (SA) • Cultivation must be accompanied by appropriate risk management activities (BR) • Approval of large-scale projects requires greater majority approval from committee (BR) • Prioritize preventative risk measures over curative measures (AU)	• Single national competent authority (institution; BR, CA, CH, CU, GE, SA) minister (JN) • Individual regulator (AU) • Committee/council within one government agency (BR, SA) • Three coordinated government agencies (US)	**Addressing uncertainty** • Types of uncertainty are described and identified (AU) • Conservative approach to risk management (AU) • Use of confined field trials (CA, CH) • Training in safe handling of LMO to prevent escape from contained settings (CH, CU) • Periodic re-registering of LMO (CU, US) **Post-release monitoring plan** • Required (BR, CA, CH, CU, GE) • May be required (AU, JN, SA) • Training of staff in monitoring procedures must be documented (CU) **Use of new information** • General • New information must be submitted (CU, US) • Pre-release: • To supplement incomplete applications (AU, BR, CA, CU, US) • Approval may be postponed until more information is provided (CU) • Post-release: • New adverse effects must be documented (US) • New adverse effects may trigger reassessment of LMO (BR) • Decision may be reversed (BR, CH, CU) • Guidance document may be revised (JN) • New information on the LMO and its effects may cause risk assessment to be readdressed (CA, CU, GE)

Chapter 13. Conclusion

We compared nine countries' risk assessment frameworks for the regulation of living modified organisms (LMOs). The countries we studied represent a range of geographic locations and socio-economic development levels. Our analysis highlights the diversity of approaches taken to address the principles and methodologies outlined in Annex III of the Cartagena Protocol on Biosafety, and it also examines how specific risk assessment criteria fit within broader Regulatory landscapes. This report provides a resource for agencies seeking to develop or expand their own country's LMO regulatory framework and for researchers and government workers wishing to gain an understanding of how LMO risk assessment approaches vary among countries. Our report will contribute to improving LMO risk assessment procedures at a time when the use of LMOs is becoming increasingly widespread.

The regulatory approaches of some countries (e.g. Cuba) closely match the elements of Annex III. However, because most countries have developed frameworks that only partially match these elements, direct comparison of risk assessment approaches to Annex III was often difficult. For example, Annex III includes separate elements for identification of traits that may cause adverse effects, the likelihood that adverse effects will occur, and consequences of adverse effects, but the frameworks of some countries do not require differentiation between types and consequences of adverse effects. These differences among countries do not necessarily indicate that one approach is better than another, and indeed, the degree to which different approaches result in effective regulation of LMO technology remains unclear. The variety of existing approaches does suggest that a global agreement on best principles and methodologies for LMO risk assessment may be difficult to achieve. A diversity of potential approaches may be necessary given the different cultures, levels of desired precaution, and socio-economic considerations in different countries.

> This report provides a resource for agencies seeking to develop or expand their own country's LMO regulatory framework and for researchers and government workers wishing to gain an understanding of how LMO risk assessment approaches vary among countries.

We identified several major differences in how countries approach LMO risk assessment. One major distinction among countries is in the criteria that trigger the risk assessment process. Whereas most countries decide whether regulation is required based on whether an organism has been genetically modified (i.e. the process-based approach; examples include U.S., Germany, China, Australia), Canada's triggering process hinges on whether the LMO contains novel traits, regardless of the production method (i.e. product-based approach). The implications of implementing these alternative approaches, and specifically, the effectiveness with which potentially harmful organisms are identified and screened, remains unclear. The argument that genetic manip-

ulation is inherently risky is highly contested[1], and viewpoints on this issue are likely to directly influence whether a process or product-based approach is adopted. Further research of and experience with modern biotechnology, as well as exploration of public attitudes and cultural viewpoints, will inform decisions about criteria for triggering LMO risk assessment.

Another major distinction is in how a lack of information or consensus is dealt with in reaching a risk determination. Regulations for some countries closely mirror Annex III's language regarding this element (Cuba) or explicitly mandate the use of a precautionary approach (e.g. Australia, Brazil, Germany). For example, Australia's framework mandates that scientific uncertainty should not prevent actions from being taken that will prevent environmental degradation. Other frameworks refrain from explicitly invoking the precautionary principle or the language of Annex III when referring to incomplete information in the decision-making and/or risk management process. This less prescriptive language may arise from the multiple underlying facets of the precautionary principle and implications of alternative interpretations of these facets. Broad agreement on application of the precautionary approach will be difficult; however, international discussion is needed to better understand whether, in what circumstances, and how precaution can contribute to successful LMO risk assessment.

The nine countries also differ in their over-arching legislation and Regulatory landscape for LMOs. Whereas competent national authorities in some countries act under legislation specifically developed for LMO regulation (e.g. South Africa's Genetically Modified Organism Act), the oversight of agencies in other countries is based on legislation that broadly applies to crop or environmental protection, not to LMOs specifically (e.g. the Plant Protection Acts of Canada & the United States). The former approach provides specific guidelines for particular LMO cases and, potentially, a more straightforward regulation process; however, regulations often require updates or amendments in response to technology advances or unique situations. The latter approach requires agencies to implement oversight of LMOs within a less well-defined framework but also provides more flexibility for dealing with unique cases and rapid technology advances. Given rapid advances in biotechnology, increasing numbers of applications for experimental LMO release, and unregulated release into the environment, future LMO legislation must achieve a balance between flexibility and specificity to avoid lagging behind technology.

Our analysis reveals several aspects of LMO risk assessment that will benefit from further research. Formal uncertainty analysis is an area of risk assessment that is especially underdeveloped. Although several countries informally address uncertainty by requesting further information about a LMO's traits or adverse effects, only Australia's framework directly addresses uncertainty by discussing variability, incertitude, and descriptive and cognitive uncertainties associated with risk estimates. Furthermore, Australia bases risk decisions on probability distributions of risk, which can incorporate the multiple sources of uncertainty associated with point estimates. Further adoption of uncertainty analyses into risk assessment will allow risk designations to be made in a more informed and less subjective manner.

> The nine countries also differ in their over-arching legislation and Regulatory landscape for LMOs. Whereas competent national authorities in some countries act under legislation specifically developed for LMO regulation, the oversight of agencies in other countries is based on legislation that broadly applies to crop or environmental protection, not to LMOs specifically

Related to uncertainty analysis is the need for development of systematic and evidence-based methods of likelihood estimation and risk characterization. Most countries use qualitative methods (e.g. expert knowledge and non-systematic reviews of scientific literature) to estimate the likelihood of exposure and overall risk associated with LMOs. Qualitative methods can include formal expert or stakeholder ranking of risks, but are often as informal as stated

1 McHughen, A., Smyth, S. 2008. US regulatory system for genetically modified [genetically modified organism (GMO, rDNA or transgenic)] crop cultivars. Plant Biotechnology Journal 6:2-12.

conclusions from a decision-making authority. Even when empirical results from LMO field testing or previous studies are used to estimate the likelihood of adverse effects, final risk characterization is rarely done quantitatively, and the methods used to reach final risk estimates are often poorly documented. Further development of quantitative methods (e.g. mathematical modeling, statistical modeling, and simulation) will be necessary for dealing with the increasingly complex risk scenarios that arise with advances in modern biotechnology. Systematic, yet not fully quantitative, approaches (e.g. use of risk matrices or dichotomous keys for assigning risks associated with adverse effects) may also provide a more rigorous approach to risk characterization than current qualitative methods.

As the use of modern biotechnology becomes more widespread, assessing risks associated with LMOs is increasingly important for preventing undesirable impacts to the environment. Further research and development of LMO risk assessment principles and methodologies is needed. Nonetheless, a diversity of approaches is already being implemented. This diversity of practices across the globe, together with an over-arching international agreement, the Cartagena Protocol, provides an invaluable resource that can assist countries in developing or re-assessing their own LMO risk assessment frameworks.

APPENDIX: Cartagena Protocol on Biosafety - ANNEX III

RISK ASSESSMENT

OBJECTIVE

1. The objective of risk assessment, under this Protocol, is to identify and evaluate the potential adverse effects of living modified organisms on the conservation and sustainable use of biological diversity in the likely potential receiving environment, taking also into account risks to human health.

USE OF RISK ASSESSMENT

2. Risk assessment is, inter alia, used by competent authorities to make informed decisions regarding living modified organisms.

GENERAL PRINCIPLES

3. Risk assessment should be carried out in a scientifically sound and transparent manner, and can take into account expert advice of, and guidelines developed by, relevant international organizations.

4. Lack of scientific knowledge or scientific consensus should not necessarily be interpreted as indicating a particular level of risk, an absence of risk, or an acceptable risk.

5. Risks associated with living modified organisms or products thereof, namely, processed materials that are of living modified organism origin, containing detectable novel combinations of replicable genetic material obtained through the use of modern biotechnology, should be considered in the context of the risks posed by the non-modified recipients or parental organisms in the likely potential receiving environment.

6. Risk assessment should be carried out on a case-by-case basis. The required information may vary in nature and level of detail from case to case, depending on the living modified organism concerned, its intended use and the likely potential receiving environment.

METHODOLOGY

7. The process of risk assessment may on the one hand give rise to a need for further information about specific subjects, which may be identified and requested during the assessment process, while on the other hand information on other subjects may not be relevant in some instances.

8. To fulfill its objective, risk assessment entails, as appropriate, the following steps:

(a) An identification of any novel genotypic and phenotypic characteristics associated with the living modified organism that may have adverse effects on biological diversity in the likely potential receiving environment, taking also into account risks to human health;
(b) An evaluation of the likelihood of these adverse effects being realized, taking into account the level and kind of exposure of the likely potential receiving environment to the living modified organism;
(c) An evaluation of the consequences should these adverse effects be realized;
(d) An estimation of the overall risk posed by the living modified organism based on the evaluation of the likelihood and consequences of the identified adverse effects being realized;
(e) A recommendation as to whether or not the risks are acceptable or manageable, including, where necessary, identification of strategies to manage these risks; and
(f) Where there is uncertainty regarding the level of risk, it may be addressed by requesting further information on the specific issues of concern or by implementing appropriate risk management strategies and/or monitoring the living modified organism in the receiving environment.

POINTS TO CONSIDER

9. Depending on the case, risk assessment takes into account the relevant technical and scientific details regarding the characteristics of the following subjects:

(a) Recipient organism or parental organisms. The biological characteristics of the recipient organism or parental organisms, including information on taxonomic status, common name, origin, centres of origin and centres of genetic diversity, if known, and a description of the habitat where the organisms may persist or proliferate;
(b) Donor organism or organisms. Taxonomic status and common name, source, and the relevant biological characteristics of the donor organisms;
(c) Vector. Characteristics of the vector, including its identity, if any, and its source or origin, and its host range;
(d) Insert or inserts and/or characteristics of modification. Genetic characteristics of the inserted nucleic acid and the function it specifies, and/or characteristics of the modification introduced;
(e) Living modified organism. Identity of the living modified organism, and the differences between the biological characteristics of the living modified organism and those of the recipient organism or parental organisms;
(f) Detection and identification of the living modified organism. Suggested detection and identification methods and their specificity, sensitivity and reliability;
(g) Information relating to the intended use. Information relating to the intended use of the living modified organism, including new or changed use compared to the recipient organism or parental organisms; and
(h) Receiving environment. Information on the location, geographical, climatic and ecological characteristics, including relevant information on biological diversity and centres of origin of the likely potential receiving environment.