
The GMO Guidelines Project: Development of International Scientific Environmental Biosafety Testing Guidelines for Transgenic Plants

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GMO-Guidelines Project***

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Introduction

The Cartagena Protocol on Biosafety of Living Modified Organisms (Biosafety Protocol) under the Convention on Biodiversity (CBD) and many other international forums identify a clear need in both developing and developed countries for comprehensive, transparent, scientific guidelines for meaningful pre-release testing and post-release monitoring of transgenic plants, to ensure their environmental safety and sustainable use. The lack of such guidelines globally, and the need for such guidelines in developing countries, has been repeatedly expressed by both the private and public sector (CBD, 2000). For example, Chapter 16 of Agenda 21 recognizes that the maximum benefits of genetically modified crops can be achieved only if appropriate guidelines for their biosafety are in place and the relevant capacities to implement the guidelines are acquired (UN-DSD, 1999).

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In addition, there is wide recognition that the regulatory and scientific capacity for conducting risk assessments needs to be strengthened in most countries. Most importantly, the needs of developing countries for capacity building and policy development must be addressed. Article 22 of the Biosafety Protocol requires that parties shall cooperate in the development and/or strengthening of human resources and institutional capacities in biosafety (UN-DSD, 1999). It is also recognized that this capacity-building activity will require significant investments, as many countries do not have the capability to make independent risk assessments or to evaluate independently submitted risk assessments on biosafety (CBD, 2000).

The GMO Guidelines Project 'Development of International Scientific Biosafety Testing Guidelines for Transgenic Plants' aims to develop international, scientific, conclusive and acceptable guidelines for assessing the environmental risks posed by a genetically modified organism (GMO). The project was launched by scientists of the Global Working Group on 'Transgenic Organisms in Integrated Pest Management and Biological Control' under the patronage of the International Organization for Biological Control (IOBC). We focus our efforts in capacity building on facilitating scientist-to-scientist exchange, because a sound, consistent science base may be easier to transfer among countries than a regulatory system. Consequently, the project focuses its capacity-building efforts on a few countries with reasonably developed scientific infrastructures. By strengthening the scientific capacities for risk assessment in these countries, we expect the expertise to diffuse more readily to neighbouring countries, and a good regional representation in the regional groups and on the advisory board of the project will assist this process.

The guidelines can be envisaged as a set of interlinked modules, consisting of scientific questions related to risk assessment and corresponding scientific methodologies to answer those questions. Table 10.1 illustrates what the guidelines are and what they are not. The guidelines will have no regulatory legitimacy themselves, but regulatory authorities can choose to implement parts, or all, of the guidelines as they desire or need, with confidence in the scientific soundness behind the information gathered using our identified methodologies. They are designed for use before approval is given for the GM plant. The compiled guidelines strive to address all issues and questions pertinent to the scientific sections, as comprehensively as possible. Not all of the questions must be addressed for every GMO. Based on the specific GMO and target region for release, for most GMOs, a case-specific subset of questions will need to be addressed for an assessment of their ecological impact. The guidelines will not be in the form of a decision tree, but they can easily be incorporated into one, which would have to be region, country or case specific, according to the regulatory situation and case-study requirements. The guidelines are not a guide to cost (or risk)-benefit analysis of transgenic organisms, as this presupposes a valuation system for comparing effects, which is outside the domain of scientific methodology, but they will guide the evaluation of any environmental effect, which can then be analysed in the appropriate political context (Table 10.1, section 1).

Table 10.1. What the GMO Guidelines are and what they are not.

The guidelines are:	The guidelines are not:
1 Comprehensive scientific questions of which a case-specific subset can be extracted for ecological impact assessment, depending on GMO and target region for release	Regulatory guidelines (e.g. decision tree or decision guide)
2 Relevant to the environmental and agricultural impacts of GMOs	For evaluation of human health impacts or ethical implications
3 All or some questions can be considered (many may prove to be irrelevant in a particular country's context)	All questions must always be answered in all cases
4 Protocols that will lead to scientifically defensible results that can be used in risk assessment	Prescriptive protocols that must always be used to answer a particular scientific question
5 Serve as a scientific standard for the data that support risk assessment	Validation of poor scientific methods for generating data for risk assessment
6 Guidelines that provide the necessary scientific information to address a scientific question related to risk assessment	Guidelines that require the generation of data that are not necessary for risk assessment

They will cover the environmental and agricultural impacts of GMOs, and they will not evaluate human health impacts or ethical implications. The guidelines should be applicable to most GM plants, but are at present focused on those GM plants modified to produce a novel gene product currently used in pest control. There is more information available on this class of GMO than any other class, and the expertise of the group is concentrated in the disciplines related to pest control (Table 10.1, section 2).

The guidelines will be designed for use on a case-by-case basis, as specified in the Biosafety Protocol and the EU Directive on release of GM plants. A case-by-case approach is necessary because there is insufficient experience available to allow aggregate analysis and assessment. Each GM plant and ecosystem must be looked at separately. The relevant questions will therefore differ on a case-by-case and country-by-country basis, but with any of the selected questions and associated protocols, the user of the guidelines can have confidence that the protocols will produce scientifically sound data (Table 10.1, sections 3 and 4).

Existing data can be evaluated against the guidelines, so that the strengths and weaknesses of the existing data can be clarified. They will therefore also provide guidance for judging other possible protocols. By setting a clear scientific standard, the data for risk assessment is likely to converge and stabilize around that standard. The protocols will indicate the information that is essential for

answering the question, and will provide additional guidance on collecting data that is not essential but none the less useful (see Table 10.1, sections 5 and 6).

The scientific scope of the guidelines is divided into five scientific sections: needs assessment, plant characterization, non-target and biodiversity impacts, gene flow and its consequences, and resistance management. In the following part of the chapter, we summarize the areas covered by each section. This summary represents the current status of the project, and will be subject to change as the project is an ongoing process.

Needs Assessment

Problem Formulation
and Options Assessment
(PFOA)

The ^{PFOA} ~~needs assessment~~ section provides a framework for evaluating the need for the transgenic plant in specific crop production contexts and comparing it against other potential solutions to the problem. A science-driven needs assessment must be a deliberative process designed to provide for social reflection and discussion about transgenic organisms (Forester, 1999; Susskind *et al.*, 2000). This includes providing an approach for evaluating projected changes in crop production practices that result from the implementation of the GMO or alternative solution(s). This section sets the context for the environmental analyses that follow in the non-target, gene flow and resistance sections. It defines the target agroecosystems in which the use of the GMO or alternative solution is proposed, including the crop system, farming system and ecological and structural context, and the people who will be affected by the use of the GMO or alternative solution. It establishes the need for the GMO to perform a particular function in the target agroecosystem, and addresses how potential alternatives compare to the GMO proposal. The assessment is based on an application of the precautionary approach or principle.

For many political systems in the world, the legitimating authority exists to incorporate needs assessment in a legislative or regulatory context. For some legislative or regulatory situations (e.g. US regulations), a needs assessment can be incorporated into the public consultative process prior to regulation, or it may be added as an alternative process that informs the debate in traditional decision-making bodies. Stakeholder participation will also be addressed.

The first part of the assessment addresses the question of problem identification, and addresses questions such as: What is the agricultural problem the GMO is designed to address? How extensive and severe is the problem? Identification and characterization of affected people, farming systems and agroecosystems, perception of affected people: do they regard the agricultural problem as a core need? What factors do they see as important impacts on their agricultural success? What needs do they have that might conflict with proposed solutions?

The assessment also focuses on identifying potential problem solutions. The GMO is one potential alternative, but other potential solutions may include changes in farm management practices, changes in local community practices,

changes in government support and structures, and/or changes in the structure of agricultural production. The section will also provide a systematic approach for evaluating the potential efficacy of the alternative solutions and how they meet the needs identified previously. Potential solutions can be compared on the basis of effectiveness, efficiency, efficacy and sustainability.

Finally, the needs assessment addresses the potential socio-economic effects of the identified solutions: What are the potential consequences from implementing the solution? Possible impacts internal to the farming system include changes in crop management practices. Possible impacts external to the farming system include impact other nearby cropping systems, structure of agricultural production, market prices and availability. Which impacts are potentially adverse and are they reversible? Can adverse impacts be mitigated by the imposition of restrictions on the user? Do structures exist that can monitor compliance with any management strategies or guidelines and report adverse impacts?

The assessment will result in a range of feasible alternative solutions of which the GMO is one, and an evaluation of their efficacy or suitability. It will also provide background information on the target cropping systems, non-target cropping systems, target farmers and current practices, etc., to focus the analysis in the subsequent sections.

Plant Characterization

Transgene Expression
and Locus Structure
(TELS)

The ~~plant characterization~~ ^{TELS} section will specify methodologies to determine the stability of the genotype (structural stability), the phenotype (stability of expression) and stability during inheritance. Genotypic stability may be related to the nature of the insertion, the insertion location, or the nature of the surrounding DNA. It can be evaluated by determining the number of transgene insertions and sequencing the transgene(s) and regions flanking the insert(s).

Further, the section will specify the phenotypic effects of the transgene in the plant, including position, pleiotrophic and epistatic effects, genotype by environment interaction, transcription products of both marker genes and target genes, and how, what plant parts, and when product concentrations should be measured in transgenic plants to facilitate risk assessment and management of environmental effects. Some of these characteristics should be measured in the field, and others can be measured in the lab. There is a need to develop uniform reporting standards for gene product concentrations in plant tissues, so that they can be used in any regulatory oversight system in the world. The plant phenological stages and the tissues that should be sampled during those stages have been variously reported (Agbios, 2003; compare reports of Bt expression in various transgenic Bt events and crop plants). Additional work is needed to clarify what is essential for evaluating non-target effects and resistance management.

Finally, the section will determine whether the phenotype of the transgene is inherited stably over multiple generations. A transgene can be stably integrated into the genome but its phenotype can be altered because the genetic background

changes or because the gene is silenced or enhanced. However, nutritional characterization of the harvested GMO product is outside the scope of this project, unless it results in some environmental effect.

Non-target and Biodiversity Effects

The central problem for non-target and biodiversity impact assessments is how to focus assessment procedures appropriately. In the Guidelines Project, this is done through two main tasks. First, the section will specify procedures to determine which non-target species, structural characteristics of the biota, and/or function/processes (e.g. ecosystem functions and processes) should be tested (= selection procedures). Secondly, the section will specify scientific procedures for testing these species/structures/functions/processes (= testing procedures). Presently, these testing procedures concentrate on the methodologies for tier I testing, i.e. short-term, acute ecotoxicology tests for hazard identification of pesticides. The procedures also consider how to evaluate cumulative effects on successive generations. Results will include an estimation of maximum potential hazard for key non-target species (the maximum mortality, growth suppression and sub-lethal effects the transgenic plant can cause), and estimations of the potential impact of the transgenic crop on key non-target species and ecosystem functions.

Identified categories for non-target testing include the following: non-target pests or potential pests, biological control agents of pests (natural enemies), crop pollination by animals, soil ecosystem functions, species of conservation concern and species of cultural significance. This list may be subject to change during the project, since a number of issues are under discussion. For example, the definition of target and non-target pests is not as trivial as it seems. All target pests should be 'controlled' (i.e. negatively affected) by the transgenic crop, while non-target pests may or may not be 'controlled' in this way, but the impacts of the non-target pests may be exacerbated by the effects of the transgenic crop, creating additional control problems.

A challenging question is what is the role of other 'neutral' or 'value unknown' non-target species? The vast majority of species found in an agricultural field are 'neutral' or 'value unknown' species. Criteria need to be developed to determine when some of these 'neutral' or 'value unknown' species need to be evaluated, such as if the species is important in another crop or in natural areas, or if the species is an important alternative food source for polyphagous natural enemies.

Five criteria have been identified for selecting non-target species to be tested: co-occurrence (What is the species assemblage of the target agroecosystem?), abundance (What species or suite of species are most abundant in the agroecosystem?), association (What species are more constantly associated with the target crop?), trophic linkage (What species have a strong link with the crop? for example, herbivores or saprovores that feed on GM plant material, pollen or exudates, or their natural enemies, or species that feed on excreta or exudates of

herbivores or saprovores) and significance to humans (known non-target pests, particularly those that reach levels where crop damage occurs or are candidate secondary pests, biological control organisms and pollinators). In what follows, the biological control (through arthropod natural enemies) and soil functions categories will be described in more detail to illustrate the approach used.

Arthropod natural enemies (NE) can be affected by the novel compounds in GM plants via multiple pathways (Fig. 10.1). These pathways involve a variety of trophic connections, and the potential effects of metabolites of the novel GM compound. In addition, these compounds and metabolites can interact with existing primary and secondary metabolites of the plant. For many natural enemies the primary exposure pathway will be mediated via the herbivore, as prey or host (Wolfenbarger and Phifer, 2000; Hilbeck, 2001). However, many natural enemy species, also feed on plants or plant parts, consuming pollen, nectar, sap, aphid honeydew and/or intracellular fluids. The plant can also influence the herbivore–natural enemy interaction, which can complicate procedures to test for the effects of the herbivore on natural enemies. The potential interactions within plants and prey/hosts can alter plant or prey/host physiology. Alterations in physiology can act indirectly on natural enemies, and often exert themselves by changing the quality of the food resource for the natural enemy (Hilbeck, 2002). These indirect effects of altered food quality (including interaction effects with natural secondary compounds in plants and their herbivorous insects) are not developed in detail in Fig. 10.1, but are subsumed within the effect of the whole plant or the herbivore. The transgene products or metabolites might also interact with other secondary plant compounds, magnifying or neutralizing the effects of the transgene products on the herbivore and/or its natural enemies. All of the major potential pathways by which a transgene could affect a natural enemy are illustrated in Fig. 10.1. This can then serve as a basis for further exposure analysis.

In recommending testing procedures, we need to consider which of the natural enemies identified can be exposed to the toxin. Of those that can be exposed, the guiding principle is to expose them to the toxin in an ecologically relevant way at higher than typical concentrations. This requires characterizing the material to which the natural enemy would be exposed and characterizing the effects of the toxins on target and non-target pest species over time. In addition, it may mean that risk is assessed in a tri-trophic system, a bi-trophic system, or both. Data on ecological effects caused by reduced prey quality, quantity and availability also need to be included in biosafety testing guidelines. Higher than typical concentrations are desired to enable characterization of maximum hazard to the non-target species in tier 1 tests.

Another part of the non-target impacts section will consider soil issues. Developing testing guidelines for impact of transgenic plants on soil organisms and soil ecosystem processes is a great challenge. This is primarily because we know only little about soil-inhabiting microorganisms and their functions (*c.* 1–5% that can be cultured). We have only a slightly better working knowledge and understanding of the soil macro-biota; we do know that both macro- and micro-biota have a crucial role in soil ecosystem functioning.

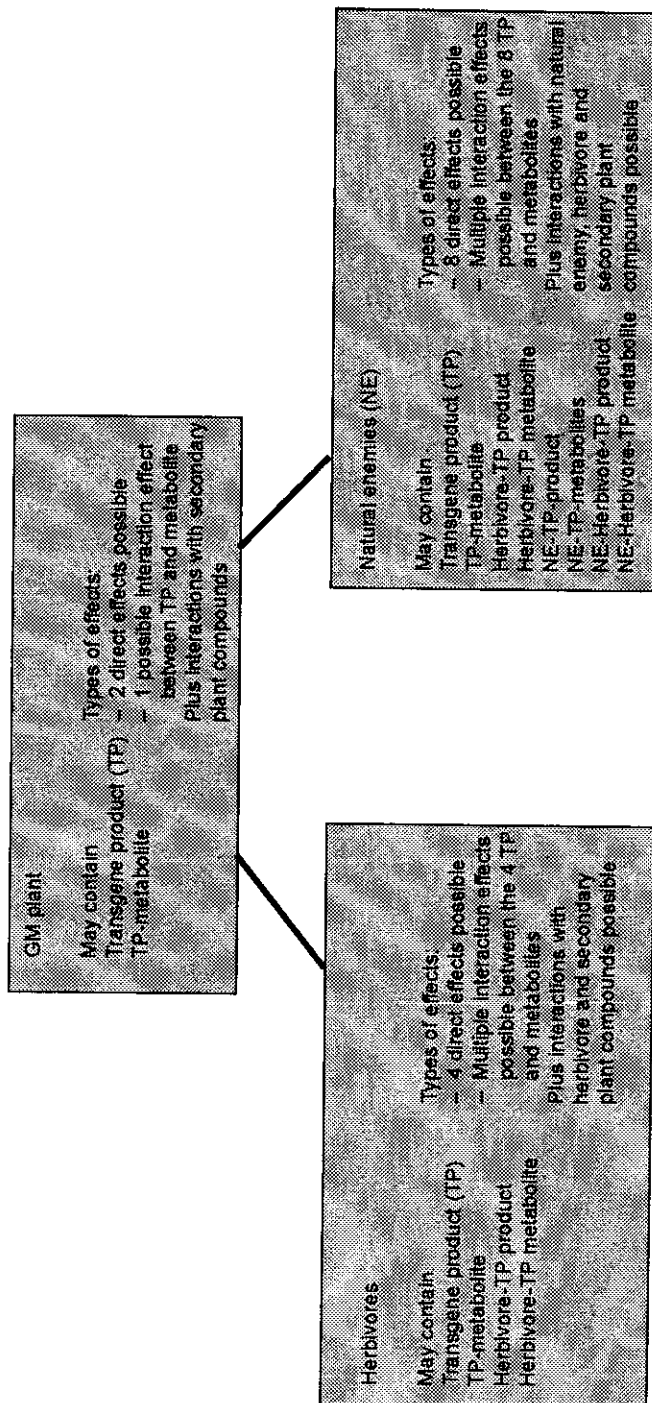


Fig. 10.1. The various bi- and tri-trophic routes, types of compounds and effects that can possibly impact natural enemies. **GM**, genetically modified; **NE**, natural enemies; **TP**, transgene product (e.g. novel protein encoded by transgene); **TP-Metabolite**, a plant-produced metabolite of the transgene product; **Herbivore-TP Product**, a herbivore-produced metabolite of the plant-produced transgene product (e.g. the novel plant protein); **Herbivore-TP Metabolite**, a herbivore-produced metabolite of the plant-produced transgene metabolite; **NE-TP-Product**, a NE-produced metabolite of the plant-produced transgene product; **NE-TP-Metabolite**, a NE-produced metabolite of the plant-produced transgene metabolite; **NE-Herbivore-TP-Product**, a NE-produced metabolite of the herbivore-produced plant transgene product; **NE-Herbivore-TP Metabolite**, a NE-produced metabolite of the herbivore-produced plant transgene metabolite.

Because of these scientific knowledge gaps, the guidelines pursue two routes simultaneously for safety testing of transgenic plants in soil: a taxon-specific route, which will probably work for known macro-biota, and an ecosystem function route. The taxon-specific route will proceed via: (i) defining selection criteria for testing species; (ii) conducting exposure analyses; and (iii) developing testing procedures for the identified species. Soil ecosystem functions can include respiration assays to measure the level of activity in soil, which is related to soil microbial biomass, basal respiration, substrate-induced respiration, nitrogen mineralization including ammonification, which is the crucial first step in nitrogen cycling, mineralization or decomposition of plant material (transgenic and non-transgenic), and phosphorus immobilization. Impacts on functional microbial diversity can be measured by changes in microbial genetic diversity community composition. Methods are being developed to determine species genetic diversity of microorganisms by DNA fingerprinting and/or other molecular techniques.

The diversity of soil macroorganisms must be considered. The selection criteria discussed for non-target testing above can be applied, including abundance and functional significance [for example, direct consumers of plant residue (e.g. earthworms, beetles, mites) that degrade large pieces of residue into smaller pieces, thereby facilitating/enhancing microbial degradation; organisms that are important for soil physico-chemical structure (e.g. creating soil macro- and micro-pores influencing water drainage, leaching, soil aeration, etc.), and soil natural enemies].

Exposure analysis of soil macroorganisms is necessary, but conducting a meaningful exposure analysis in soil ecosystems is complicated because the organisms are exposed to dead or decaying plant material and, to a lesser extent, to living plant material, including plant secretions such as root exudates. Further, once released from the plant tissue, the novel transgene products/proteins will interact physically and chemically with the soil and its constituent components, such as humic acids, clay minerals and colloids (Stotzky, 2002). Far less is known about the fate of complex organic molecules, such as proteins, in soils, compared with smaller organic or inorganic chemicals, such as pesticides or industrial pollutants. Therefore, as basis for an exposure analysis, the following parameters would need to be determined. First, the various routes of movement and transport of transgenic plant material and its novel transgene products need to be identified (e.g. root exudates or leakages, movement associated with plant residues, including roots, release of proteins from the plant residues, etc.). This requires good working knowledge of protein expression, the soil-plant interface, and residue movement and management. Secondly, the fate of such plant material, and of the novel protein(s) released from it, needs to be understood and quantified (e.g. adsorption to clay minerals, humic acids, etc., resulting potentially in accumulation of the protein, immobilization or leaching of transgenic proteins, etc.). Testing procedures should then be developed using a process similar to that suggested for other non-target organisms, i.e. determining endpoints of an exposure analysis and developing protocols that simulate, as closely as possible, an ecologically relevant delivery system.

Gene Flow and its Consequences

The gene flow section is determining protocols for establishing: (i) the likelihood of intra- and interspecific gene flow; (ii) the possibility of subsequent geographic spread of transgenes; and (iii) the potential ecological effects resulting from gene flow, such as invasiveness, weediness, effects on non-target species, agricultural production and biodiversity, reduction of genetic diversity and impact on conservation issues.

Gene flow between genetically modified (GM) crops and their wild relatives has been cited as one of the main ecological risks associated with the application of biotechnology to crop production (Rissler and Mellon, 1996; Ellstrand *et al.*, 1999). Here, we propose a framework for identifying risk issues related to gene flow. Several types of recipient populations are considered, such as wild species that interbreed with the crop (including weedy relatives and rare relatives), and non-GM crop varieties. The impetus for considering risks associated with gene flow is that once transgenes have moved into new populations the process cannot be reversed. With appropriate DNA markers, it is possible to detect gene flow from transgenic crops, but is difficult to predict the ecological effects of transgenes that are integrated into different genetic backgrounds or expressed in different ecological contexts. Plants that acquire transgenes will continue to evolve, subject to natural and artificial selection pressures in the agricultural setting and beyond. The hazards or consequences of transgene escape may vary widely, depending on the type of trait, the type of population into which it becomes integrated, and the ecological context. The first steps in assessing the possible risks of gene flow are determining whether pollen-mediated gene flow can occur among both cultivated and wild relatives in a given region, and whether transgenes could also be dispersed via seeds and/or vegetative propagules. If this is the case, we then ask whether transgenes will increase in frequency due to natural and/or artificial selection, and what ecological consequences of this process should be considered, including what the recipient ecosystem will be, and what organisms in that recipient ecosystem could be affected.

Resistance Management

The resistance management section will determine the resistance risk (the risk that a pest will evolve resistance to the transgenic crop or cropping practices associated with the crop), and management responses needed to reduce this risk. The resistance section is developing methodologies to specify, for each of the target and other affected pests to be considered. This section has developed a stepwise approach to the data needs for risk analysis. The first step involves data collection, which should occur prior to field release. The second step specifies the data that needs to be collected during the field-testing stage of development and before commercial release. The final step occurs after commercial release.

Data needs prior to field testing:

- Potential resistance risk: species ranking based on exposure and future exposure, selective intensity (potential maximum hazard from non-target section), and history of resistance problems.
- Potential consequences of resistance: factors for prioritizing species (key pests, pests that are difficult to control or require management practices with significant human health or environmental risks).
- Operational definition of resistance.
- Possibility for resistance management.
- Possibility for monitoring and response plan.

Data needs during field testing, but before commercial release:

- Resistance risk: improve understanding of exposure, hazard, resistance frequency and potential dominance in the field.
- Refine operational definition of resistance.
- Develop an implementable resistance management plan.
- Specify monitoring methods, response plan and roles of stakeholders

Data needs after commercialization:

- Quality control of monitoring effort
- Using monitoring information – processing and reporting
- Implementation of the response plan

Conclusion

While the task is large and complex, the project is also critically important, as outlined in the introduction. We welcome involvement of all public-sector scientists and encourage interested researchers to contact us at the given addresses. The more people become involved and engage in developing the product, the better the guidelines we will be able to produce. Simultaneously, the guidelines will be more widely spread and recognized. Interested public-sector scientists can enrol in the project at <http://www.gmo-guidelines.info>, but can also contact us directly at the e-mail and postal addresses provided on the above website.

References

- Agbios (2003) *Essential Biosafety*. 2nd edn. Available on CD or online at: <http://www.essentialbiosafety.info>
- CBD (Secretariat of the Convention on Biological Diversity) (2000) *Cartagena Protocol on Biosafety to the Convention on Biological Diversity: Text and Annexes*. Secretariat of the Convention on Biological Diversity, Montreal. (www.biodiv.org/doc/legal/cartagena-protocol-en-pdf).
- Ellstrand, N.C., Prentice, H.C. and Hancock, J.F. (1999) Gene flow and introgression from domesticated plants into their wild relatives. *Annual Review of Ecology and Systematics* 30, 539–563.

- Forester, J. (1999) *The Deliberative Practitioner: Encouraging Participatory Planning Processes*. MIT Press, Cambridge, Massachusetts.
- Hilbeck, A. (2001) Implications of transgenic, insecticidal plants for insect and plant biodiversity. *Perspectives in Plant Ecology, Evolution and Systematics* 4, 43–61.
- Hilbeck, A. (2002) Transgenic host plant resistance and non-target effects. In: Letourneau, D.K. and Burrows, B.E. (eds) *Genetically Engineered Organisms – Assessing Environmental and Human Health Effects*. CRC Press, Boca Raton, Florida, pp. 167–185.
- Rissler, J. and Mellon, M. (1996) *The Ecological Risks of Engineered Crops*. MIT Press, Cambridge, Massachusetts.
- Stotzky, G. (2002) Release, persistence, and biological activity in soil of insecticidal proteins from *Bacillus thuringiensis*. In: Letourneau, D.K. and Burrows, B.E. (eds) *Genetically Engineered Organisms – Assessing Environmental and Human Health Effects*. CRC Press, Boca Raton, Florida, pp. 187–222.
- Susskind, L., Levy, P. and Thomas-Larmer, J. (2000) *Negotiating Environmental Agreements: How to Avoid Escalating Confrontation, Needless Costs, and Unnecessary Litigation*. Island Press, Washington, DC.
- UN-DSD (Division for Sustainable Development) (1999) *Agenda 21. Chapter 16: Environmentally Sound Management of Biotechnology*. (<http://www.un.org/esa/sustdev/agenda21chapter16.htm>)
- Wolfenbarger, L.L. and Phifer, P.R. (2000) The ecological risks and benefits of genetically engineered plants. *Science* 290, 2088–2093.