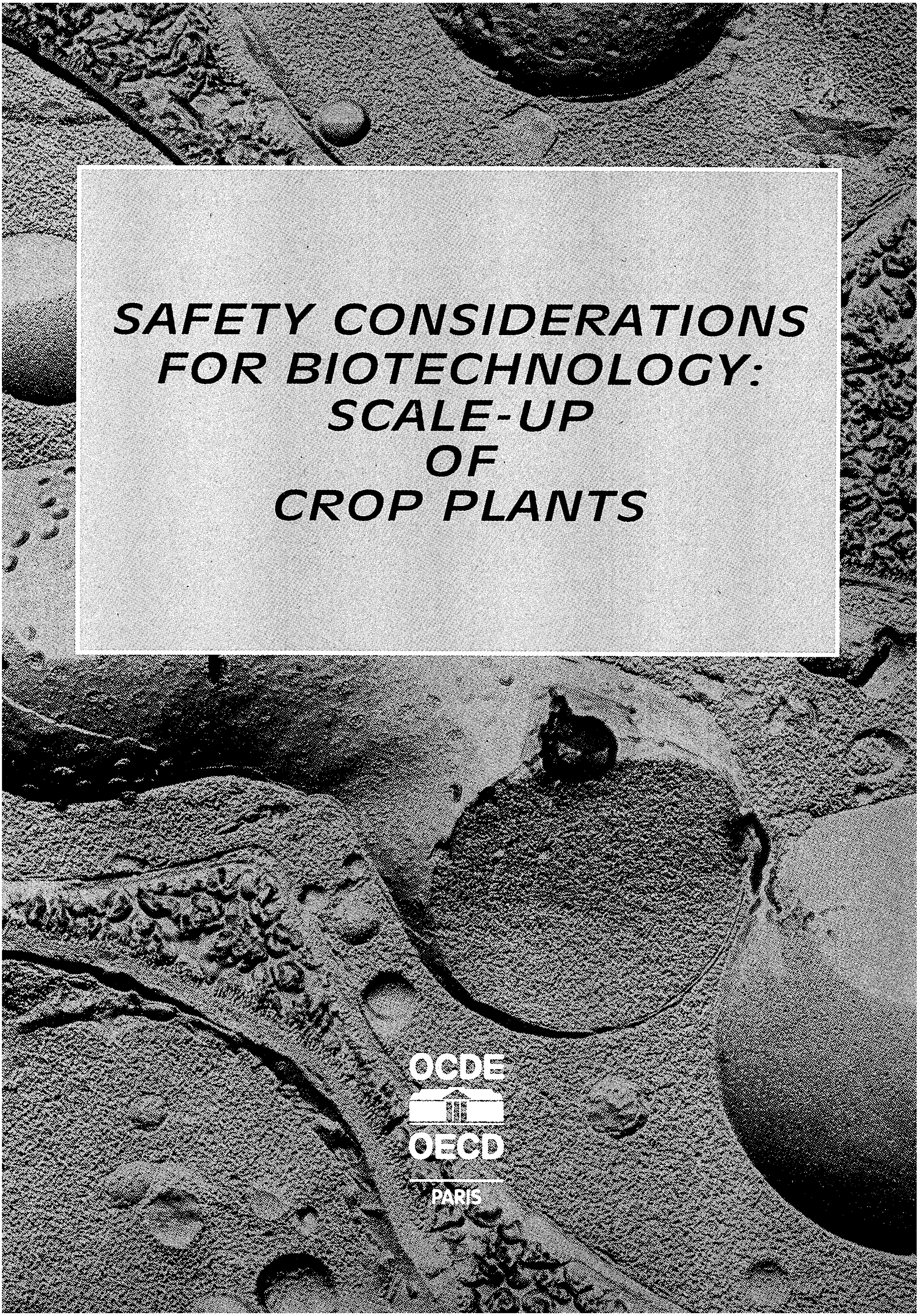

SAFETY CONSIDERATIONS FOR BIOTECHNOLOGY: SCALE-UP OF CROP PLANTS

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ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

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PASSAGE A L'ÉCHELLE SUPÉRIEURE DES PLANTES CULTIVÉES

Foreword

This report updates and extends the OECD's earlier work on ''Recombinant DNA Safety Considerations'' (1986) and ''Good Developmental Principles (GDP) for Small-Scale Field Research'' (1992) which had set out safety guidelines for biotechnology applications in industry, agriculture and the environment. It is the outcome of work carried out over two years, from June, 1991, and of many meetings of a ''Preamble Subgroup,'' chaired by Mr. P. Van Der Meer of the Netherlands, and a ''Crop Plant Subgroup,'' chaired by Mr. J. Cook of the United States, of Working Group III of the OECD Group of National Experts on Safety in Biotechnology (GNE). Working Group III was chaired by Mr. P. de Haan of the Netherlands

The Preamble of this report places earlier OECD work in a general overall context to reflect the dynamic evolution of biotechnology. The section on crop plants describes how the concept of ''familiarity'' – with the plant, the introduced trait, the environment and their interaction – may be applied to facilitate risk/safety analysis and to manage possible risks in the context of scaling up modified crop plants towards commercial release.

This report was prepared by the OECD Directorate for Science, Technology and Industry, in collaboration with the Environment Directorate, and is published under the responsibility of the Secretary-General.

The OECD work on safety aspects of biotechnology, of which the present publication forms a part, has been made possible in particular by the generous financial support received from the Commission of the European Communities and from the Government of Japan.

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I. Preamble

INTRODUCTION

The introduction of new molecular technologies in the early 1970s initiated discussion on safety in biotechnology. When the power of moving genes between unrelated organisms with the new techniques was appreciated, the Asilomar (California) conference was convened to explore the advisability of using the new rDNA technology and the conditions under which experiments should proceed. Uncertainty led to concerns that use of the new techniques might lead to increased risk from modified organisms.

This discussion resulted in a number of national and international recommendations, guidelines or regulations, and legislation. The 1986 OECD report *Recombinant DNA Safety Considerations* (the so-called "Blue Book") was one of the first international scientific frameworks for the safe use of organisms derived from rDNA techniques in industry, agriculture and the environment. This book set out general principles for the safe development of rDNA organisms. The reason for focusing specifically on rDNA organisms in the Blue Book was that techniques were being used to produce organisms with novel genetic combinations, and there was limited or no experience with such organisms.

By the mid-1980s rDNA techniques were considered increasingly to represent an extension of conventional genetic procedures and rDNA organisms to present risks that are the same in kind as those posed by any other organism. There was also recognition that the same physical and biological laws control the behaviour of organisms, whether modified by conventional, or by rDNA techniques.

However, the conventional and newer molecular techniques differ in two respects. Molecular techniques allow firstly a greater diversity of genes to be introduced into organisms and, secondly, in general, greater precision in the introduction of genetic material, yielding a more thoroughly characterised and potentially more predictable organism. As the characteristics of the organism depend on its genetic make-up, the view has been expressed that there may be a particular concern if there is a lack of experience with organisms having particular genetic combinations from different sources.

The OECD Group of National Experts on Safety in Biotechnology (GNE) has worked since April 1988 to update and develop further the particular principles set out in the Blue Book, aiming at the development of scientifically sound principles and practices for the application of organisms referred to in the Blue Book.

The GNE began work in this area with the preparation of good developmental principles (GDP) for small-scale field trials of genetically modified plants and micro-organisms, published under the title *Safety Considerations for Biotechnology – 1992.* In the programme for further work, the GNE initiated similar activities on large-scale field trials.

At the meeting of June 1991, the GNE decided that a preamble should be prepared which places the different initiatives in a general overall context and which reflects the fact that biotechnology is a dynamic and rapidly evolving area.

The purpose of the Preamble and the reports to follow are therefore to evaluate, interpret and apply the general principles for safety in biotechnology, thus reflecting current knowledge in order to offer a basis for further work in the area of introductions into the environment.

Scientific and technical methodologies for evaluating safety are likely to vary from one group of organisms to another and therefore subsequent reports will treat separately specific groups of organisms (*e.g.* micro-organisms).

It is recognised that the safety of an organism is independent of the process of genetic modification *per se.* As stated in GDP, it is the characteristics of the organism, including new traits (however introduced), the environment and the application that determine the (likelihood of) risk of the introduction. The work of the GNE is carried out in the context of safety in modern biotechnology, but the principles for safety laid down in the subsequent paragraphs and reports apply to any organism.

General principles for safety in biotechnology

Safety in biotechnology is achieved by the appropriate application of risk/safety analysis and risk management.

Risk/safety analysis

Risk/safety analysis comprises:

- hazard identification and, if a hazard has been identified;
- risk assessment.

It is recognised that:

a) Risk/safety analysis is based on the characteristics of the organism, the introduced trait, the environment into which the organism is introduced, the interactions between these, and the intended application. Knowledge of and experience with any or all of these provides familiarity which plays an important role in risk/safety analysis. Further explanation and examples of familiarity can be found in detail in the subsequent reports. Familiarity is not synonymous with safety; rather, it means having enough information to be able to judge the safety of the introduction or to indicate ways of handling the risks. A relatively low degree of familiarity may be compensated for by appropriate management practices. Familiarity can be increased as a result of a trial or experiment. This increased familiarity can then form a basis for future risk/safety analyses.

b) Risk/safety analysis is conducted prior to an intended action and is typically a routine and ongoing component of research, development and testing of new organisms, whether performed in a laboratory or a field setting. It can range from a routine *ad hoc* judgement by the researcher as an implicit part of good experimental practices, to adherence to a formalised assessment.

c) Risk/safety analysis is a scientific procedure which does not imply or exclude regulatory oversight or imply that every case will necessarily be reviewed by a national or other authority.

Risk management

In this report, the term risk management refers to the way appropriate methods are applied in order to minimise the scientifically identified risks. It does not encompass additional factors such as socio-political values, etc. In principle, appropriate management is based on and should be in proportion to the results of the risk/safety analysis.

All organisms are subject to natural biological, physical and chemical influences on their survival, reproduction and spread in the environment. Knowledge and experience of the effects of these natural influences on the organism, and of interactions between the organism and its environment can be used to manage the organism. Risk management encompasses all aspects of the management of the organism indirectly through management of the environment into which the organism is introduced, or directly, by management of the organism itself.

The practices used for managing the risk of different types of introductions depend on the type of organism and hence are dealt with in detail in the subsequent reports. Such practices may include the use of biological, chemical, physical, spatial, environmental, temporal or other isolation conditions, outside strict containment, to provide barriers to minimise the dissemination and impacts of organisms or their genetic material outside the area of application. For example, flowers or other reproductive structures may be removed in order to preclude gene transfer, and special decontamination treatments may be used to prevent persistence and dissemination.

Risk management to ensure safety is employed during the development and evaluation of an organism in a systematic and stepwise fashion, through an appropriate continuum, for example from the laboratory, through stages of field testing, to final (*e.g.* commercial) application.

The number and modalities of the stages to be visited in this continuum are not fixed, but depend on the outcome of the risk/safety analysis at the different stages. Progression through the appropriate developmental stages generally entails a reduction in control and possibly in monitoring, whilst often increasing scale in order to gain knowledge, or for functional purposes. Any particular developmental stage begins after incorporating information and experience from an earlier stage, or other appropriate information such as from monitoring, into that risk/safety analysis.

Operation of the concept of stepwise development and evaluation

Operational principles of risk/safety analysis and risk management

Several operational principles governing the stepwise development of organisms can be identified:

i) Progression through the continuum of developmental stages is based on information gathered from previous experiments, from other appropriate sources, or from empirical observations. Experiments will include observation and measurement of organisms and their impact as appropriate, in order to obtain data relevant to safety. A risk/safety analysis may indicate that: *a)* progression can proceed to a more advanced stage; *b)* work should not proceed to another stage but that further work at the same stage is required, for example to accumulate data; or *c)* further developmental work at an even earlier stage is required.

ii) When appropriate risk/safety analysis and risk management are conducted, performance trials can be carried out at any developmental stage. Performance trials *per se* do not necessarily provide information relevant to the risk/safety analysis and risk management, but can be designed to do so.

Factors affecting the operation of the concept of stepwise development

As discussed above, progression through developmental stages is flexible and tailored to the particular situation. Factors that influence the operation of this stepwise concept include:

i) familiarity with the characteristics of the organism, the trait introduced, the interactions between these, and the intended application;
ii) familiarity with the conditions and the environment into which the organisms are intended to be introduced;
iii) familiarity with interactions among the organism, the trait and the environment.

Operation of the concept of stepwise development for specific groups of organisms

The principles set out above are of a general nature. Both the detailed design of the developmental stages and the information appropriate to proceeding with any particular stage may vary from one group of organisms to another.

As was indicated by the GNE, the scientific and technical methodologies for risk/safety analysis and risk management for specific groups of organisms will be dealt with separately in subsequent reports.

II. Scientific considerations pertaining to the environmental safety of the scale-up of crops plants developed by biotechnology

PREFACE

In October 1990, the 3rd session of the Group of National Experts on Safety in Biotechnology (GNE) agreed to initiate a work project on large-scale release (scale-up) of genetically modified organisms. This project was to be undertaken by Working Group III on Safety Assessment as a follow-up to their work on ''Good Developmental Principles (GDP): Guidance for the Design of Small-Scale Research with Genetically Modified Plants and Micro-organisms''.

A project on scientific considerations pertaining to the safety of large-scale releases of genetically modified plants and micro-organisms was considered necessary in view of the expected movement of potential biotechnology products from small-scale field research into large-scale testing and eventually into general use. Following several meetings in 1991, Working Group III agreed that different kinds of organisms would generate a different set of safety issues which may need to be considered in the context of large-scale introductions. This project was initiated to identify and address the environmental safety[1] issues applicable to large-scale introductions of crop plants[2] developed by the newer molecular techniques of biotechnology (*e.g.* rDNA technology).

This report on crop plants is one of a series of separate but parallel and related reports dealing with different kinds of organisms developed by biotechnology. These reports will form a flexible compendium of the projects on large-scale field trials. The compendium begins with a Preamble that sets out general principles for safety in biotechnology. The Preamble describes the application of a risk/safety analysis[3] and, where appropriate, risk management[4] to minimise the risks.

It is expected that the scientific and technical methodologies for conducting risk/safety analyses will vary according to groups of organisms and applications. Thus an expansion and clarification of the above principles are needed for crop plants to provide guidance for achieving safety. This is consistent with recognition in the Preamble that ''safety in biotechnology is achieved by the appropriate application of risk/safety analysis and risk management''.

In general, there is considerable knowledge, experience, and understanding of the procedures for managing the introductions of crop plants developed by a wide range of breeding methods. Crop plants with genetic traits introduced by the newer molecular techniques initially may raise certain questions regarding safety because of a lack of experience with the particular genetic combinations. Virtually all crop plants differ genotypically from their wild progenitors.

Each new method of plant breeding has increased both the number of tools and genetic variability available for plant breeding. Through time a great deal of experience has been gained with such plants. As recognised in the Preamble, "the same physical and biological laws control the behaviour of organisms, whether modified by conventional or rDNA techniques". It was therefore considered that the knowledge and experience (familiarity) gained with crop plants developed by traditional breeding methods as well as experience with transgenic plants[5] could be applied to address the terms of reference to this project.

Since scientific knowledge and experience in this area of research and development are increasing rapidly, this report is only intended as a view of the subject in this window in time. At this time, for example, transgenic crop plants are entering or are in performance evaluations or other advanced testing and some are in use as parents in conventional breeding programmes.

As discussions on crop plants were pursued, it became evident that a clarification of terminology was necessary. The term "large-scale", was difficult to define and was not always appropriate to plants. It could be used for example to describe multisite testing, testing of a single gene or genetic construct within many different genetic backgrounds of the same crop species, or it could simply imply that there were a large number of organisms at a single site or that a large area was used. Thus the term "scale-up"[6] is introduced, in preference to "large scale", to describe the continuum of research and development involving increasing scale from preliminary field testing to general use. The developmental stages will vary with the crop and the particular cultivar. Thus, scale-up does not refer to a specific stage within a defined sequence of stages; rather, the term refers to any of a number of advanced stages commonly used during crop plant development to gain information on the plant's performance or for functional purposes such as increasing the seed supply.

Risk/safety analysis involves hazard identification and risk assessment. This allows a determination of the consequence and likelihood of hazards and can be used to indicate appropriate risk management. In developing a procedure for risk/safety analysis in relation to the scale-up process for crop plants, the terms safety issue and safety concern are introduced. A "safety issue" describes the property of a plant relative to safety, but which may or may not give rise to an adverse effect in the environment. A safety issue gives rise to a "safety concern" when one or more of the factors necessary for a potential adverse effect are specifically identified with a new plant line or crop cultivar in a specific environment. Identification of a safety concern indicates where the analysis should then focus. As stated in the Preamble, "Safety is achieved by the appropriate application of risk/safety analysis and risk management".

Crop management practices are considered which may form part of "risk management" as defined in the Preamble. Crop plants, by definition, are cultivated for direct or indirect use by humans. Crop management practices, that is, "cultural practices",[7] may vary within the same crop species and from country to country or region to region because of variations in climate and soils, among other factors. These cultural practices in all cases will restrict the crop to a greater or lesser extent to a managed environment. Risk management for crop plants developed by rDNA technology may involve the use of the same standard cultural practices used to manage crop plants developed by more traditional technologies. However, if a hazard is identified, and depending on the hazard identified and the magnitude of the risk, certain other management practices[8] may be employed, or it may be necessary to design experiments to obtain further information before scale-up, in order to assure environmental safety.

1. Purpose and scope

This work project discusses the scientific considerations pertaining to the environmental safety of new plant lines and crop cultivars.[9] It provides a framework for hazard identification, risk assessment, and risk management for crop plants, and applies the process to crop plants developed by the modern tools of biotechnology.

The concept of familiarity as introduced in the Preamble is developed and presented for crop plants in Section 5. Familiarity is the knowledge and experience that can be used for:

a) hazard identification and risk assessment (risk/safety analysis) which involves:
  i) indicating saftey issue(s);
  ii) indicating safety concern(s);
  iii) revealing and assessing potentially adverse effect(s);
b) applying risk management, which includes:
  i) indicating when standard cultural practices are adequate;
  ii) indicating when other management practices are needed;
  iii) indicating when not to scale up because practices to achieve safety are not available or acceptable;
c) indicating where more information is needed.

Environmental safety considerations are relevant at any scale, including field tests conducted at small-scale. However, the scale-up of plant lines and crop cultivars results in increased interactions with the environment. From a scientific standpoint, scale-up may be necessary to test the statistical validity of assumptions made or conclusions reached during more preliminary laboratory or greenhouse/glasshouse experiments or small-scale field research. Scale-up may also be required for increase of seed or other planting material in preparation for more extensive investigations or for general use of the cultivar.

Although this report focuses on performance evaluations and other developmental stages up to and including increases in seed or other planting material, the same or similar scientific considerations may be applicable to commercial use of these crop plants. Similarly, although this report focuses on crop plants developed for traditional uses, the same or similar scientific considerations may be applicable to the scale-up of crop plants developed for non-traditional uses.

This report does not address the safety of the use of crop plants as end products, *e.g.* as food, feed, or fibre, etc. The scientific principles addressing consumer safety of food derived from modern biotechnology have been presented in a separate report entitled *Safety Evaluation of Foods Derived by Modern Biotechnology: Concepts and Principles* by another Working Group (Working Group IV) of the GNE.

This document is intended for a broad audience, including academia, industry, government agencies and individuals interested in or responsible for the safe development of crop plants. The safety issues and concerns identified and discussed in this document are not intended to bypass or prejudice any approval procedures or regulatory actions but rather to provide the scientific basis for evaluating the environmental safety of the scale-up of new crop lines or crop cultivars.

2. Background on plant breeding

This section provides a brief background on plant breeding. The goals, terminology, and methods used in plant breeding are discussed, and a description is given of performance trials in relation to safety issues. More information on plant breeding is given in the *Traditional Crop Breeding Practices* (OECD, 1994).

Crop plants are continually improved to maintain a secure and sustainable supply of food, fibre, and other agricultural commodities in order to meet current and future needs of people.

Plant breeding is the means whereby new crop cultivars are developed. The major goals are consistency, quality, and yield. Consistency is achieved through increased resistance to pests and diseases and tolerance to environmental stress. Quality means suitability for specific uses, for example improvement of food or feed components which make them safer (lower amount of alkaloids, protease inhibitors or other toxicants) or more nutritious or suitable for processing or for non food use. Yield is based on genetic potential and ability of the crop to respond to cultural practices within the limits of the natural environment. These goals have to be maintained while also helping to make agriculture more sustainable economically and ecologically.

Crop plants are genotypically different from the original wild-forms from which they were derived. Cultivated plants maintained by the early civilisations were also genotypically different from their progenitors, because farmers repeatedly selected the most desirable and disease- or pest-resistant (robust) plants as a source of seeds. This process of selection and planting seeds of certain lines (landraces) is carried on to this day by farmers in regions in or near the geographic origins of these crops (Harlan and Zohary, 1966; Worde, 1992).

Field tests are conducted routinely with new lines and cultivars of crop plants, including over a wider and more diverse geographic area and larger scale. Field tests provide information progressively on the interaction of plant lines or cultivars with particular environments and management interventions. Such tests are also used to reveal effects on field performance or characteristics of the harvested products of the line that may be associated with genetic modifications.

a) Cultivar development

The development of a new crop cultivar by plant breeding typically involves a succession of events and many years (generations) (Fehr, 1987). Broadly speaking, the biology of a crop species determines whether the final cultivar is an inbred pure breeding line, a hybrid line, or a population, each of which have different breeding strategies as follows.

- *Inbred lines*: The first step in the development of inbred lines involves crosses between a number of lines to produce segregating families from which the desired types are selected. The objective is to produce pure-breeding, phenotypically uniform (homozygous) lines. It is the inbred line that eventually goes into commercial use, if it fulfils the required performance criteria. Soybean is an example of a crop plant with cultivars developed as inbred lines.
- *Hybrids*: The initial stages of a hybrid programme are similar to those for development of an inbred cultivar, in that the objective is to produce genetically and phenotypically uniform lines. However, the cultivar released to growers is a hybrid between two or more of these lines, and consequently advanced field testing for performance in a hybrid breeding programme is carried out with the progeny of crosses between the inbred lines not with the inbred lines themselves. The hybrid line that goes into general use is not

necessarily genetically uniform but will be phenotypically uniform for production characters. Maize is an example of a crop plant developed as hybrid lines.
- *Populations*: The initial stages in a population (or bulk) breeding programme involve many crosses to produce a genetically and phenotypically diverse population. Over many cycles of selection, undesirable phenotypes are eliminated to produce a population that is more or less phenotypically uniform for production traits (*e.g.* consistency, quality of harvested product, and yield [not necessarily genetically uniform]). Alfalfa (lucern) is an example of a crop plant with cultivars developed as populations.

Underlying all three breeding strategies is the general principle of an initial step of hybridisation between genetically different individuals followed by selection of the desired types over many generations. The cultivar development process is used to eliminate lines based on failure to meet the multiple goals of the breeding programme. Thousands or hundreds of thousands of genetically different lines may be evaluated to find one (or a few) for use as a cultivar that will then be introduced into agricultural practice. While some cultivars may remain in use for years or decades, others are regularly replaced as more improvements in field performance, end-use quality, and capacity to stay ahead of ever changing pest populations, are combined in the ongoing breeding and selection process.

b) Methods used in plant breeding

The scientific basis for modern plant breeding and genetics goes back about one century to the work of Gregor Mendel. Initially, plant breeders expanded the pool of genetic variability available to them by use of intraspecific hybridisations through sexual crosses. This is still the predominant method of plant breeding today. The other methods used at the present time to increase genetic variability and create new genetic combinations to produce improved cultivars for use in agriculture are listed below:

- hybridisation between related, sometimes distantly related species referred to as ''wide crosses'', and commonly accomplished with the aid of special techniques such as embryo rescue and bridging crosses;
- intra- and interspecific chromosome manipulations using aneuploids of the crop plant as a parent to add or substitute individual chromosomes or parts of chromosomes from related to very distantly related species;
- mutagenesis techniques, including the use of chemical and physical mutagens (undirected mutagenesis);
- somatic cell hybridisation (protoplast fusion);
- somaclonal variation; and
- molecular techniques, including gene transfer by biological vectors, electroporation, micro-injection, and ballistic techniques.

The newer molecular technologies allow plant breeders to access more traits from a wider ''taxonomic base'' to better meet specific objectives of plant breeding programmes. Regardless of the particular combination of techniques used, the development of a new crop cultivar typically will require many site-years of field tests before selection of new cultivars for seed increase and introduction into agriculture. This allows the breeder to observe the interaction (or performance) of the plant containing a trait with combinations of other traits and environments and to make comparisons with other familiar lines or cultivars with the same or similar traits.

In contrast to conventional plant breeding, which is a highly random process, it is possible with molecular techniques to insert the precise genetic information of interest (Fraley *et al.*, 1986). In general, a particular gene will encode the same primary product regardless of the organism in which the trait is expressed or from which it originated. For this reason, the exact primary gene products can more likely be predicted when a plant is modified by molecular methods than when undefined or uncharacterised genetic material is introduced through less precise methods such as cell fusion or chromosome substitution. However, even though the approximate phenotype usually can be predicted, it is not entirely possible to predict exactly the interactions of a gene in a new genetic background. As a consequence it is necessary to conduct a programme of field tests in the same way as for lines developed by conventional techniques.

c) Performance trials in relation to safety issues

Performance trials are field tests conducted with the more advanced lines under consideration as potential cultivars. Because of the large number of plant lines produced in plant breeding programmes, the great majority of the lines must be screened out as early as possible in the development of cultivars. Only the most promising ones (based on the objectives of the breeding programme) can be advanced into performance trials. Lines that are genotypically or phenotypically unstable and lines that are uncharacteristic of the desired plant type usually can be recognised during preliminary evaluations, and under most circumstances would not be advanced into performance trials. The term, ''performance trial'' is used in this report in a broad sense rather than as part of formal testing, since different countries may use different kinds of tests to evaluate performance.

Performance trials are used to observe, verify, evaluate, or quantify simultaneously as many attributes of the plant lines under study as appropriate, practicable, or technically feasible. They can be designed to experimentally measure specific attributes of interest such as adaptation of lines to the environment of the site, tolerance of local stress events, yielding ability and end-use quality and safety characteristics of the harvested product. Performance trials can also reveal to experienced observers certain attributes of new lines that may have implications to environmental safety. Such attributes are essentially equivalent to those described under safety issues (see Section 4) and include:

- any tendency of a self-pollinated line to outcross because of self-sterility or other factors;
- any tendency of specific lines to carry over at the site and become a weed;
- any tendency of specific traits to produce a known toxicant in the harvested product in quantities greater than an accepted standard;
- any tendency of specific lines/cultivars to react/respond to other organisms in the environment; and
- any tendency for unwanted genetic or phenotypic variability beyond that observable during more preliminary evaluations in small-scale tests.

Much of the current understanding of crop plants and their management relative to safety comes from the familiarity gained through past performance trials. Knowledge and experience gained through performance trials with particular lines further increases the level of familiarity with those lines.

3. Scale-dependency effects

The size of any field experiment, including the area of land planted to a new plant line, affects both the kind of data that can be collected and the potential to detect a rare event. The majority of potential effects of new traits on appearance or behaviour of a new plant line or cultivar, including effects related to environmental safety, can be recognised during preliminary evaluations in the greenhouse/glasshouse or small-scale field trials. However, some effects, being scale-dependent, will more likely be detected with increasing scale of the release. For example:

- A small-scale field test to determine the effectiveness of a new trait for pest resistance may not detect all strains/biotypes of the target pest able to overcome the resistance. The small-scale experiment will therefore overestimate the resistance to the entire target pest population.
- A small-scale field test may not be designed to detect events that occur at low frequency/probability, such as out-crossing with a wild or weedy relative of the crop plant within or near the site where the plant is grown.

Since failure to detect small differences or low-probability events (Type II error in statistical terms) may be due to the limited size or design of the trial, experimental plans to detect certain events should take into account the sensitivity of the experimental plan as well as the design of previous experiments.

Since small-scale experiments may place limits on the sensitivity of what can be detected, or the degree of accuracy of detection of a rare event or effect, experiments of a larger size, *e.g.* conducted over a wider geographic area may be the only means to provide the data needed to answer certain questions. Some events may not be detected until a cultivar is grown at commercial scale for several years. This is normal and, based on familiarity, it is possible to predict, test, and plan for many events that may be of concern prior to wide-scale testing or general use.

4. Identification of safety issues and discussions of safety concerns and appropriate management practices

This section: *a)* identifies the environmental safety issues pertaining to new plant lines and crop cultivars relative to the scale-up process; *b)* discusses the potential safety concerns; and *c)* presents examples of appropriate management practices in the context of risk management.

a) Safety issues

Based on the scientific information available and experiences (familiarity) to date, six safety issues (broadly defined) can be identified that, if relevant to a given plant line with a new trait in a particular environment, could give rise to a safety concern:

- gene transfer;
- weediness;
- trait effects;
- genetic and phenotypic variability;
- biological vector effects and genetic material from pathogens;
- worker (human) safety.

b) *Discussion of safety issues, identification of potential safety concerns and examples of appropriate management practices*

The relevance of any one safety issue to the scale-up of a new plant line in a particular environment is dependent on the biological properties/characteristics of the plant line with its new trait and on the agricultural or in some cases the surrounding natural environment.

Where, based on a risk/safety analysis, the information available indicates a safety concern, in order to proceed with further testing it may be necessary to consider whether standard cultural practices will be adequate or if other management practices are needed as a temporary measure until more information is available. In some cases, further small-scale field research may be appropriate. As stated in the Preamble, "Appropriate management is based on and should be in proportion to results of the risk/safety analysis." For crop plants, standard cultural practices are an important element of appropriate management practices. Whether other management practices will be appropriate or should become part of the standard practices for the new line or cultivar depends on the identification of a hazard and the subsequent risk assessment. These determinations, in turn, are facilitated by the degree of familiarity with the crop, the trait, the environment in which the trial is to take place, and interactions between/among the crop plant, trait and environment (see Section 5).

i) Gene transfer

Genes may be transferred by pollen to other cultivars of the same crop or, more rarely, to wild or weedy relatives that grow in the agricultural environment, or in partially managed, natural, or undisturbed (wild) environments. Gene transfer by means other than pollen has been raised but there is no documented evidence that such transfer occurs between higher plants. Whether transfer of one or a few genes can enhance the ability of the progeny of a recipient plant to survive and compete (cause an increase in weediness or incremental increases in competitiveness of wild relatives) in a particular environment would depend upon the plant, the gene(s), and the environment (see "Weediness", below).

The chances for movement of genes from a crop to a wild or weedy relative by pollen can be defined as the result of the coincidence of a number of specific events. If any one of these events cannot occur, transfer of genes by pollen cannot occur and there will not be potential for an adverse effect in the environment resulting from gene transfer. These events are as follows:

- a plant sexually compatible with the crop plant grows within the range of movement, whether by wind or insects, when viable pollen from the crop plant is available;
- the related plant forms receptive flowers near or at the time of movement of pollen from the crop plant;
- a flower of the related plant is fertilised and viable seed is produced;
- the seeds survive to germinate and grow; and
- the plant produced from the hybrid seed and the progeny of that plant are fertile, *i.e.* can produce seed by self- or cross-pollination, or can survive vegetatively.

Gene transfer by pollen to a wild relative within a population is analogous to a mutation arising in the population. Whether that trait becomes initially established in the population depends more on chance effects than fitness, since the great majority of mutants are lost from the population because of genetic drift, even if the trait confers specific advantages (Gale, 1990). For species with a reasonable level of outcrossing, repeated pollination of individuals that carry the trait by the dominating wild population will lead to the integration of the trait into the wild genetic background. The expression of that trait in the new population may vary with genetic backgrounds of the individuals within that population.

The probability of these events occurring will depend upon the scale of the planting in relation to the numbers, if present, of compatible plants and viability and fertility of progeny. Other factors that will have more influence as scale increases include weather, topography, cropping patterns, and richness and viability of the pollen source.

In cases where no compatible wild or weedy relatives exist or no other cultivars of the crop plant grow where the new cultivar is grown, gene flow from a new cultivar to other plants will not be identified as a safety issue and, accordingly, there is no likelihood of an adverse effect in the environment even though pollen is disseminated. Similarly in cases where the chances of gene transfer to related plants is nonexistent or negligible because one or more of the critical requirements for successful transfer will not be met for that crop plant within that environment, there is no likelihood of an adverse effect in the environment, even though relatives may occur in the area. In other cases, the nature of the trait itself, if transferred, needs to be considered. In still other cases, cultural or other management practices (isolation, inspection, monitoring, mowing, herbicides) may need to be considered to reduce the risk of gene transfer (see ''Appropriate management practices'' section). In special cases, seeds dispersed by birds/animals could lead to new opportunities where gene transfer could occur (see section on ''Weediness'').

Certain phenotypes resulting from gene transfer via pollen movement from a crop plant may confer a competitive advantage to a wild or weedy relative. Such phenotypes could either include greater resistance to a disease or insect pest that is present in the agricultural and/or natural environments, or greater tolerance to environmental stresses characteristic of local environments.

Control of these pests and increased tolerance to these stresses are objectives of plant breeding. The following points should be considered in addressing this safety concern:

- *Wild relatives in natural environments.* During their evolution in natural environments, plants are thought to survive and succeed in competition with other plants, in part, due to their greater tolerance or resistance to natural disease epidemics and pest attacks or greater tolerance to environmental stresses. These wild plants have been a common source of genes for disease and pest resistance and environmental stress tolerance introduced by hybridisation into related crop plants. Any concern about transfer of a specific resistance trait from a new plant line or crop cultivar as a consequence of the scale-up process should consider whether the disease or pest to be controlled by the introduced trait is a factor in the ecology of related wild plants in the natural environment, or whether the trait, if transferred to related wild plants, would affect interactions of that plant with natural populations of pests or diseases of that plant.
- *Weedy relatives in agricultural environments.* Weeds in agricultural environments have characteristics such as prolific production of seed, dormancy of seeds, ability to disseminate, and adaptation to the management used to grow the crop. A possible safety concern is increased weediness as the consequence of acquired ability of a plant species to out-compete other plants through greater resistance to a specific disease or pest of the crop, however unlikely this may be.

Special attention might be warranted in examples where the crop plant has weedy characteristics, where compatible wild or weedy relatives exist in the environment where grown, and/or where it is known that the same or closely related disease or insect pests controlled by the gene in the crop plant is helping to suppress the population of potentially weedy plants (is providing a natural biological control of the weed).

Many kinds of traits, including those for a plant's composition in lipid, protein, or fibre, may increase, decrease, or have no effect on the ability of a plant to survive independently. Such effects may alter the ability of a crop plant to survive within either an agricultural or wild environment. Traditionally, plant breeders look for alterations in susceptibility to a range of disease and pest agents in field trials. Traits can be identified based on familiarity that, if transferred to related species within the environment, would confer no competitive advantage and may confer a competitive disadvantage, including greater susceptibility to pests or diseases. For example, the double-sweet gene in sweet corn increases susceptibility of the germinating seeds to pre-emergence damping off (Guzman *et al.*, 1983).

Appropriate management practices

Standard cultural practices for management of gene transfer by cross fertilisation have evolved and are used to protect plant lines or crop cultivars against formation of unwanted hybrids within sites (performance trial sites or seed-increase fields) as a consequence of ingress of pollen from relatives or other lines/cultivars of the crop plant. These can include but are not limited to:

- isolation of test sites from areas inhabited by relatives (based on knowledge of movement of viable pollen of the relatives);
- control of pollen sources by mowing or herbicides;
- isolation of test sites from sites used to grow other lines or cultivars of the same crop plant (based on knowledge of movement of pollen of the crop plant);
- monitoring seed-production fields for unwanted hybrids.

Isolation distances of test sites or seed fields based on knowledge of ingress of pollen may be adequate to protect against formation of hybrids with relatives beyond the test site by egress of pollen. However, this will depend on knowledge of the effective dispersal area for viable pollen of the crop plant. Egress of pollen will depend on the amount of pollen available at the source, the distance it can travel, and viability of the pollen. Where a risk/safety analysis indicates the need for risk management, the standard cultural practices for that crop may be adequate or other management practices may be needed. The planting date could be changed or a hormone treatment could be used so as to cause the plant line or the cultivar to flower at a different time than wild relatives in the area. Familiarity may also be increased with information obtained by monitoring for formation of hybrids at distances from the test site.

ii) Weediness

A crop plant is considered a weed when it carries over (grows in subsequent seasons) or establishes in neighbouring fields and competes with subsequent crops. Some crop plants have a propensity for weediness, and some cultivars have a greater propensity than others of the same crop species to carry over at the original site where planted. A crop plant could also become a problem if it were to invade and persist in neighbouring ecosystems within the dispersal range of the plant. A crop plant, that becomes a weed, or a more important weed, at or beyond the original site where tested because of one or a few genes (*e.g.*, for disease or insect resistance or tolerance to an environmental stress), may be identified as a safety concern.

Most crop plants are so dependent on human nurturing as to be unable to compete successfully on their own. There are, however, examples of crops that are minor weeds in natural or agricultural ecosystems, examples being oilseed rape, sunflower and cereal rye. A safety concern may be identified if the genetic change will make the crop plant more likely to become a weed or more difficult to control by standard cultural practices either within or beyond the agricultural environment compared with the same crop plant in the same environment but without the new trait.

Many theories have been put forward as to how to predict whether a plant could become a weed. One approach by Baker (1965, 1974) uses a set of characteristics of weediness that may be identified in a crop plant. This information should allow for the prediction of the potential of a crop plant for weediness. Baker's theory suggests that weediness is a multicharacter attribute and that the addition of one gene is unlikely to cause that crop to become a weed. Fitter *et al.* (1990) and Williamson *et al.* (1990), on the other hand, suggest that predicting weediness is not an easy task and that the alteration of one gene may indeed be enough to change a crop plant into a weed.

If the crop plant has very few weedy characteristics, the addition of one or a few genes would be unlikely to cause that crop plant to become a weed problem. Special attention might be warranted where the crop plant has weedy characteristics or the added genes might be expected to improve competitive ability in natural or agricultural ecosystems.

When predicting weediness, not only the characteristics of the crop plant but also the characteristics of the habitat in which it is grown should be considered. An important crop in one environment may be a weed in another environment.

An indication of the tendency of the crop plant or certain cultivars to carry over at the site may be obtained from previous experience (familiarity) with the crop, trait, and environment in which the plant will be grown and their interactions. Crop plants that may raise safety concerns when considering weediness within the agricultural environment are those that may already be considered to be a problem.

When warranted, any tendency of a crop plant to invade and establish in ecosystems beyond where it is intentionally grown may be assessed using information available on the crop plant, trait, and environment, including the environment beyond the agricultural environment, and their interactions. In general, this may give rise to a safety concern only with crops that already exhibit such tendencies. Such crops or cultivars of crops that are or have been weeds can be identified from local, regional, or national lists of weeds available in most countries.

The ability to invade natural ecosystems may not be detected or tested during small scale trials where few plants and environments are involved. An increase in scale could therefore reveal an event that may only be detected by monitoring neighbouring ecosystems. Traits that confer on the crop plant any tendency for invasiveness beyond the agricultural environment can be identified based on a knowledge of the trait, the particular crop plant, environment, and interactions (see Section 5, "Concept of familiarity"). Relevant research, including results from previous research carried out at small scale and/or in natural ecosystems, should be taken into account. This information can also be used to identify traits that may be predicted to confer no competitive advantage and may even confer a competitive disadvantage to the crop plant.

Appropriate management practices

Standard cultural practices are widely available for the control of weeds within the agricultural environment, including control of carry-over of plant lines and crop cultivars at the test site (*e.g.* performance trial sites or seed-increase fields) and of spread to neighbouring fields. These practices include tillage, mowing, herbicide use and crop rotation. Some crop plant species are also controlled naturally, *e.g.* by winter kill, depending on the crop species and environment.

In general, practices that effectively prevent or limit carry over and spread of a crop species within the agricultural environment can also be expected to greatly limit the chances for spread and establishment (invasiveness) of that crop species beyond the agricultural environment. Possible exceptions might be those crop species with wind-dispersed seeds, or seeds dispersed by birds, where control at or near the test site might not preclude spread well beyond the test site, *e.g.* into unmanaged environments. In these cases, a risk/safety analysis may indicate the need for use of other management practices in addition to the standard cultural practices to minimise any potential risks identified. These could include:

- using sterile plant lines (unable to produce seed) in the case of clonally propagated plant lines or crop cultivars;
- selecting sites well within the agricultural environment, *i.e.* surrounded by large areas of cultivated land, rather than bordering on unmanaged land;
- monitoring surrounding partially managed or unmanaged ecosystems and, if invasiveness is detected, rogue or treat with an appropriate herbicide;
- using methods proposed by the plant breeder responsible for development of the new plant line or cultivar.

iii) Trait effects

Crop plants are developed with traits that adapt them to different environmental conditions, cultural practices, and agricultural production systems. This includes the development of cultivars with traits intended to have direct effects on pest species and disease-causing agents. The safety issues relative to the effect of such traits and dependent on scale are:

- direct effects on population size and evolution of target organisms, *i.e.* pest and disease agents; and
- direct/indirect effects on non-target organisms, particularly beneficial organisms and endangered species.

Effects of traits if expressed in other plants as a consequence of gene transfer are discussed above and effects of traits on workers (humans) are discussed below.

Each crop plant and its associated traits will tend to cause shifts in populations of organisms, particularly weeds, insects and micro-organisms, towards communities and individual species (or subspecies) specifically adapted to that crop and production system, including cultural practices. Among the range of organisms interactive with the crop, some are injurious (pests or disease agents), some are beneficial (nitrogen-fixing bacteria, pollinators) and some (most) are neutral opportunists.

Plants defend themselves naturally from injurious organisms by making many kinds of compounds, including allelochemicals, phytoalexins, coumarins, enzymes, alkaloids, protease inhibitors, tannins, and lignins, that are deleterious to pest and disease agents. Breeders have sought genes mediating pest and disease resistance from distantly related and often wild plants, and have imparted them to crop plants by crossing the traits into breeding lines. It has become a constant and dynamic necessity of breeders to provide plants with resistance to ever-changing populations of insect pests and disease agents that are constantly assaulting crop plants. Any effects of a trait in a new line or cultivar of a crop plant on nontarget organisms will depend primarily upon specific pest/pathogen interactions with the plant.

With the advent of molecular breeding technologies, new crop cultivars may be specifically modified genetically to increase the expression of traits important in the general defence of the plant to pests and diseases, or of traits known to have direct effects on target pests or disease agents. Two examples of transgenic plants with targeted resistance follow. In either case, any organism that ingests or comes into contact with such plants is exposed in the same way that organisms are exposed to the many kinds of plant-defence systems operative in native, non-cultivated plants.

In the first example, transgenic plants are made to express a delta endotoxin of a strain of *Bacillus thuringiensis* (Bt) for control of specific insect pests. The Bt toxins are a family of proteins that have an enterotoxic effect on insects or insect larvae. It is thought that the proteins interact with specific receptor molecules on the gut epithelium of the target insect species, and the range of insect species sensitive to the activity of one specific toxin is typically quite narrow. Unlike other insect control agents, *e.g.* protease inhibitors, the known Bt toxins to date have no known toxic or deleterious effects on organisms outside the range of affected insects. However, Bt strains are continually being isolated and modified.

It is probable that the wide-spread use of transgenic crop plants producing Bt toxin will select for a genetic population of insect pests with resistance to that Bt toxin. Resistance has already been found in a population of grain storage insects where Bt has long been used as a biopesticide (McGaughey, 1985). The exposure and development of resistance to the Bt delta endotoxin through plants may differ from that through application of the bacteria. Nevertheless, ability to overcome plant traits for defence against insect pests or diseases as well as develop resistance to chemical and biological pesticides is common. Organisms under conditions of natural selection tend to evolve toward greater adaptation and fitness.

In the second example, transgenic plants are made to express the coat protein of a virus with the intent of enhancing the defence of the plant to that virus (Beachy *et al.*, 1990; Gadani *et al.*, 1990). The nature of this enhancement appears analogous to the practice of virus control by cross-protection with a mild strain of a virus. In plants naturally infected with virus, viral coat protein is produced in high quantities and ultimately assembles with viral nucleic acid in a precise manner into particles often found as aggregates in specific tissues or organs of the plant.

In contrast to naturally infected plants, transgenically-encoded coat proteins can be distributed throughout the plants if expression is driven by a constitutive promoter, but generally attain a comparatively lower concentration and, of course, do not assemble into virus particles. A safety issue is whether these differences in distribution, concentration, and form could change the pattern of exposure of other organisms to the coat protein. However, given the extensive familiarity with using virus-infected plants and the lack of documented direct effects of plant viruses or viral coat proteins on other species that either consume or are exposed to infected plants, little or no effect on non-target organisms is expected.

In view of the widespread use of plants with transgenically expressed coat protein, consideration should be given to whether or not a change could occur in another virus infecting the plant, and a new virus strain with altered host range or ecological properties could arise. It has been documented that, with time and selection pressure, new virus strains arise that overcome crop plant genes mediating resistance. Little is known about this kind of event except that it varies widely in frequency between plants and virus types and that changes in the viral genome are often minimal.

In transgenic plants, two events could possibly lead to adverse effects: transcapsidation (de Zoeten, 1991; Farinelli *et al.*, 1992) and recombination by template switching (Palukaitis, 1990; De Jong and Ahlquest, 1992). Both of these events also occur during a natural mixed infection with two or more viruses (Creamer and Falk, 1990; Dodds and Hamilton, 1976), but the frequency and significance relative to creating new strains is not known in either case.

Transcapsidation occurs if a second unrelated virus infects the plant and the transgene-encoded coat protein encapsidates the nucleic acid of the second virus, provided the functional genome of the second virus is not too large or too small. Transcapsidation has a transient effect specifically on coat protein-mediated phenotypes such as vector specificity. When the transcapsidated nucleic acid replicates in a new host it produces its original coat protein, thereby eliminating the transgene product. No permanent genetic change occurs upon virus replication because the nucleic acid is unchanged.

Recombination may result in the creation of a new virus containing the coat protein gene copied from an mRNA transcribed from the transgene. Recombination may occur when a second unrelated virus infects the plant, and the RNA polymerase that replicates viral RNA switches its template during the process and the resulting RNA strand is a combination of two initial templates, namely the second viral RNA and the mRNA from the transgene that encodes viral coat protein. Unlike transcapsidation, template switching leads to a recombined, *i.e.* genetically altered, viral genome. When the recombined nucleic acid infects a plant, the resulting virus coat protein is the transgene product.

In the case of traits introduced to target organisms, the potential of the trait to affect non-target organisms will depend on a number of factors, including the actual gene(s), the number of gene copies integrated into the genome, the characteristics of the promoter and other regulating elements governing the expression of the transgene, the stability of the biosynthetic product produced, the processing and intra- or intercellular targeting of the product, and the sensitivity and potential for new exposure of non-target organisms to the product. With molecular technologies, the same gene or genetic construct may be transferred to different kinds of plants or specifically expressed in different tissues of the same plant. Different safety concerns may be raised depending on the plant species or specific plant tissues producing the gene product(s).

The potential for secondary trophic effects should also be considered. Thus, a severe reduction in the population size of a target (pest) organism could lead to depletion of a source of food to other organisms predatory on the target organism or a toxin effect on predators. Such secondary effects as a consequence of pest control achieved with a trait should be of minor concern where the trait serves primarily to bring the pest population down to an ecologically more natural level.

The natural emergence of resistance of weeds to herbicides, the transfer of herbicide-resistance genes from crop plants to weedy relatives, and the possible carry-over of herbicide-resistant crops have been raised as safety concerns. Within the scope of this report the safety concern is whether the introduction of herbicide-resistant crop plants into agricultural production systems could result in the generation of weeds resistant to the herbicide by gene transfer (see section on gene transfer) or extensive use of the herbicide. The environmental quality of the herbicide in question (persistence in the soil, biodegradability, toxicological effects) and other environmental consequences of widespread use of the relevant herbicide are beyond the scope of this report. Some plant lines or crop cultivars may be altered genetically to detoxify not only herbicides but also soil pollutants. The non-target effects of possible intermediate compounds and final products of these toxicants may be identified as safety concerns. Experience with previous risk assessments and with the herbicide or pollutant may be useful in addressing these safety concerns.

Non-target effects of a trait or crop plant on native plant communities may be of concern if seed dispersal can occur or if related weedy or neighbouring wild plants exist within the pollination range of the plants, depending on the factors described in the section on gene transfer.

Trait effects on native animals, including mammals, birds and insects, will depend upon their sensitivity and exposure to the plants and thus the compounds produced by the plants. Certain native animals will not visit agricultural areas. In general, animals, particularly higher animals in nature, have highly developed discriminatory powers and learn quickly to avoid plants harmful to them. In some cases, the confinement of a chemical to the plant itself may reduce the overall impact of an alternative such as a chemical sprayed topically. However, under conditions of high exposure to the crop plant and in the absence of other food sources the natural avoidance mechanisms of animals may not apply.

Appropriate management practices

Practices are available and many have become part of standard cultural practices to delay or prevent the evolution of populations of target (pest) organisms with resistance/tolerance to plant-defence traits such as Bt endotoxin. These practices include:

- the use of more than one trait (multiple traits) for defence against the same pest;
- genetic control of the level, timing, or site of expression of the gene within the plant, to minimise exposure and hence selection pressure on the pest;
- rotation with cultivars having different traits for defence against the pest; and
- inclusion of susceptible (sensitive) individuals mixed with resistant individuals of the cultivar (multilines or cultivar mixtures).

Emergence of new (recombinant) genotypes of viruses resulting from the use of virus-defence genes can be identified by monitoring those organisms of specific concern and which interact with the plants and are managed by practices used to manage virus transmission. Wide-scale cultivation of the new crop cultivar may not be possible if there is evidence during scale-up for new genotypes of viruses.

Direct or indirect effects of traits on non-target organisms can be assessed by monitoring at the test site if appropriate. Any negative effects on beneficial insects (such as pollinator bees) or wild life (including endangered species) will usually be limited to specific areas. Detection of significant negative effects on non-target organisms of concern could preclude further scale-up of the plant line or crop cultivar.

In general, standard cultural practices will be sufficient for managing a trait effect when a risk/safety analysis indicates the risk for the new plant line or crop cultivar is no greater than that for plant lines or crop cultivars of the same crop species but without the trait or with similar traits. Other management practices may be warranted to manage unwanted trait effects in cases where: *a)* familiarity is lacking; or *b)* familiarity indicates that there is a potential adverse effect in the environment. As an example, a plant line or cultivar of the same species but lacking the trait of concern could be planted as a buffer around the site in order to minimise the chances for visits of wildlife at the site.

If the risk/safety analysis indicates that an adverse effect in the environment is likely for a trait effect in its new genetic background, and there are no practices available or acceptable to achieve reasonable safety, then this could preclude scale-up of the new line or cultivar.

iv) Genetic and phenotypic variability

Plant lines with new traits, no matter how precise the method of introduction of the trait(s), may exhibit unintended genetic and phenotypic variability, as indicated by genetic instability, unexpected phenotypes and possible pleiotropic effects. Genetic or phenotypic variability *per se* is not a safety concern. However, if an unintended or unexpected phenotype or pleiotropic effect causes an increase in the chances for gene transfer, weediness, or trait effects leading to adverse effects in the environment, as examples, then genetic or phenotypic variability could give rise to a safety concern.

The development of new crop cultivars by plant breeding depends on the availability of useful genetic and phenotypic variability. Traditional techniques such as wide crosses with embryo rescue, chromosome substitutions from wild relatives, and the generation of somaclonal variants from somatic cells or tissue culture typically produce a wide range of genetic and phenotypic variability, some highly useful but most not useful or unstable. As a matter of routine, plant breeders eliminate the unwanted and unstable phenotypes during the first two or three generations carried out in the greenhouse/glasshouse or small-scale field trials, or they use backcrossing and other methods to produce acceptable agronomic types with the desired traits.

Plant lines produced by molecular techniques can also exhibit unexpected and unwanted genetic and phenotypic variability. Some of the reasons for this variability are as follows:

- plant lines regenerated from tissue culture or individual protoplasts following the introduction of a specific gene or construct may exhibit unexpected phenotypes because of somaclonal variation;
- an active gene may be inactivated as the result of physical interruption of its regulatory or coding region because of molecular insertion of the gene or construct;
- an inactive gene or ''silent'' metabolic pathway may be activated as the result of introduction of a new regulatory region or insertional inactivation of a repressor;
- an identical construct inserted in different positions in the genome may result in variability in expression of the trait (position effect);
- mutations such as occur coincidentally during growth and development or from the intentional use of mutagenic treatments may result in new traits;
- changes in biosynthetic and energy demands may cause biochemical changes in the cells expressing the new traits.

An unexpected increase in the incidence of self-sterility of a normally self-fertilised crop plant could increase the chances for cross-fertilisation of such plants from incoming pollen. Hybrids could then be formed due to incoming pollen from relatives. Whether this is a safety concern depends on whether the seed from such a hybrid will remain at the site or be removed with the harvest, or if left at the site, whether the plants produced from the seed would survive and be fertile and produce viable progeny and are considered a nuisance (see ''Gene transfer'' section).

Most unwanted genetic variability, including any tendencies for weediness, can be identified through basic research or small scale-field trials. Advanced testing over a larger area and under different climatic or management conditions may reveal more subtle effects such as any tendency of the plant line to carry over at the site (see ''Weediness'' section).

The potential for enhanced expression of known toxic components in the plant, such as glycoalkaloids in potatoes, can be detected by available assay procedures for the toxic component (see ''Trait effects'' section).

In a great number of cases, unexpected phenotypes, regardless of the method used to produce genetic variability, are evident as negative effects on the plant itself or its performance in the field.

Appropriate management practices

Plant breeding programmes tend to eliminate the genetically or phenotypically variable lines during preliminary testing (small-scale) on the basis of performance considerations. Some genetically or phenotypically variable lines may be kept at small-scale as a genetic resource for use in hybridisation with agronomically more acceptable lines of the crop species. In either case, the line is not selected for scale-up and any safety concerns that may arise from genetic and phenotypic variability are generally limited to the tests conducted at small scale.

In some cases, a genetically or phenotypically variable line will be selected for testing over a wider geographic area or in large numbers to test a hypothesis or obtain more information on performance. Where the variability is known or suspected to increase self-sterility (and hence enhance the formation of hybrids with incoming pollen from relatives), weediness, or expression of a toxicant at an unacceptable level, depending on the risk/safety analysis, certain other management practices may be employed, at least temporarily until more information is available.

v) Biological vector effects and genetic material from pathogens

The transfer of specific genes or genetic constructs into the genome of a plant is accomplished in some cases by use of biological vectors. To date, these vectors have been derived from plant pathogens such as the bacteria *Agrobacterium tumefaciens* and *A. rhizogenes.* These pathogens cause the diseases crown gall and hairy root, respectively. *A. tumefaciens* is the most common of the vectors currently being used, and has a substantial host range of dicotyledonous species. Crown gall occurs when T-DNA of the Ti plasmid, part of the genetic material of *A. tumefaciens,* is transferred from the bacterium into the plant and becomes integrated and stably maintained in the plant genome. The safety issue with these vectors is the potential for transfer of genetic material into the plant that may cause disease through several means discussed below.

Typically, when the Ti plasmid of *A. tumefaciens* is used as a vector for plant transformation, the plasmid is disarmed through removal of some or all of the genes that produce galls. The induction of disease by genetic material transferred into the plant as part of a biological vector, if still possible, would be apparent during preliminary small-scale or basic research and is not scale-dependent. There is no evidence and no biological or epidemiological basis for suggesting that plant lines that show no evidence of disease during the early stages of study might exhibit disease during the scale-up process.

Consideration needs to be given to the possibility that bacteria capable of causing disease may remain associated with the plant. Verification that pathogenic bacteria have been eliminated from the plant material will alleviate concern over the potential for the pathogen and/or diseased plants being transferred into the field. These pathogens, if present, would normally be detected in initial tests at small scale and therefore would not be a concern during scale-up. No pathogens would be present if ballistic methods were used to inject the genes of interest or if progeny from seeds of initially transformed plants are used.

Consideration also needs to be given to the possibility that components of the inserted construct, including regulatory sequences that function in the expression of the desired trait, might cause undesired effects. One of these effects might be recombination with a gene of an incoming pathogen (see section on "Trait effects and viral recombinations"). Another effect might be transfer of genes or coding regions by a biological vector to other pathogens once the vector is in the plant. This has not been a concern with the Ti plasmid because the potential for transfer is eliminated once the genetic material is in the plant. There is less information and experience with viral vectors. Such biological vector effects will likely be recognised or can be tested during preliminary stages of study.

vi) Worker (human) safety

Scaled-up trials with new crop cultivars or plant lines developed by the newer molecular techniques of biotechnology and intended for traditional agricultural purposes are unlikely to raise any different safety concerns for human health and safety than for lines or crop cultivars developed by traditional technology.

Some crop plants produce sap and other exudates which can be associated with human health problems. Exposure to various plant components (*e.g.* pollen and plant exudates) may give rise to safety concerns. For example, exudates may lead to skin sensitisation or pollen may cause a reaction through inhalation.

The following may require observation or evaluation as part of the scale-up process, depending on the trait and the crop, apart from food safety:

- whether the gene product is produced in pollen (presenting novel allergens) and could sensitise previously unaffected individuals;
- whether the new plant line or crop cultivar releases larger amounts of sap that contains a new product of concern for worker safety, and the crop requires considerable handling by workers, and may have health implications for the workers.

Management of most human health and safety concerns should be relatively simple in terms of controlling exposure to significant amounts of allergens/toxicants. Furthermore, the management used should ensure that personnel involved in the trials have adequate training. Such management would, in most cases, be the same or similar to that already commonly in use to protect workers involved with crop plants developed by traditional technology.

5. The concept of familiarity

Familiarity comes from the knowledge and experience available for conducting a risk/safety analysis prior to scale-up of any new plant line or crop cultivar in a particular environment. Familiarity takes account of but need not be restricted to knowledge and experience with:

- the crop plant, including its flowering/reproductive characteristics, ecological requirements, and past breeding experiences;
- the agricultural and surrounding environment of the trial site;
- specific trait(s) transferred to plant line(s);
- results from previous basic research including greenhouse/glasshouse and small-scale field research with the new plant line or with other plant lines having the same trait;
- the scale-up of lines of the crop plant developed by more traditional techniques of plant breeding;
- the scale-up of other plant lines developed by the same technique;

- the presence of related (and sexually compatible) plants in the surrounding natural environment, and knowledge of the potential for gene transfer between the crop plant and the relative; and
- interactions between/among the crop plant, environment and trait.

Familiarity with the crop plant, environment, trait and interactions does not determine whether the new combination is either safe or risky (NAS, 1989). Rather, familiarity with the elements of an introduction facilitates a risk/safety analysis. Familiarity can also be used to indicate appropriate management practices including whether standard cultural practices are adequate or whether other management practices are needed until more information is obtained on safety. The sections that follow explain the concept of familiarity in more detail.

a) Familiarity with the crop plant

Familiarity with a new plant line or crop cultivar can come from: *a)* knowledge and experience with that same crop plant species or subspecies, scaled up and grown in different environments with traits introduced by traditional plant breeding; *b)* information on the nature and behaviour of the actual genotype(s) of lines/cultivars related to the new line of the crop plant under consideration for scale-up and the degree to which behaviour varies in different environments; and *c)* results of preliminary experiments and small-scale field tests with the new line or cultivar of the crop plant.

Familiarity with the new plant line or crop cultivar will, in a particular environment, vary depending on whether the crop as a species has been used in agriculture for a long time or is relatively new (exotic) to the environment. Historically, relatively unfamiliar crop plants have become increasingly more familiar with the progression from initial observations in small plots as new introductions, through performance trials carried out at several locations over several years, and continuing indefinitely with cycles of creating, testing and selecting new lines as cultivars for seed increase and general use. In the same way, plant lines representing certain new genetic combinations, and relatively unfamiliar when first produced, become increasingly more familiar with the progression from initial observations, to basic research on inheritance and genetics, to advanced testing in performance trials carried out at different locations with different cultural practices over several years.

b) Familiarity with the environment

Familiarity with the environment where the new line or cultivar of the crop plant will be scaled up and grown can come from knowledge of both the managed agricultural environment (agroecosystem) and the wider partially managed or natural surrounding (wild) environment.

Familiarity with the managed agricultural environment can come from knowledge of the climate and soils of the region/area where the crop is grown, the spatial or temporal effects of standard cultural practices (crop rotation, tillage, planting dates, herbicide use), the adequacy of standard cultural practices to manage the crop plant in the environment, and the existence of endemic or potentially epidemic pests or diseases of the crop. Familiarity can include knowledge of the suitability of the crop plant to the environment and the potential for lines or cultivars with new traits to succeed in the new or wider environment where lines or cultivars without the trait(s) would not succeed.

Familiarity with the wider partially managed or natural surrounding (wild) environment can come from knowledge of the presence of wild or weedy relatives with which the introduced plant can cross-fertilise under field conditions within range of pollen movement to or from the crop plants. Familiarity with the surrounding environment can also come from knowledge of naturally-occurring sources of pests, pollinating insects, birds and other wild life.

c) Familiarity with the trait

Familiarity with the trait in a new plant line or crop cultivar in a particular environment can come from knowledge of the genetics of the trait including: *a)* the origin of the trait; *b)* the genetic construct introduced into the plant lines, including regulatory sequences; *c)* experimental data obtained through preliminary and basic research on inheritance and genetics of the trait expressed in the crop plant; and *d)* experience with the genetics of the same trait expressed in other crop plants or other organisms.

Familiarity with the trait can also come from knowledge of function(s) of the trait in the donor and/or recipient organisms. As examples, some traits affect ability of plants to survive at low or high temperatures, others provide for defence against pests or disease agents, and still others affect the chemical or physical properties of the harvested products of crop plants. Familiarity with function of the trait in the crop plant comes from knowledge of what the trait does for the plant, including how it affects growth, survival and reproductive ability of the crop plant.

d) Familiarity with interactions

Familiarity with interactions also comes from knowledge and experience with different combinations of crop plants and the trait. A given trait may respond/perform differently in different crop species or possibly even in different genetic backgrounds of the same crop species. Knowledge and experience with different combinations of trait and species or genetic background of the crop plant can come from studies of interactions conducted with small-scale tests in the greenhouse/glasshouse and in the field. Such studies could include tests with the same trait introduced in tens, hundreds, or even thousands of different genotypes of the crop plant and grown out as individuals for one or more generations.

Familiarity with interactions also comes from knowledge and experience with different combinations of the crop plant trait and environments. Different genotypes of crop plants commonly respond/perform differently in different environments (genotype × environment interactions) because of differences in climate, soil conditions, local pest populations, other organisms, and cultural practices. Knowledge and experience with the different combinations of crop plant, trait and environment will come from studies of plant genotype × environment interactions at several locations representative of different conditions. Experience gained from studies of genotype × environment interactions using lines or cultivars developed by traditional techniques can be used to develop and test hypotheses on genotype × environment interactions and with genetic combinations for which there is less experience.

e) Application of the concept of familiarity

Familiarity is dynamic not absolute. It continuously grows with increasing knowledge and experience obtained through observations, controlled experiments, empirical measurements during the developmental stages, testing of new plant lines and crop cultivars, and information exchange.

Because the concept of familiarity is flexible, knowledge and experience at the ecosystem, organismal, cellular, and/or molecular levels with any one or more of the different elements of the interacting plant, trait, and environment can be used to conduct a safety/risk analysis and indicate appropriate management practices. Some examples are as follows:

- Whether standard cultural practices would be adequate to manage a relatively unfamiliar new plant line or cultivar (*i.e.*, the combination of plant and trait is relatively unfamiliar) can be assessed based on familiarity with a closely related line in conjunction with results from laboratory and preliminary field work with the new line.
- Whether standard cultural practices would be adequate to manage a relatively unfamiliar new plant line or cultivar can also be addressed based on familiarity with the trait and its expression in the plant.
- Whether standard cultural practices would be adequate to manage a plant line or cultivar can be assessed based on knowledge of whether the trait is expressed: *a)* in all tissues throughout the life of the plant; *b)* only in certain tissues in response to a certain signal; or *c)* only at a certain stage of plant development.

Some new combinations of plant, environment, and trait are relatively unfamiliar and will only become more familiar following study in trials of a larger scale or over a wider geographic area. It may be necessary, in these cases, to scale up to obtain the knowledge and experience to make a determination as to risk or safety. The concept of familiarity can be used to indicate when there is a lack of familiarity and hence the need for specific and appropriate practices as a precautionary measure until information is gained that indicates more clearly which practices are needed as a matter of routine.

Where there is sufficient familiarity with the crop plant, the new trait and the environment of the proposed scale-up, the risk/safety analysis may be expedited. Where a risk/safety analysis raises no safety concern then the line or cultivar can be scaled up and managed with the standard cultural practices for that crop in that environment.

6. Summary

This report identifies and addresses the scientific considerations pertaining to the environmental safety issues applicable to the scale-up of new crop plants developed by biotechnology. The term ''scale-up'' is used in preference to ''large-scale releases'' to describe the continuum of research and development involving increasing scale from preliminary field tests up to general use.

The scientific considerations are discussed in this report to provide a framework to evaluate the safety of scale-up of new plant lines and crop cultivars. The concept of familiarity forms the basis for this framework.

There is considerable knowledge and experience (familiarity) with the procedures for managing the introductions of crop plants developed by a wide range of breeding methods. It was therefore considered that the knowledge and experience gained with crop plants developed by the various breeding methods as well as experience with plants developed by rDNA methods (transgenic plants) could be applied to address the safety of scale-up.

The majority of effects of new traits on appearance or behaviour of crop plants will be recognised during preliminary evaluations in small-scale field tests, depending on the design of the test. However, some effects, including some effects related to safety, being scale-dependent, may only become apparent during the scale-up process. Specific tests may be designed to detect the occurence of these effects, if appropriate.

Familiarity comes from the knowledge and experience available to conduct a risk/safety analysis for new plant lines or crop cultivars. It can be used to identify hazards, determine the magnitude of risk, and indicate appropriate management. Familiarity can also be used to recognise where more information is needed to analyse the risk/safety.

For crop plants, hazard identification begins with identification of relevant safety issues based on biological properties/characteristics of the new line in a particular environment. A safety concern arises when the factors necessary for a potential adverse effect are specifically identified with a new plant line or crop cultivar in a particular environment.

Crop plants are restricted to a greater or lesser extent to environments managed by cultural practices. These practices have evolved empirically and in response to research results in different countries or regions as the standard cultural practices effective for managing that crop within the particular environment. Standard cultural practices may be effective for managing particular identified risks, or other management practices may be devised to minimise a risk. The risk/safety analysis includes determining the effectiveness of the standard cultural or other management practices used to minimise the risks from any hazards identified.

There will be cases where, based on a risk/safety analysis, a particular plant line or crop cultivar with a new trait and considered for scale-up in a defined environment will raise no safety concern. In these cases, the line or cultivar can be scaled up and managed with the standard cultural practices for that crop in that environment.

Notes

1. Environmental safety includes safety of the work environment and therefore includes issues of human/worker safety.
2. Crop plants are plants grown for commercial uses, including uses as food, animal feed, fibre, fuel and ornamentals. Trees are included if grown as crops, *e.g.* fruit or fibre, but not forests.
3. Risk/safety analysis comprises hazard identification and, if a hazard has been identified, risk assessment.
4. Risk management refers to ways that appropriate methods are applied in order to minimise risks and should be determined by and in proportion to the results of the risk/safety analysis. It does not include broader considerations of a political, socio-economic, value and/or ethical nature.
5. ''A transgenic plant is a plant with a gene or genetic construct (trait) introduced by a molecular technique'' (Old and Primrose, 1990). The term ''transgenic'' was introduced by Gordon *et al.* (1980) and Gordon and Ruddle (1981) to describe the genetic transformation of a mouse with new DNA sequences permanently inserted as part of the genome and sexually transmitted to progeny. While used originally in reference to animals, this term is now widely used to refer to plants with such genetic changes.
6. Scale-up includes unconfined (other than by natural barriers and cultural practices) performance evaluations, advance testing, demonstration trials and seed increase with new plant lines and crop cultivars beyond basic and preliminary field research in which special confinement measures can be applied.
7. Cultural practices are those practices already recommended or used more or less routinely (standard) to grow and maintain the crop.
8. Other management practices could include, for example, cultural practices not normally used to grow and maintain that crop in a particular region, or specific management applicable to a new cultivar to ensure environmental safety or to gain familiarity. These practices could eventually be discontinued or they could become part of the standard cultural practices for the new cultivar if appropriate for the crop.
9. The traditional terms ''plant line'' and ''crop cultivar'' (*cultivated variety*) are used for new variants of crop plants. A plant line is a relatively homogeneous collection, selection, progeny or sibling within a plant species; typically it has a distinct or unique genotype or genetic pedigree. A crop cultivar is a plant line chosen for seed increase and general use following satisfactory evaluations and appropriate description of its characteristics. Crop cultivars usually are named and plant lines are identified/distinguished by genetic pedigree if known.

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