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Classification of Genetically Modified Crops

A proposed classification model aimed to facilitate the notification procedure for market introductions of GM crops of Directive 2001/18/EC of the European Union

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Summary

In traditional breeding desired traits, read genes, are actively introduced into cultivated crops by crossing with related species carrying these traits/genes. The genetic background of the traits is usually not known or fully characterized and the breeding schemes can take considerable time because of the requirement for several backcrosses to the recurrent crop parent. The latter is necessary in order to get rid of traits from the donor that are undesired or even negative and that came along with the gene-of-interest, due to so-called linkage drag. Introgression breeding is an important tool in the development of new varieties making use of the natural variation in natural or agricultural sources. The gene-of-interest, responsible for resistance to insects, nematodes, viruses, fungi or herbicides, or for quality traits, is transferred from related species to the crop species by crossing and because of the several steps of backcrossing necessary to reduce to linkage drag, this process can be called "multiple step domestication". A relatively new tool in breeding and in implementing the available genetic variation is genetic modification. Here, only the cloned gene coding for the trait of interest is introduced by random insertion. When this is done with a natural plant gene from a sexually compatible, related species and thus without linkage drag, it may be called "single step domestication".

Before any Genetically Modified (GM) crop can be put on the market in the European Union, it has to comply with EU Directives 2001/18/EC or EC/1829/2003, concerned with the environmental safety of the GM crop. The notification procedure that is required under Directive 2001/18/EC for GM crop market introduction, prescribes all information to be provided, primarily aimed to assess potential environmental risks of the specific GM crop, e.g. on the recipient, the genetic modification, the GM plant etc. Food and feed safety of the GM crop are not part of the scope of this Directive. The procedure under 2001/18/EC is based on a case-by-case assessment assuming a worst-case scenario.

Still, Directive 2001/18/EC also provides some opportunities to facilitate the notification procedure. Based on results from earlier releases for e.g. field trials or on other substantive scientific grounds, a notifier could consider that a market introduction for a specific GM crop does not pose an extra risk compared to the previously checked situation and he can propose not to provide part or all of the information required in Annex IV, section B (see Article 13 paragraph 2). This information is concerned with unintended release or misuse and with storage, handling, packaging and labelling and with monitoring and reporting, however not with aspects of environmental risk assessment. Another kind of facilitation is described within Article 13 paragraph 4 and gives the notifier the opportunity to refer to data or results from releases notified earlier or within another context that he considers relevant, rather than having to generate them himself. These data or results can be on environmental risk issues. In this report, considerations are presented to provide the Dutch competent authority substantive, reasoned scientific arguments to suggest an extension of the possibilities to facilitate the notification procedure for specific, well-described classes of GM crops (for the classification model, see chapter 6), specifically on aspects of environmental risk assessment. Directive 2001/18/EC anticipates on these kinds of initiatives by competent authorities or by the Commission in Article 16.

Within the classification model the present full notification procedure remains the general rule for the great majority of new GM crops, category 1 in this report. Facilitation is suggested for two categories, a) new events within the same gene/crop combination and b) new cisgenic (see below) GM events. For ten years now, GM crops with transgenes derived from other organisms have been grown globally on an ever increasing scale. In 2004 the cultivation area covered 81 million hectares in 17 countries. This area was planted with only eight GM cultivars of six species, insect-resistant maize and cotton, herbicide-tolerant canola, maize, cotton and soybean and virus-resistant papaya and squash (melon-type). So far, no adverse effects on the different environments in these countries or on human and animal health have been reported for these GM crop events. This general observation is supported by the results of more detailed, in depth scientific research in many separate and specific cases of GM plants on many aspects of environmental risks, such as e.g. invasiveness, outcrossing, horizontal gene transfer and risks to human and animal health. For these reasons, it is concluded that new events within the same GM gene/crop combination, for which insertion events have already been approved by the European authorities, can be exempt in the notification procedure from the information on environmental risk assessments and on labelling, packaging, monitoring etc. This represents the

information requested under Article 13, paragraph 2a, Annex III section B7 and sections D6-11; Annex IVB (see above); paragraph 2b, Annex II section D2. These GM gene/crop combinations constitute category 2.

The most recent developments in plant molecular biology and genomics have increased the availability of plant-derived genes and promoters. They allow the generation of a new series of GM crops, i.e. those with only plant-derived gene and regulatory (i.e. promoter and terminator) sequences in sense orientation and without any undesired DNA coding sequences (e.g. selectable marker genes). In the cases in which the plant-derived genes with their own regulatory sequences originate from plant species with which the recipient can exchange genetic material by traditional breeding techniques (cisgenes), the end-products of genetic modification resemble largely the end-products of traditional breeding. For the varieties obtained by the traditional breeding toolbox, and for the GM crops already exempted from Directive 2001/18/EC (i.e. obtained by mutagenesis or cell fusion of plant cells from organisms which can exchange genetic material through traditional breeding methods) no extra environmental analyses have been deemed to be necessary in the past and these techniques are well-accepted by society.

With traditional breeding as a benchmark, it is concluded that new GM events, where the introduced genes with their own regulatory sequences (cisgenes) have been derived from donor plant species with which the recipient species can exchange genetic material through traditional breeding methods, can be exempt in the notification procedure from the information requested under Article 13, paragraph 2a, Annex III section B7 and sections D3 and D6-11, Annex IVB; paragraph 2b, Annex II section D2. These cisgenic GM gene/crop combinations constitute category 3.

1. Introduction, scope and definitions

1.1 Introduction

Modern, non-GMO-based plant breeding uses the genetic variation present in natural and agricultural sources via many technological tools to improve existing varieties or to develop new ones. The improved or new varieties generated by methods present within the traditional breeding toolbox are generally subjected to a thorough screening, selection and evaluation procedure by the breeding companies. Subsequently, the new varieties are tested according to governmental rules and legislation guaranteeing food safety and quality and to the procedures involved in acquiring cultivar registration and breeder's rights. The emphasis is on the end-product, i.e. the new variety, and not on the method used to obtain it. The safety of food products is checked according to (inter)national standards, e.g. for the Netherlands the Hazard Analysis Critical Control Points (HACCP). The HACCP is one of the four standards approved by the Global Food Safety Initiative. All of this means that the consumer can be assured that what is present in the shops and with retailers is safe for human consumption.

The products of traditional breeding efforts (varieties) are traditionally not subject to environmental safety assessments. When about twenty five years ago genetic modification became available as a plant breeding tool, a set of additional safety assessments was put in place before allowing release of GM varieties in the environment and on the market. These safety assessments were called for, because the novelty of the process of making GM crops and the use of genes from evolutionarily unrelated (non-plant) organisms led to concerns about the possibility of creating hitherto unknown risks to human health and the environment. The regulations are based on a worst-case scenario and require substantial risk assessment studies and monitoring, case by case and step by step. In Europe, the directive on deliberate release into the environment of a GM crop is Directive 2001/18/EC and it applies to all plants that are produced using the technique of genetic modification, as defined within the Directive. This means that the production process determines whether a crop is a GM crop and has to be subjected to Directive 2001/18/EC and not the end-product. The Directive is aimed at the deliberate release into the environment of genetically modified organisms and this encompasses release into the environment for any other purpose than placing on the market, e.g. field trials (part B), and release for placing genetically modified organisms on the market as or in products (part C). This report only focuses on part C.

Other relevant EU GM legislation includes among others Regulation EC/1829/2003 on genetically modified food and feed.

Because we have gained knowledge in the past decades on genetic modification with random T-DNA insertions, on cultivation and usage in food and feed of its products, and because great advances in plant genomics research in the past decade have led to the identification and isolation of plant-derived genes, allowing application of those plant-derived genes in genetic modification, it is time to reflect on whether the worst-case scenario still has to

be the starting point for all types of GM crops with respect to the EU legislative requirements for GM crops. The aim of this report is to explore whether arguments based on experience with safe use and on results of scientific research can be found to facilitate the notification procedure of Directive 2001/18/EC, i.c. certain safety analyses on GM plants that are required up till now, for market introductions of certain classes of GM crops.

1.2 Scope and delimitation of this report

This report will explore the possibilities to facilitate the notification procedure for market introductions of GM crops of Directive 2001/18/EC by classifying GM crops in categories with different levels of environmental risks and concomitant assessment requirements. The Directive (Annex A of this report) will remain the starting point and will not necessarily have to be changed, primarily. The list of information that has to be provided by a notifier in case of a market introduction will be checked for aspects and conditions that could be open for facilitation. The focus will be on environmental safety, which is the focus of Directive 2001/18/EC and the scope of the COGEM, which commissioned this report. COGEM stands for the Netherlands Commission Genetic Modification and has the legal task to advise the Dutch government on potential environmental risk aspects of genetically modified organisms and to bring, commissioned or uncommissioned, ethical and social aspects linked to genetic modification under the attention of the Ministers involved.

The setup of the report is as follows: in chapter ***2*** traditional breeding and the relevant introgression techniques leading to varieties that resemble the varieties obtained by genetic modification are described. Thus, traditional breeding provides the benchmark for comparisons of GM crops. Chapter***3*** will summarize the history of GM crop cultivation and the experiences obtained with it. Aspects of environmental risk assessment and of ecological safety of the cultivation of GM crops are presented separately in chapter ***4***. The recent developments in genomics research that opened up new possibilities, including the use of only plant- or even species-derived genes and avoiding the presence in the end-product of superfluous DNA (chapter ***5***) are in their own right already considered as grounds for a classification of GM crops (Nielsen, 2003; Bradford et al. 2005). However in this report, the considerations of these four chapters are taken together and lead to the classification model presented in chapter ***6*** that is linked to suggestions for a facilitation of the notification procedure. Chapter ***7*** contains the conclusions and some grounds for further discussions and subsequent facilitations in the future.

1.3 Definitions

1.3.1 GMO

The official EU definition of a GMO, a genetically modified organism, according to Directive 2001/18/EC (see Annex A of this report) is:

A GMO is an organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination. An organism is any biological entity capable of replication or of transferring genetic material.

Ways or techniques considered generally to give rise to GMOs are amongst others,

- recombinant nucleic acid techniques involving new vector formations outside an organism and their subsequent incorporation into a host organism in which they do not occur naturally but in which they are capable of continued propagation.
- direct introduction into an organism of heritable material prepared outside the organism
- cell or protoplast fusion resulting in the formation of live cells with new combinations of heritable genetic material through methods that do not occur naturally.

Two categories of exceptions have been identified, firstly techniques that can be considered as 'not leading to GMOs' and secondly techniques that will give rise to GMOs to which the Directive does not apply.
The first category includes:

- *in vitro* fertilisation
- natural processes, such as conjugation, transduction or transformation
- polyploidy induction

The second category includes:

- mutagenesis
- cell or protoplast fusion of plant cells of organisms *which can exchange genetic material through traditional breeding methods*.

1.3.2. Event

A specific, well-defined and well-described combination of newly introduced DNA, i.e. gene(s) and regulatory sequences such as promoters and terminators, and a recipient crop cultivar. Events are considered as 'different' in a number of situations, e.g. when other DNA sequences are inserted into another crop, when the same coding region (= gene) is combined with another promoter in an identical crop cultivar, when identical gene and regulatory sequences are inserted in the same crop cultivar in another location of the recipient's genome. The latter events are the result of other insertion events, either from within the same transformation experiment or from another transformation experiment with the same DNA and recipient. The nature of the event can have consequences for the considerations on the implementation of the notification procedure, as will be explained later.

1.3.3 Environmental risk assessment

In Directive 2001/18/EC (Annex A) the environmental risk assessment is defined as:

The evaluation of risks to human health and the environment, whether direct or indirect, immediate or delayed posed by deliberate release into the environment or by placing on the market of GMOs.

In the procedure before placing a GMO on the market a notification to the competent authority of a Member State has to be submitted. This notification has to contain general information about the GMO, but more importantly all

information on a GMO necessary to assess possible risks of the GMO to human health and the environment. The relevant text passages from Directive 2001/18/EC relating to these risks, a.o. the environmental risk assessment, can be found in Article 13, paragraph 2a, more specifically in Annex IIIB, B7 and D3 (a & b), D6-11, in paragraph 2b, in Annex II, D2, 1-8 and paragraph 2e. The information requested can be provided in the form of data or results from earlier notifications, data or results from substantive, reasoned scientific research or, whenever necessary, additional studies on specific aspects of the potential hazards leading to an evaluation of the risks. Additional studies are only required when the information from earlier notifications or scientific research still allow room for uncertainties.
The call for this type of information is described in the following sections of the Directive (full text of Directive 2001/18/EC in Annex A of this report):
Annex II, D2

1. The likelihood of the GMO to become more persistent or invasive.
2. Acquired selective advantages or disadvantages.
3. Potential for gene transfer to the same or sexually compatible plant species and selective advantage or disadvantage to those species.
4. Potential immediate and/or delayed environmental impact from direct and indirect interactions of the GMO and target organisms (if applicable).
5. Ibid. with non-target organisms.
6. Possible immediate and/or delayed effects on human health from potential direct and indirect interactions.
7. Ibid. on animal health resulting from consumption of the GMO and any products derived from it.
8. Possible immediate and/or delayed effects on biogeochemical processes resulting from potential direct and indirect interactions of the GMO and target and non-target organisms in the vicinity of the GMO release.

Annex IIIB, B7

Other potential interactions, relevant to the GMO, of the plant with organisms in the ecosystem where it is usually grown, or elsewhere, including toxic effects on humans, animals and other organisms.

Annex IIIB, D

3a. Information on the developmental expression of the insert during the lifecycle of the plant and methods used for its characterisation.
3b. Parts of the plant where the insert is expressed.
6. Any change to the ability of the GMO to transfer genetic material to other organisms.
7. Information on any toxic, allergenic or other harmful effects on human health arising from the genetic modification.
8. Information on the safety of the GMO to animal health.
9. Mechanism of interactions between the GMO and target organisms.
10. Potential changes in the interactions of the GMO with non-target organisms.
11. Potential interaction with the abiotic environment.

Paragraph 2e

A plan for monitoring in accordance with Annex VII, including a proposal for the time-period of the monitoring plan.

In short, the required information that is required for safety assessments is concerned with risks of the GMO to become a weed, in changes in fitness, in

outcrossing, in effects on other organisms (both target and non-target), in effects on human or animal health, on biochemical processes in the soil and the effects of expression of the introduced gene (time and place). There has to be a realistic expectation of effects of the specific GMO (case-by-case) on certain aspects of risks to human health or the environment before more detailed information or additional studies on these aspects will have to be provided. The monitoring plan is aimed at following these and other aspects during the time the GMO is introduced into the environment and cultivated and afterwards. This type of information will be the subject of scrutiny of this report.

1.3.4 Toolbox of traditional breeding

The toolbox of traditional breeding includes all known and used techniques to improve existing varieties or to develop new varieties in crops. For this, the natural genetic variation present within the crop species itself and in related, crossable species can be mobilised and recombined. In this report the toolbox specifically refers to the techniques of introgression breeding by meiotic recombination of insertion and of mutation breeding. After introgression breeding the resulting variety carries new genetic information, either added or exchanged (substituted) in similar locations on chromosomes as in the donor, or on other locations (translocations). Genes coding for traits are actively changed in case of mutagenesis. The varieties produced in these ways resemble to a large extent certain GM crops. Recent publications have demonstrated that also in non-GM breeding lines within a crop species the genetic load can be variable, that genes can be in a different 'gene-environment' and that they can be moved around by transposons. This illustrates the existing dynamic nature of the plant genome and its importance in evolution.

1.3.5. Introgression

Introgression is defined as the movement of genes from one population into another through inter- or intraspecific hybridization followed by backcrossing with the crop species as the recurrent parent. Usually, it refers to movement of traits from one species to the crop species or among sub-species of the crop. Stable introduction of the desired traits and genes requires recombination between recipient and donor homoeologous chromosomes. This may lead to addition or substitution of genetic material. Translocation of a piece of DNA carrying the trait can be actively induced by irradiation. In this case, the donor part can be inserted at random places on whatever chromosome. In every case the end-product is a crop carrying a domesticated, new gene, coding for the trait-of-interest with linkage drag. Linkage drag is the genetic burden, i.c. undesired genes/traits that accompanied the gene-of-interest and cannot be further eliminated.

1.3.6. Genetic variation

Genetic variation is the phenotypic variability of a trait in a population attributed to genetic heterogeneity. Genetic heterogeneity is the range of gene-copies, i.c. alleles, present within a species or a set of related, intercrossable species. A specific allelic combination constitutes a genotype; expression of the specific set of alleles will lead to a specific phenotype.

1.3.7. Cisgenesis

Cisgenesis is genetic modification, in which only natural genes in sense orientation under control of their own regulatory sequences derived from the crop species itself or from related, sexually compatible species (cisgenes) are introduced. No other genes, e.g. for selection, are present in the end-product, the so-called cisgenic GM plants.

1.3.8. Facilitation of the notification procedure

The notification procedure as described in article 13 of Directive 2001/18/EC for the market introduction of GM crops requires specific information to be provided by the notifier. *Facilitation of the procedure is described within article 13 and means that under well-described conditions the notifier can refer to earlier notifications or to notifications in another context.* The facilitation mentioned in article 13 is aimed at information concerned with unintended release or misuse and with storage, handling, packaging and labelling and with monitoring and reporting, not with aspects of environmental risk assessment. In this report facilitation means that the conditions mentioned earlier are broadened and that the amount of information required is reduced, but only for specific categories of GM gene/crops combinations, as suggested in this report. This in accordance to the possibilities for derogation of Article 13 as described in Article 16 of the Directive.

2. Traditional breeding

Modern plant breeding uses many technological tools to improve existing varieties or to develop new ones. The products of the traditional breeding process, i.e. the new varieties, are all subjected to screening and selection, to rules and legislation involved in variety registration and breeder's rights, and as food products to normal food safety practice, but they are exempt of specific government notifications. To put GMO technology into perspective, a survey of technologies being actively applied at present in plant breeding and cultivar development and bearing basically resemblance in their resultant end-products to the products of genetic modification is presented below (for reviews introducing general scientific conceptions in the area of plant breeding, the reader is referred to Borojevic, 1990; Allard, 1999; Ramanna & Jacobsen, 1999 and Simmonds & Smartt, 1999. Specific examples are given in Box 1).

i) Wide crosses with distant or wild relatives followed by backcrossing with a recurrent parent leading to the addition or substitution of entire chromosomes. Selection is for the introduction of the desired traits. As a result a series of mono- or disomic addition or substitution lines can be generated. When transfer to the progeny is sufficiently high, a new cultivar is produced. Entire 'wild' chromosomes can become an integral part of the genomic constitution of the new plant product or cultivar in this way. *In short, the new variety has one or two chromosomes extra or one or two of its own chromosomes were replaced by chromosomes of another species.*

ii) Wide crosses with distant or wild relatives followed by backcrossing with a recurrent parent leading to recombination between chromosome arms (introgression). The site of recombination cannot be controlled or predicted, rendering the process rather imprecise. Selection is for the introduction of the desired traits. The result is reorganization at the chromosome level. Large pieces of the 'wild' chromosomes can become an integral part of the genomic constitution of the new plant product or cultivar. The breeder has to breed and select further to compensate for the negative traits linked to and introgressed together with the beneficial, e.g. disease resistance, genes (linkage drag). *In short, a chromosome has exchanged a part of itself with a 'sister' chromosome of the other species.*

iii) The plant products prepared through approaches i) and ii) can be subjected to further treatment, e.g. by irradiation or chemical treatment, to actively induce recombination or translocation between recipient and newly introduced chromosomes or chromosome parts. Again, the site of recombination or translocation cannot be controlled or predicted. *In short, a part of a chromosome of the other species is now integrated randomly in a chromosome of the recipient.*

iv) Mutation breeding uses radiation or chemical treatment to induce random mutations in the plant genome. The mutations will usually lead to knocking out genes and functions. Comparable to this is the use of naturally occurring moving genetic elements, such as transposons. For instance, 'waxy' maize varieties were developed using the Ac/Ds transposon system. In all these approaches, the subsequent selection is for the trait-of-interest and viability and phenotype. There is no way to predict or control the site or number of mutations induced or the effects of the accumulated mutations. Via backcrosses undesired mutations can be removed, especially when they are located on other chromosomes than the mutant allele of interest.

Box 1 Examples

i)

- Modern maize (*Zea mays*) originated from hybridization and mutual introgression between domesticated pure maize and a wild teosinte (*Zea diploperennis*) within the last 5000 years (Bird, 1996). This happened without human interference; more recently man has also used wild relatives of maize for introgression of useful traits, especially disease resistance. Teosinte and *Tripsacum dactyloides* are primarily used for this, leading to new maize varieties (Tang *et al*. 2005).
- Hexaploid triticale (AABBRR) is the result of a cross between wheat *(Triticum aestivum;* AABBDD) and rye (*Secale cereale*; RRRR). It is widely cultivated at present (Franke & Meinel, 1990). However for further improvement, triticale has been crossed with wheat in order to achieve introgression of some wheat (D-genome) characteristics in triticale (Budak *et al.* 2004).

ii)

- Sugar beet cultivars were created after introgression of part of chromosome 1 of *Beta procumbens* into *Beta vulgaris* (sugar beet) conferring resistance to beet cyst nematodes (Heijbroek *et al.* 2002).
- From a cross between *Lycopersicon esculentum* and *L.chmielewskii* followed by repeated backcrosses to *L.esculentum*, tomato lines were derived showing introgression of *L.chmielewskii* sequences in tomato chromosome 7, middle and terminal regions and in chromosome 10 terminal region affecting fruit quality during ripening (Azanza *et al*. 1994).

iii)

- Wheat has been crossed frequently with a wide range of close or more distant relatives for introduction of disease (fungal) resistance, e.g. with rye resulting in 1BL/1RS translocations where part of the wheat chromosome 1B has been exchanged with part of a rye chromosome 1R (Islam-Faridi & Mujeeb-Kazi, 1995). Also *Agropyron elongatum* has been used in crosses with wheat leading to new cultivars (e.g. cv. 'Agent' which carried a recombination in chromosome 3) (Schachermayr *et al.* 1995). Irradiation of pollen is used to actively induce translocations, e.g. in the generation of cv. 'Transfer'. The result is a random introgression of an *Agropyron* chromosome part containing the disease resistance gene and many other genes of *Agropyron*.

iv)

- In several crops cultivars were produced after induction of mutations by radiation, e.g. in Bermuda grass cv. Tifeagle (with shorter stolons) and in the common bean cv Seaway (early maturing), or by chemical treatment, e.g. in lettuce cvs. Mini-green and Ice-cube (small-sized), all resulting from a process of careful screening and selection for the trait-of-interest and maintenance of agronomic performance. A survey on the global impact of the more than 2250 varieties derived through induced mutations that have been released during the past seventy years is presented by Ahloowalia *et al.* (2004).

Multiple step or single step domestication

The above-mentioned toolbox has led to the generation of new or improved crops and cultivars and has become accepted and 'common practice' in breeding. In general, the methods of the toolbox contribute to the induction or rather the enlargement of genetic variation, an absolute requirement in modern plant breeding. However, these techniques for inducing variation do not provide the breeder with specific control over the process of modifying the genetic material of the plants with which he/she is working. In traditional breeding, introgression of a desired trait is accompanied by simultaneous transfer of a set of closely linked, mostly unknown genes, the number of which depends on the method used (from entire chromosomes carrying thousands of genes to introgressed chromosomal parts, probably still carrying dozens of genes). To reduce the number of undesired neighbouring traits, several backcrosses might be required. Molecular markers can be used to control and speed up this part of the process. However, it will not be possible to get rid of all accompanying traits by recombination (linkage drag). The process of selecting for the best possible breeding product with the least or only smaller negative side-effects of the donor material could be referred to as 'multiple step domestication'. Although in genetic modification, the insertion site still can not be controlled, the insertion process by itself still compares rather favourably with for instance mutation breeding, in which many more random mutations occur, across the entire genome or even translocations of chromosome parts. On the other hand, in traditional introgression breeding the cross-over sites determining the amount of linkage drag can also not be controlled. The GMO approach could be referred to as 'single step domestication', i.e. comparable to introgression breeding but without the linkage drag of undesired genes and by a different process for generating new variation.

Process versus product

Breeding and crop cultivation, in other words agriculture in general has been going on for thousands of years and has had and still has an enormous impact on man and the environment.

Introgression breeding adds genes to plant species by sexual hybridization on quite a different scale and to quite a different extent as takes place by hybridization in nature. Also the techniques in the toolbox of traditional breeding are not very precise. Eventually, the process by which variation is induced is not considered to be the most decisive factor, but the selection of the end-product is. Thus, the processes of increasing variation are

always followed by processes of careful screening and selection. Selection for desired traits, but also, inherently, against undesired aberrations. For some crops, in which potential risks to human health have been identified in the past, the normal process of having cultivars registered encompasses specific trials and tests ensuring that only 'safe' cultivars reach the market, e.g. in potato where the content of toxic solanidine glycosides is checked. So far, with a history of 200 years in plant breeding applying the customary company or governmental rules or practices, undesired side-effects in cultivating such varieties have been encountered so rarely that is was never deemed necessary to have additional environmental safety assessments. Both techniques and end-products of traditional, non-GMO breeding are accepted by society and consumers. In GM crops, on the other hand, the emphasis seems to be more on the process by which they are produced, i.e. genetic modification, and not primarily on the end-product.

Genome dynamics

In addition, the following recent scientific publications have significant relevance in the comparison of the end-situation of traditional breeding versus molecular breeding by genetic modification, especially with cisgenes. A molecular comparison of allelic chromosomal regions of two maize inbred lines (both **non**-GMO) showed that more than 50% of the 2.8 million basepairs checked was not colinear, i.e. differed between the two lines. The differences are due to the presence of long terminal repeat (LTR)-retrotransposons that occur naturally in maize and other plants. It was concluded that these retroelement insertions frequently create a different sequence environment adjacent to genes (Brunner et al. 2005). Lai *et al.* (2005) describe their discovery of eukaryotic transposons, so-called Helitrons. These Helitrons are responsible for movement of genes or gene fragments, thus violating genetic colinearity intraspecifically, i.e. within maize inbred lines. The ability to move genes around the genome confers a potential role to these transposable elements in gene evolution. Hence, changes in 'gene-environment', relevant in considering the role of the insertion site in GM, are a phenomenon that is shared between GMO and non-GMO crops and does not present a difference between the two breeding techniques. Most importantly, the GMO end-products obviously are subjected to the same process of selection and scrutiny as traditional plant breeding products before reaching the market.

Conclusion

Traditional breeding is aimed at exploiting existing or new genetic variation. New genetic variation is actively induced in an undirected fashion by techniques present in the toolbox. End-products carry new, rearranged or altered (mutated) genetic information. Selection of plants best adapted to societal requirements is the essential part of the entire procedure of development and marketing of varieties. Technologies and products are generally accepted and have a long history of safe use, both with respect to human and animal health as well as with respect to the environment. Many examples of cultivars obtained through traditional breeding techniques (as end-products) resemble quite strongly some GM varieties, i.c. the cisgenic GM crops (as end-products; see chapter 5). Therefore, it is suggested that traditional breeding serves as the benchmark to which GM crops should be compared.

3. Short history of GM crop development and cultivation

In 1984, it was demonstrated that the soil bacterium *Agrobacterium tumefaciens* could be used to transfer foreign genes into plant cells and to get them integrated into the recipient's genome. This opened the way for the genetic modification of plants. Earlier on, this had already been possible in bacteria and animal cells. The first genes introduced in plants by *Agrobacterium* were recombinant genes consisting of promoter (5' upstream regulatory) sequences from (Agro)bacterial or viral (cauliflower mosaic virus) origin and coding regions from bacterial origin encoding selectable marker genes, mostly antibiotic resistance genes. After the identification of a reporter gene, easily detectable by histochemistry, the focus of plant biotechnological efforts was on the development of transformation protocols in a great variety of plant species. In the early 1990's many plant species had been found amenable to gene uptake, either directly by e.g. particle bombardment or by *Agrobacterium*; and thus, selection and reporter genes had been introduced in a large number of plant species. So, the potential was there to take it further and to aim at important economical traits.

In 1994 the first GM crop, the Flavr Savr™ tomato, was put on the market by Calgene. The tomato was genetically modified to extend its shelf-life and it was received favourably, even enthusiastically by the public. Eventually, it did not succeed in becoming a commercial success largely because the starting cultivar (the recipient) suffered from a poor field performance. From 1996 onwards more and more GM crops were placed on the market for cultivation and production. In 1996 the cultivation area was 1.7 million hectares and in 2004 this area had increased up to 81.0 million hectares with countries as China, India, Brazil and South Africa showing the largest growth percentages. The main crops are cotton, maize, soybean and canola and the traits introduced are herbicide tolerance and insect resistance (James, 2004). The GM plants as or in products are widely used in food and feed.

At present, after ten years of global growing, processing and consuming plants of GM varieties as or in products, released by the appropriate governments, no verifiable record has been published on major, irreversible adverse effects on human and animal health or on the many different environment types that have been exposed to them based upon the diverse, global nature of the cultivation area (James, 2004). GM-crops carry genes that have been checked and tested extensively, before approval, by governmental bodies. Most of the GM crops grown world-wide nowadays have been subjected to scrutiny by US government bodies, such as the USDA and EPA, for safety aspects for human health and environment and have been approved and adopted. Many of the countries in which they are grown or imported have their own regulatory and monitoring procedures for safety to human and animal health and the environment, as does the European Union with its Directive 2001/18/EC.

With Directive 2001/18/EC the EU has made provisions for the deliberate release in the environment of GM crops. The Directive consists of three parts, part A contains the general provisions, part B is concerned with the deliberate

release of GMOs ‘for any other purpose than for placing on the market’, e.g. field trials and part C focuses on placing on the market of GMOs. This could be for cultivation, importation or processing. The provisions for part C encompass a series of environmental risk assessments as explained in chapter 1. Under Directive 2001/18/EC up till now three crops/events are authorised to enter the EU, the NK603 maize tolerant to glyphosate herbicide, the MON863 maize resistant to insects and recently GT73, an herbicide tolerant oilseed rape. Their use is confined to import and use in feed or industrial processing. Although up till now no GM crop has been authorised for cultivation in the EU under 2001/18/EC, several notifications are pending involving crops such as potato, oilseed rape and maize. Under Council Directive 90/220/EEC which preceded 2001/18/EC cultivation of two crops, oilseed rape and maize, was permitted. E.g. since 1998 in Spain on an area of 20.000 to 25.000 ha a GM maize line of Syngenta (Bt176) has been grown commercially for several years in a row, now. The cultivation opened opportunities to monitor agronomic performance of this specific GM crop/gene combination (event) in Europe, its resistance to the corn borer (insect pest) in areas with severe pest problems and the level of outcrossing and the likelihood of co-existence problems. Hence, it combined commercial production and an experimental trial. As said, the trial was aimed at examining the gene flow between co-existing GM and non-GM maize, an important societal aspect. This specific GM-event concerns as gene-crop combination maize and the Bt gene, coding for the *Cry1A(b)* insecticidal protein derived from *Bacillus thuringiensis* strain *kurstaki* and as the selectable marker the *pat* gene from *Streptomyces hygroscopicus*. The conclusions of this trial and case-study are that co-existence is possible and that the likelihood of problems arising in the future is limited, meaning that gene-flow is limited and manageable (Brookes and Barfoot, 2003). However, it is important to keep in mind that within the risk-assessment of Directive 2001/18/EC the emphasis is not on whether outcrossing can or cannot occur, but on the environmental impact of the gene-flow (case-by-case, i.e. for every event) working from the assumption that it will take place.

Still, with this the EU is in the process of establishing its own history of experience in the cultivation of GM events and monitoring environmental risk aspects, albeit at a very small scale. Up till now, EU and Spanish competent authorities saw no appreciable environmental risks for this particular GM crop event. For other events, field trials are being conducted in several European countries, contributing in this way to building up experience on potential environmental risks within Europe itself.

Based on the track record now after several years of safe cultivation in the USA without any extraordinary observations, the US authorities have defined a specific status which has been granted to some of the GM events, leading to attenuated regulations; the latter as an example of possibilities for a relaxation of implementation of rules. Re-evaluation of GM crops/events with the aim to facilitate the notification procedure is, therefore, not unprecedented and, as stated earlier, is the aim of this report as well.

Conclusion

There is ten years of experience with commercial, large-scale cultivation of GM crops in a great variety of different environments globally. So far, no adverse effects have been reported, hence, the specific GM varieties (events) concerned can be regarded as safe both for human and animal health as well as for the environment. Within the EU there is no large-scale cultivation of GM crops; however, field trials are being performed. So far in the EU, expertise build-up is rather slow and the general public is still hesitant in accepting the scientific claims that no harmful effects of GM crop cultivation are to be expected.

4. Short survey of ecological studies on GM biosafety

Aspects of the environmental risk assessment as required in the notification procedure for market introductions of GM crops of Directive 2001/18/EC entail:
a) weediness and invasiveness
b) outcrossing
c) horizontal gene transfer
d) effects on (non)-target organisms
e) effects on human and animal health and
f) effects on biogeochemical processes.
The above-mentioned aspects represent the culmination of perceived potential risks for the environment as formulated by scientists, non-governmental organizations and governments. Concerns that have been expressed in the past 25 years with respect to the cultivation of GM crops are related to one or more of these aspects. It is important to stress, once again, that only detailed information or additional studies will be required under the Directive when there is a reasonable chance or expectation that the specific genetic modification will have an impact on one of the above-mentioned aspects.
The reader is referred to the article of Conner *et al*. (2003) which gives a thorough overview of all aspects of ecological risk assessment of GM crops based on carefully screening more than 250 scientific publications.

a) Weediness or invasiveness of GM crops.

In general, the rule applies that the longer the domestication period of a crop, the less able it is to escape and revert to weediness (Zeven & De Wet, 1982). Many of the characteristics responsible for a weedy nature have been selected against and have disappeared from modern varieties. Since the weedy nature is made up of many different traits, such as seed dormancy, phenotypic plasticity, indeterminate growth, continuous flowering and seed production and dispersal (Baker 1965, 1974), a relatively simple genetic modification with well-characterized, 'non-weediness' genes cannot lead to reversion. Because of its relatively recent development into a crop oilseed rape is considered a model crop for studying aspects of weediness and the potential for reversion. Also, the availability of GM oilseed rape lines contributes to its usefulness as a research object in this. A comprehensive study comparing non-GM and GM lines in four crops (oilseed rape, maize, sugar beet and potato) found no evidence for increased invasiveness or persistence of the GM lines over their non-GM counterparts (Crawley *et al*. 2001). The modifications in the GM lines studied here were aimed at conferring herbicide tolerance or insect resistance, traits that could potentially have an (positive) impact on fitness and persistence. Although there is no evidence so far in scientific literature for increased risks for weediness in GM crops or in related wild species after gene-flow from GM crops (see next paragraph) there is a public concern about the emergence of 'superweeds' as a result of genetic modification, especially after the introduction in separate events of tolerance to different herbicides. Combination within one crop after outcrossing of tolerance to several herbicides would create a plant that would be hard to kill, i.c. a superweed. In 2001 it was reported in the popular press, e.g. the Guardian and the Sunday Times that Canadian farmers

did find oilseed rape volunteers that showed tolerance to three herbicides. Subsequently, the farmers had to resort to other, less environmentally friendly chemicals in order to get rid of those plants. The circumstances were rather special in that three GM oilseed rape varieties were grown in an area at close distances to each other, where all three herbicides were applied. Also, the same phenomenon could occur with herbicide-tolerant varieties that are produced by traditional breeding after out-crossing. Nevertheless, it will be clear that with traits like this, careful crop and herbicide management in cultivation are necessary.

b) Outcrossing

Gene flow between crop and wild relatives has been shown to occur in many crop species worldwide (Ellstrand 2003). During the last fifteen years, many reports have appeared on gene flow in diverse crops, such as Brassicas, maize, beet, and grasses (for recent reviews, Van de Wiel et al. 2003, Jenczewski et al 2003). As an GM example the reader is referred to a DEFRA (Department for Environment, Food and Rural Affairs, UK) report in which outcrossing was monitored from herbicide tolerant GM oilseed rape to wild relatives (Daniels *et al.,* 2005). 95459 Seedlings of wild relatives collected in or near the oilseed rape fields were tested and 2 *Brassica rapa* plants proved tolerant. In the following year wild relatives were tested by applying herbicide and a single plant of *Sinapis arvensis* (charlock) showed no reaction and proved to contain the transgene. Such a hybrid between oilseed rape and *S. arvensis* had never been found before. The seeds obtained from this individual did not germinate. The effect on fitness of the transfer to charlock of the transgene could not be assessed in this study but is presumed to be negligible (Hails & Morley, 2005). Still, the fact that outcrossing between oilseed rape and charlock did occur, although perceived to be an extremely rare event, did cause some concern (P. Brown, environment correspondent, The Guardian, 25 July 2005; www.guardian.co.uk/gmdebate/story/0,2763,1535428,00.html). It is important to keep in mind that such a hybrid can persist only if it has obtained a selective advantage. This is not the case in areas, e.g. outside cultivation fields, where no herbicides are applied.

On the other hand, relatively little has been published yet about effects of introgression of transgenes on natural populations. The few studies testing experimentally the effects of a transgene on fitness traits have shown different results, encompassing negative, neutral as well as positive effects depending on the transgene/genotype combination (the event). Recently, the first report on effects of a transgene in a natural setting, in the USA, was published by Snow et al. (2003): backcrossed wild sunflowers containing a Bt transgene showed decreased herbivory and so a higher seed set in a natural setting, which would give them a competitive advantage and increased fitness. It remains to be tested by further monitoring whether this also leads to a predominance of wild sunflower plants carrying the Bt transgene in the natural population in the long term. In this regard, there is also little knowledge about the frame of reference for assessment, that is, the influence that introgression from traditional crops may already have had on wild populations. Until the GM era, little interest existed for this phenomenon and generally no negative effects were perceived. Up till now, only a few reports are available and they have indicated significant effects of gene flow from traditional crops: swamping of wild *Medicago falcata* by cultivated alfalfa in Switzerland (Rufener Al Mazyad & Ammann 1999) and the

origin of the noxious weed *Sorghum halepense* was sought in introgression from cultivated *Sorghum bicolor* (Ellstrand et al. 1999). Also, reconstructing introgression between crop and wild forms in the recent past has not always proven to be straightforward (Van de Wiel 2003). In summary, outcrossing can occur in some crops and depending on the gene introduced it can have an impact on fitness to some extent. Also effects on non-target organisms or on the soil can be envisaged, resulting from outcrossing. However, this is not inherent to the technique of genetic modification; it can also occur through gene transfer from traditional cultivars to wild relatives.

c) Horizontal gene transfer

Horizontal gene transfer is quite common among bacteria and a source for genome variation (Ochman *et al*. 2000) involving plasmids and transposons. As stated earlier also in higher plants (as well as in humans), genome variation can be induced by the presence and movement of transposons of both prokaryotic and eukaryotic origin (Brunner *et al.* 2005; Lai *et al.* 2005). A reason for concern is when genes will be transferred from crops to e.g. bacteria and cause harm. In general, a plant contains 30,000 to 40,000 genes of its own; a GM variety will contain one to several (2 to 6) additional genes. Integration of plant genes in genomes of organisms eating them in one way or the other is a very unlikely event. There has been no reason up till now to examine the occurrence of this phenomenon, except in cases of potential transfer of specific genes to pathogenic organisms such as bacteria, fungi or viruses. However, several studies failed to demonstrate horizontal gene transfer from plants to bacteria (a.o. Bertolla & Simonet, 1999; Nielsen *et al*. 1998). Only using marker-rescue experiments with antibiotic resistance genes, artificially introduced homologous stretches of DNA and selection pressure the kanamycin gene from GM maize could be retrieved in an *Actinobacter* strain (De Vries & Wackernagel, 1998). Frequencies are very low, also in transfer to fungi (Hoffmann *et al.* 1994) or viruses (Tepfer, 1993). A prerequisite is a clear selective advantage for the recipient organism (Faber & Van Elsas, 2005). Present-day GM crops do not carry the appropriate promoters/genes combinations to confer a selective advantage. An additional consideration is whether a gene after horizontal gene transfer is likely to lead to harmful effects, e.g. the kanamycin resistance gene could constitute a selective advantage in a surrounding where specific antibiotics (kanamycin, neomycin) are used. However, the gene has been carefully checked and is considered safe, also in this respect (Nap *et al.* 1992).

d) Effects on (non-)target organisms

With respect to this item, one could pose a simplified model of two sets of GM crops. First there are the GM crops modified in order to have an increased resistance against pathogen attack, and second there are the GM crops modified for any other purpose. In the first category, the pathogen against which the introduced gene is meant to provide an increased level of resistance is the target organism. Per definition the GM crop will have an effect on this organism. The goal of the modification is to lower disease pressure by the specific pathogen in the areas of cultivation, either by killing the organism or by reducing the effectiveness of its reproduction. In the end, this will mean that that particular pest organism will disappear from those areas. In many cases, this will not be regarded as a negative effect, comparable to the eradication of the smallpox virus (Arita, 1999). On the other hand, it is not likely to occur because resistance

systems are rarely 100% effective over a prolonged period of time and refugees will be able to maintain themselves in niches where no resistance is present in the host species. The complexity of the host and non-host plant pathogen interactions and the evolutionary potential of the pathogen populations are not fully understood yet, but they do play an important role in ensuring the maintenance of viable pathogen populations (Heath, 2000; Odjakova & Hadjiivanova, 2001; McDonald & Linde, 2002).

All effects of introduced resistance genes on organisms other than the target organism or of genes aimed at other properties on any organism can be considered as effects on non-target organisms and as such are always unintended. They represent the second set of GM crops in the simplified model. An important factor in this is the specificity of the action of the gene product. Two main categories of effects can be identified, i.e. direct or indirect. A direct negative (e.g. toxic) effect on non-target organisms can be the result of the action spectrum of the resistance gene product being broader than the intended plant pathogen. When this is the case with viruses, bacteria or fungi, there does not seem to be much reason for concern, because of refuges being always present and because of the great population dynamics and large evolutionary potential of these types of organisms (McDonald & Linde, 2002). Concern is there when organism classes have beneficial representatives in addition to the well-known negative ones. Examples that can be given are mycorrhiza as beneficial fungi and butterflies and bees as beneficial representatives of insects. Caterpillars of specific butterflies can be a severe problem in agriculture and usually chemicals are used to control them. Introduction of the well-known Bt gene is aimed at controlling Lepidopteran insects such as the European corn borer and it is working very well. It was reported that in a laboratory experiment pollen of Bt maize caused the death of Monarch butterfly caterpillars (another Lepidoptera member) when this Bt pollen was fed to them (Losey *et al*. 1999). However, further experimentation and scrutiny of the results and setup proved that the observed effect was in no way representative for the actual field situation (for overview, see Conner *et al.* 2003).

Another ecologically important, beneficial insect is the honey bee. It is highly dependent on plant products, such as pollen and honey, for its life-cycle. When introducing e.g. protease inhibitor genes aimed at conferring resistance to insects as aphids or thrips, impact on honey bees is not intended and desired. This aspect has been studied thoroughly and so far, no evidence has been found either for direct toxicity or for indirect characteristics, e.g. colony performance (Malone and Pham-Delègue, 2001) or learning ability (Girard *et al.* 1998; Jouanin *et al*. 1998).

The so-called multitrophic interactions are more complex and therefore more complicated to evaluate at present and present an example of indirect effects. With this predators or parasites feeding or parasitizing on e.g. insects feeding on GM plants are meant. When direct toxicity is not an issue, e.g. in the case of Bt toxins (Glare and O'Callaghan, 2000), impacts could be indirect through reduced levels of food quantity or quality that are available. In the interaction between aphids and their predator, the two-spot ladybird, retarded development and extended pupation time proved to be attributable to the reduced weight of the aphids reared on GM potatoes (Down *et al.* 2000). Similar effects on prey quality and quantity is seen in common agricultural practice using spraying of chemicals against aphids.

Beneficial side-effects of the cultivation of GM crops have been documented as well, e.g. GM crops less affected by insects carry significantly less mycotoxins and are thus healthier in animal feed (see Conner *et al.* 2003; and next paragraph).
This means that in any new interaction between an organism and a gene-product that could potentially occur due to the genetic modification (case-by-case) and wasn't possible previously uncertainties exist on the character of the impact and additional studies are required.

e) Effects on human and animal health

Food safety of any product is a primary concern of the general public and this is particularly true for GM food and feed products. Although perhaps not really an environmental issue, information on this topic is part of the notification procedure under Directive 2001/18/EC and of great importance in the ongoing debate on GM. So far, with years of world-wide cultivation on a large area of several different GM crops no adverse effects on human and animal health have been documented (see paragraph 2.1). A study on rats fed with glyphosate-tolerant soybean meal to levels of up to 90% of their diet showed no negative effects, i.e. no deaths, no differences in necropsy findings, haematological or urinalysis values or in clinical serum parameters (Zhu *et al.* 2004). Aumaitre (2004) has published an overview of the scientific results presented in original reviewed journals as full papers (33) or abstracts (33) of studies on the performance and safety of several GM crops in animal feed. Parameters such as feed intake, weight gain, milk yield, nutritional equivalence, body and carcass composition, animal health, physiology and survival (among others) were checked and the recovery of recombinant DNA from milk, liver, spleen and muscle tissues. No effect and no recovery were observed.

However, controversy exists. This can be demonstrated by the findings of Ewen and Pusztai in 1999, which fuelled concerns and debate in the press. They reported negative biological effects in rats, e.g. on the small intestine and immune function, after feeding them GM potatoes. The validity of the report was subsequently strongly questioned and rejected by the scientific community, as exemplified by the review of the Royal Society (1999). A more recent example is the discussion, both in the public domain as well as among separate EU member states triggered by the pending authorisation by the European Commission of GM oilseed rape GT73 (granted 31 August 2005). In the notification dossier Monsanto, producer of GT73, describes animal feeding tests on rat, rainbow trout and quail. Three tests were performed with rats. The first two showed a small, but significant increase in relative liver weights, but no gross pathological changes. The third one, a comprehensive study with GT73 and 8 other varieties, showed variation in liver weights among the 8 non-GM varieties. The liver weights of the GT73 groups fell within range of the responses for the different controls. NGOs, such as Greenpeace, emphasize the importance of the aberrations as they see it, that were found in studies 1 and 2, ignoring study 3 while Monsanto stresses the inadequate setup of the first two studies and highlights the outcome of study 3. The EFSA (European Food Safety Authority, responsible for the scientific assessment of genetically modified food and feed) in its final evaluation report of GT73 was of the opinion that GT73 is as safe as traditional oilseed rape and unlikely to have an adverse effect on animal health (EFSA Journal, 2004). This did not put an end to the discussions, yet.

It will be clear that all of this is very confusing to the public or consumer, who will find it difficult to decide who they can or should believe with respect to these health trials? Important for this kind of trials is to ensure a comprehensive study with the appropriate experimental setup including all the necessary controls with consensus of the scientific community and food safety authorities.

f) Effects on biogeochemical processes

The knowledge about our soils and about everything living in it is still very scarce and the soil can be regarded as a black box. Many organisms inhabit the soil. In Canadian rainforest soil one cubic metre contains 2000 earthworms, 40.000 insects, 120.000 mites, 120.000.000 nematodes and billions of protozoa and bacteria representing more than 10.000 species of the latter (C. Batycki, David Suzuki Foundation, Canada). It is clear that we cannot fully comprehend all potential interactions between these organisms or with plants, plant parts or plants exudates. The impact on soil biology of the modern-day way of cultivating crops (non-GM) is very large. It is unclear whether the effect of GM crops with respect to the overall cultivation effect is very significant (Kowalchuk *et al.* 2003). Leaf shedding, root exudates and decomposition of cells or parts from GM plants could very well have an effect on the direct surrounding area and its inhabitants. When introduced resistance genes are directed towards bacteria or fungi, they are bound to also have potentially an effect on soil-borne non-target bacteria or fungi. It is clearly not possible to check all, but there have been studies in which a specific set of organisms has been monitored. Depending on the introduced gene, effects on mycorrhiza were or were not observed. Soil composition appeared to have an effect on the efficiency of breaking down antimicrobial proteins (Glandorf *et al.* 1997). Using different molecular fingerprinting techniques differences in bacterial rhizosphere diversity were found between one non-GM potato variety and another non-GM potato variety in Pseudomonades, but also between the second non-GM variety and its GM counterpart. No differences were found between all lines for fungal rhizosphere diversity (Milling *et al.* 2004). Shirai (2004) reviewed the effects of GM crops on non-target arthropods in the scientific literature and could not find any deleterious effects. The cultivation for more than ten years now in an ever increasing area do not present any evidence or indication that effects if any on soil microflora do have a persistent and deleterious character. Indications could be that consecutive (non)-GM crops would perform less than optimal because of a non-reversible decline in beneficial (symbiotic) micro-organisms. Of course, the latter evidence is purely circumstantial.

Also here, it is clear that due to the genetic modification a new interaction between a gene-product and the soil (microflora [=bio] and geochemical constituents) could potentially occur, that wasn't possible previously. In such cases uncertainties exist on the character of the impact and additional studies in risk assessment are required.

Conclusion

Ecological studies with GM crops have been carried out covering several aspects of environmental risk assessment. However, it is important to realize that these studies have been performed with only a small number of specific GM events and per event not for the full range of ecological aspects. So far, the information that became available does not provide grounds for concerns. Generally, it can be concluded that uncertainties can and have been identified for some of the aspects of potential environmental risks and that this holds particularly for new interactions between gene-products and the environment. The latter is important for later considerations in this report. The notification procedure of Directive 2001/18/EC is adequately equipped to handle these new situations.

5. New developments in plant biotechnology

Plant genomics

At the onset of GM crop development, there was a great lack of suitable genes, especially from plants. This explains the fact that after the first Flavr Savr™ tomato, which was equipped with an antisense sequence from a tomato gene combined with an antibiotic resistance gene of bacterial origin, the next generation of GM crops carried almost exclusively genes of bacterial or fungal origin, such as glyphosate tolerance (EPSPS gene from *Agrobacterium)*, glufosinate tolerance (*pat* gene from *Streptomyces*) or insect resistance (Bt genes from *Bacillus thuringiensis*).
Recent developments in genome research are very significant at this moment. Modern molecular biology tools for plant gene isolation, the availability of mutants and the now established way to introduce them in many different plant species for gene function analyses, have enabled many scientific and industrial research groups to identify useful plant genes, encoding interesting traits. Especially, the large genome sequencing initiatives, in which the entire genomes of *Arabidopsis thaliana* (thale crest; The Arabidopsis Initiative, 2000), and *Oryza sativa* (rice; Yu *et al.,* 2002; Goff *et al.* 2002), have been sequenced, gave a boost to plant gene identification.

Through so-called comparative and functional genomics, the knowledge on plant genes and plant gene functions has increased vastly, as has the availability of the plant genes, such as those involved in agronomic performance or disease resistance. This is also true for the knowledge on and availability of plant regulatory sequences (promoters) allowing the regulation of gene expression in place, time and upon external signals (e.g. pathogen attack). This provides the possibility to develop GM plants carrying only plant-derived genes and plant-derived regulatory sequences. Nowadays, modern technologies also enable the removal or avoidance of genes that are not necessary in the end-product, e.g. selectable marker genes of any origin (Krens *et al.*, 2004). Depending on the method of introduction and removal of undesired genes or sequences some stretches of non-plant DNA can remain present in the so-called 'clean' end-product (Schaart *et al.,* 2004). However, it is important to note that those stretches are very limited in size and they are not in any way biologically active; they cannot lead to RNA and protein, nor to a phenotype.

Cisgenic GM crops

With the increased efficiency of plant gene isolation, it has become possible to transform plant varieties with genes in sense orientation derived from the same or closely related species, equipped with their natural expression signals and without any other genes, the cisgenic GM plants. The advantage of such an approach would be a more efficient introgression of desirable traits relative to classical backcrossing schemes. At the same time, the end result would not differ from traditional introgression methods in the sense that basically the same genes are used. Thus, it can be argued that these genes, together with the customary screening and selection steps, represent a no-risk category comparable to that of traditional breeding, with the additional advantage of avoiding linkage drag. In this respect, one could also refer to the part of the definition of a GMO in Directive 2001/18/EC where it is stated that

GM organisms produced by cell fusion of plant cells from organisms which can exchange genetic material through traditional breeding methods are to be excluded from the Directive. In principle with respect to their potential environmental impact, those genes have already undergone so to speak "evolutionary testing" in a homologous context, that is, they can be expected to have been present and exchanged within the wild species complex encompassing the cross-compatible crop for longer periods of time. Therefore, the (molecular) breeding process essentially does not extend their natural reach. The only caveat is that their working field may now be extended, since their introduction into the crop may be accompanied by a wider geographic spread than through natural means. This, however, also applies to traditional introgression breeding.

Because cisgenic crops are produced by genetic modification, important features to consider being potentially different from traditionally bred hybrids are the copy number of the inserted cisgenes and the effects that the insertion might have had.

Molecular characterization of the cisgenic GM plants produced enables to select for those individuals carrying a single insert, hence only one copy. It can be envisaged that the best performing cisgenic event is one carrying multiple inserted copies. Breeding companies could be inclined to continue with variety development with those best-performing, multiple insert individuals. This should not necessarily present a problem because also in traditional breeding, varieties with improved quality traits can be the result of crosses combining more than one beneficial allele or gene. Both situations, cisgenic and traditional, are at least comparable and sometimes even quite similar. The same holds for the effects of the insertion event. This can lead to knocking-out of a resident gene, when present at that particular site, or it could induce rearrangements in the DNA (Kumar & Fladung, 2002; Forsbach *et al.*, 2003). Knock-outs are produced in traditional breeding by spontaneous or induced mutations as are rearrangements and translocations (see chapter 2). The natural or induced activity of retrotransposons also can lead to rearrangements and mutations (Brunner *et al.,* 2005; Lai *et al.,* 2005). Again, cisgenic GM varieties obtained after screening and selection can be considered similar to the end-products of some widely-accepted, traditional breeding techniques.

Conclusion

More and more plant genes are becoming available together with their own natural expression signals. No novel environmental risks are to be expected when plant genes are introduced in plant species which can exchange genetic material through traditional breeding, i.e. by cisgenesis. In this case, there are no new situations, no new confrontations between gene-products and the environment. The cisgenic GM crops are comparable or similar to products of traditional breeding. This should have consequences for the extent of information required on environmental risk assessments.

The conclusions of chapters 2 – 5 represent the arguments to identify specific classes of GM crops and to suggest facilitation of the execution of certain safety analyses of Directive 2001/18/EC (see next chapter).

6. A classification model

Based on considerations discussed extensively in the previous chapters, being:

- End-products of traditional breeding may carry new, rearranged or altered (mutated) genetic information.
- Traditional breeding products are not extensively characterized at the molecular level.
- Hybridizations by crossing in traditional breeding is taking place at a much more extended scale as compared to hybridizations occurring in nature.
- Traditional breeding is safe.
- Known approved and adopted, cultivated GM crop events can be regarded as safe.
- No environmental risks have been reported up till now for specific GM crop events, however for new combinations of genes and plant crop species uncertainties remain and cautiousness is prudent.
- Cisgenic GM crops are comparable or similar to specific traditional breeding products, at the level of genome organization as well as at the level of interactions between crops and environment.

a classification model of GM-crops is presented. It encompasses 3 categories, two of which are amenable to facilitation of the information requirements for the notification procedure as described in article 13 of Directive 2001/18/EC for market introduction of GM crops.

Category 1) *All GM crops, except for the ones falling in categories 2 and 3.*

This category encompasses all GM crops carrying genes and promoters from any source, in general. This category represents the rule. Notifiers will comply with the full requirements of article 13 of Directive 2001/18/EC for releasing this type of GM crops into the environment for cultivation and introduction on the market. The exceptions to this rule are the GM crops exempted in article 3 of the Directive that are made using techniques listed in Annex 1 B of the Directive and the GM crops defined in categories 2 and 3 below. Annex 1 B refers to GM crops made by mutagenesis and cell fusion 'of plant cells of organisms which can exchange genetic material through traditional breeding methods'.

Category 2) *GM crop/gene combinations for which insertion events have already been approved by the appropriate European authorities.*

The European authorities have allowed import of several GM crops for food, feed and ornamental purposes based on their own Regulations and Directives. Other GM crop notifications are pending and awaiting authorisation by the EU for cultivation under Directive 2001/18/EC. The complete information package required under this Directive has been submitted in these cases. All these crops are being subjected to careful scrutiny and monitoring. When cultivation is authorised and crops are grown, experience can be obtained on aspects of human and animal health and of environmental risks for particular, approved crop/gene combinations. Whenever no adverse effects are found and they can be regarded as safe, future events presenting a similar crop/gene combination could be subjected to an attenuated procedure. In fact, Directive

2001/18/EC, article 13 paragraphs 2, 3 and 4 already provides means to facilitate the notification procedure for "part or all of the information required in Annex IV, section B" and all other relevant information. The notifier can refer to data from previous releases of the same GMO either inside or outside the European Community. He can also refer to relevant data submitted by other notifiers. Annex IVB is concerned with information on measures to take in case of unintended release, recommendations for storage and handling, monitoring etc. not at environmental risk assessments.

In the evaluation of a notification with respect to the environmental risk assessment the recipient species, the introduced gene(s) and the new transgene/species combination are being checked for several aspects (see chapters 1 and 4). New events in which the same gene cassette (i.e. coding regions and regulatory sequences) has been introduced into the same species, but in a different variety or breeding line, or even into the same variety or line but resulting from a transformation event separate from the first one, do not present new cases with respect to the environmental risks. The genomic variability expected among this type of new events in similar crop/gene combination is generally not greater than among non-GM varieties (Lehesranta *et al.*, 2005). As demonstrated in chapter 2, the genetic variability and the dynamics of the genome in plants can be very large in its own, exemplified in maize inbred lines by the action of endogenous transposons (Lai *et al*. 2005; Brunner *et al*. 2005). Against this background it is argued that new events within the same crop/gene combination can be exempt in the notification procedure from providing the information requested under article 13, paragraph 2a, Annex III section B7 and sections D6-11; Annex IVB (see above); paragraph 2b, Annex II section D2. The information requested in these articles, paragraphs or annexes (see chapter 1) is concerned with expression of the introduced gene and with the different aspects of environmental risk assessment as mentioned earlier, a.o. weediness, outcrossing, horizontal gene transfer, effects on (non)-target organisms, effects on human and animal health, and effects on biogeochemical processes in the soil.

Category 3) *GM crops carrying natural genes with their own promoters derived from plant species which can exchange genetic material through traditional breeding methods (=cisgenesis).*

The exchange of genetic material through traditional breeding methods means, that gene transfer can occur naturally, and that the environment, also of the recipient species, could already have been exposed to such genes, or rather the gene products, of the donor species. The GM situation basically does not differ from the situation attainable by traditional breeding. The delimitation for this category is in line with the one set for GM organisms generated by cell or protoplast fusion that are excluded from Directive 2001/18/EC as defined in Annex 1B (see Category 1). Because of the definition of this category refers to traditional breeding, the products of traditional breeding are the frame of reference with which to compare this type of GM crops, also with respect to environmental risks assessments. As mentioned earlier, traditional breeding can be considered as a multistep domestication process in a cultivated crop of genes and traits derived from related species. For this several backcrosses with the recurrent parent are required aimed at keeping the trait of interest and getting rid of undesired genes and traits of the related species used (linkage drag). Extending the toolbox of traditional breeding in facilitating this domestication

process leads naturally to surgically taking only the gene-of-interest from a related species and introducing it into the recipient by single-step domestication or genetic modification.

When genetic material from organisms that can exchange it through traditional breeding, is used in cisgenesis, no larger risk of becoming weeds or more invasive plants exists for GM crops of this category as compared to crops generated through natural hybridization. As stated before, weediness is a multigene trait, the species from which the gene-of-interest is taken is known, the trait-of-interest is known and characterised, also genetically, and the benchmark is known. The genes have already undergone “evolutionary testing” in a homologous context.

Outcrossing occurs, but it also occurs already without genetic modification. Outcrossing in itself is not considered a risk, it is the specific gene and the effect of its expression on the environment in the newly created situation. Here, the gene-of-interest has the possibility to move around naturally; it is already present in the environment naturally and not solely because of the GM crop. There is no new situation (see also the conclusion of chapter 4).

Effects on both target as wells as non-target organisms will not be different with the cisgenic GM crops from the effects of crops generated by breeding.

The same holds for the effects on human and animal health and on biogeochemical processes.

Genes in their own, original genomic location can show fluctuations and differences in expression level (Madlung & Comai, 2004). The expression level of the genes in cisgenic GM crops will be in the same range as the expression levels observed in the donor because the genes remained combined with their own, original promoters.

In view of all this it is argued that new GM events, where the introduced genes with their own promoters have been derived from donor plant species with which the recipient species can exchange genetic material through traditional breeding methods, can be exempt in the notification procedure from the information requested under article 13, paragraph 2a, Annex III section B7 and sections D6-11; Annex IVB (see above); paragraph 2b, Annex II section D2.

It will be clear that this classification model is meant to be a dynamic one. Once sufficient experience has been acquired in time with particular genes and traits – crop combinations, these cases in general can be shifted from category 1 to the next level of assessment, i.e. category 2 with its subsequent attenuated procedure.

Some examples of applying the suggested classification model to GM crops, potentially up for introduction to the market in the EU in the near future.

Box 2:

- a GM potato variety, *Solanum tuberosum,* carrying as introduced natural gene a *Phytophthora* resistance gene, R3 or Rpi-blb1, from *Solanum demissum* or *Solanum bulbocastanum,* respectively, under control of their own promoter. It carries no other, superfluous gene sequences (is selection marker-free). Gene transfer through traditional breeding methods is possible between both wild *Solanum* species and the crop. This has in fact been done and varieties are on the market; hence this GM potato variety is a cisgenic variety and as such would fall in category 3.
- When the same GM potato does carry the selectable marker gene, *npt*II, which is approved and regarded as safe, it still presents a new gene/crop combination and, therefore, would fall in category 1. After the full evaluation of the first notification of such a gene (*npt*II)/crop (potato) combination the next series of GM potatoes carrying cisgenes and the *npt*II gene could be transferred to category 2.
- When in a GM potato the aforementioned genes are combined with other promoters, plant-derived or non-plant-derived, with or without a selectable marker gene, this GM potato would fall in category 1.

7. Concluding remarks

In Europe, there are two sets of standardized procedures for allowing new crops or cultivars on the market. On the one hand, these are the rules and regulations for plant crops as or in products that are the result of modern, yet traditional breeding methods (non-GM); all new crops, both non-GM as well as GM, are subjected to the present-day, customary set of legal and safety requirements, e.g. as laid down in the general food law (Regulation (EC) 178/2002) or by national competent authorities. In the Netherlands, national institutions engaged in food safety are e.g. the Dutch Food and Consumer Product Safety Authority (VWA), part of the Ministry of Agriculture, Nature and Food Quality, and the Central Bureau for the Retail Industry (CBL). They set and implement standards, such as the Hazard Analysis Critical Control Points (HACCP), that was recently approved by the Global Food Safety Initiative along with three other standards and is aimed at demonstrating and guaranteeing food safety. Quality control already starts with the customary procedures for selection of new cultivars by companies for agronomical traits and food safety aspects, e.g. glucosinolate levels in food products derived from *Brassica* spp. and solanidine glycosides in potato varieties, and for cultivar registration, next to the measures imposed by law. This is the standard reference situation.
On the other hand for GM crops, there is the additional notification procedure as laid down in Directive 2001/18/EC and Regulation (EC) 1829/2003. At present, regulations for GM crops are based on worst-case scenarios based on totally new combinations of not fully characterized genes from donor organisms very distant to the recipient plant species. All GM events have to comply with the same information criteria, irrespective of whether the gene/crop combination has been assessed before or whether it concerns a completely new combination of a crop and a gene from whatever source. Nowadays, new generations of GM crops will be produced that will carry well-known genes (by background, origin and interactions) from the species itself or from other plants under control of specific expression regulators from the gene or recipient plant species itself.

The large majority of GM crops will remain subjected to the full requirements of article 13 of the Directive, the notification procedure. However, two categories of GM plants are identified for which a less extensive dossier can be provided on certain, specific areas of the information package under Directive 2001/18/EC and, so to speak, could be exempt from part of the presently required GM environmental safety assessments, 1) GM crop/gene combinations for which insertion events have already been approved by the EC; 2) cisgenic GM crops carrying only natural genes in sense orientation with their own promoters isolated from plant species which can exchange genetic material through traditional breeding methods.

This more differentiated approach for handling GM crops with respect to the environmental risk assessment is suggested here based on global experience for ten years with cultivation of specific GM crops and on new developments in biotechnology, specifically the broader availability of plant-derived genes. As a result of the latter, GM crops can be created that are very similar to the products of traditional breeding, much more so than some of the products of the first generation of GM crops which contained genes from evolutionarily unrelated

organisms. In particular, when using genes in sense orientation with their native promoters from the same or cross-compatible species, the resulting GM crop would be similar to the products of normal introgression breeding, except for the process by which it was created. Therefore, from the point of view of environmental safety of the genes used, the situation would be similar to traditional breeding products. This latter type of products should be the frame of reference to which GM crops are compared.

Arguably, transgene insertion will have less drastic effects as compared to traditional methods involving introgression by recombination, translocation induction, mutation and cell fusion. The latter two methods have been defined as genetic modification techniques but are exempt of Directive 2001/18/EC with the provision for cellular fusion that the organisms involved can exchange genetic material through traditional breeding methods. Experiences accumulated with GM crops in the past ten years have indicated that they do not pose serious threats to the environment or to human and animal health. There is a history now of safe cultivation, processing and putting on the market a specific set of GM crops as or in products in a great variety of regions across the globe. Therefore, a case can be made for a relaxation of the requirements for environmental safety analyses under the standard notification procedure as prescribed in Article 13 for the category 2 and 3 crops (see chapter 6). Based on the scientific arguments presented in chapters 2 -6 this report only pleads for facilitation at this point. *However, these arguments could equally well be used to declare category 3 of GM crops exempt of Directive 2001/18/EC entirely, this in analogy to the GMOs already exempted under article 3.* This report could serve as a basis for a proposal by the Dutch competent authority on criteria and information requirements for placing on the market of the category 2 and 3 GM crops by way of derogation of Article 13 as described in Article 16 of Directive 2001/18/EC.

Similarly, arguments could also be made for an attenuated procedure for those cases where plant genes from within the species or from crossing-compatible species are used with a different context (e.g. alternative promoters or antisense) or where plant genes are optimized with respect to codon-usage for a specific plant species or cultivar (comparable to mutation breeding). These approaches are aimed at influencing gene expression levels in place (plant organ) or time (developmental stage). Also in traditional breeding, the aim of crosses or mutations can be to increase or decrease gene expression levels, leading to increased or decreased gene product levels that go beyond levels occurring up till then. However, this class of GM crops represents a great diversity of different subtypes and there is yet too little experience with safety assessments of these variants to generically suggest a change in the notification procedure for them to a similar extent as for category 2. Therefore, they are still classified into category 1 and the full notification package is required. However, it will be clear that, in time, these types of GM crops, case by case, are the next to be classified into category 2.

Conclusions:

- Generally, in Genetically Modified Higher Plants (GMHPs), the notification procedure will be as formulated in article 13 of Directive 2001/18/EC with the exemptions as already given in that Directive.
- GM crop/gene combinations for which insertion events have already been approved by the appropriate European authorities can be exempted from parts of the notification procedure required by Directive 2001/18/EC.
- GM crops carrying cisgenes in sense orientation with their own promoters isolated from plant species which can exchange genetic material through traditional breeding methods can be exempted from parts of the notification procedure required by Directive 2001/18/EC or can be exempted totally similar to GMOs produced by mutagenesis or cell fusion of plant cells of organisms which can exchange genetic material through traditional breeding methods.

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8. Literature consulted

- Ahloowalia B.S., M. Maluszynski & K. Nichterlein. 2004. Global impact of mutation-derived varieties. Euphytica 135:187-204.
- Allard R.W. 1999. Principles of Plant Breeding. John Wiley & Sons, Inc. New York, U.S.A.
- APHIS/USDA web-site: http://www.aphis.usda.gov/brs/not_reg.html
- The Arabidopsis Initiative. 2000. Analysis of the genome sequence of the flowering plant *Arabidopsis thaliana*. Nature 408:796-815
- Arita I. 1999. Standardization of smallpox vaccines and the eradication programme – a WHO perspective. Dev. Biol. Stand. 100:31-37.
- Assessment report of the Netherlands competent authority in accordance with directive 2001/18/EC. Notification C/NL/04/02.
- Aumaitre A. 2004. Safety assessment and feeding value for pigs, poultry and ruminants of pest protected (Bt) plants and herbicide tolerant (glyphosate, glufosinate) plants: interpretation of experimental results observed worldwide on GM plants. Ital. J. Animal Sci. 3:107-121.
- Azanza F., T.E. Young, D. Kim, S.D. Tanksley & J.A. Juvik. 1994. Characterization of the effects of introgressed segments of chromosome 7 and 10 from *Lycopersicon chmielewskii* on tomato soluble solids, pH and yield. Theor. Appl. Genet. 87:965-972.
- Baker H.G. 1965. Characteristics and modes of origin of weeds. In: The Genetics of Colonising Species (H.G. Baker & G.L. Stebbins, eds.) New York, NY: Academic Press, pp. 147-172.
- Baker H.G. 1974. The evolution of weeds. Annu. Rev. Ecol. Syst. 5:1-23.
- Bertolla F. & P. Simonet. 1999. Horizontal gene transfers in the environment: natural transformation as a putative process for gene transfers between transgenic plants and micro-organisms. Res. Microbiol. 150:375-384.
- Bird R.M. 1996. Dual ancestry of *Zea*: sequence evidence at the *adh1*, *adh2*, *sh1* and *o2* loci. Maize Genetics Cooperation Newsletter 70:36-37.
- Borojevic S. 1990.Principles and Methods of Plant Breeding. Elsevier Science Publishers, Amsterdam. NL
- Bradford K.J., A. Van Deynze, N. Gutterson, W. Parrott & S.H. Strauss. 2005. Regulating transgenic crops sensibly: lessons from plant breeding, biotechnology and genomics. Nature Biotechnol. 23:439-444.
- Brookes G. & P. Barfoot. 2003. Co-existence of GM and non-GM crops: case study of maize grown in Spain. www.pgeconomics.co.uk/pdf/Coexistence_spain.pdf
- Brunner S., K. Fengler, M. Morgante, S. Tingey & A. Rafalski. 2005. Evolution of DNA sequence nonhomologies among maize inbreds. The Plant Cell 17:343-360.
- Budak H. P.S. Baenziger, B.S. Beecher, R.A. Graybosch, B.T. Campbell, M.J. Shipman, M. Erayman & K.M. Eskridge. 2004. The effect of introgressions of wheat D-genome chromosomes into 'Pesto' triticale. Euphytica 137:261-270.
- Conner A.J., T.R. Glare & J.-P. Nap. 2003. The release of genetically modified crops into the environment. Part II. Overview of ecological risk assessment. The Plant J. 33:19-46.

- Crawley M.J., S.L. Brown, R.S. Hails, D.D. Kohn & M. Rees. 2001. Transgenic crops in natural habitats. Nature 409:682-683.
- Daniels R., C. Boffey, R. Mogg, J. Bond & R. Clarke. 2005. The potential for dispersal of herbicide tolerance genes from genetically-modified, herbicide-tolerant oilseed rape crops to wild-relatives. DEFRA report EPG 1/5/151. www.defra.gov.uk/environment/gm/research/pdf/epg_1-5-151.pdf
- De Vries J. & W. Wackernagel. 1998. Detection of nptII (kanamycin resistance) gene in genomes of transgenic plants by marker-rescue transformation. Mol. Gen. Genet. 257:606-613.
- Directive 2001/18/EC of the European Parliament and of the Council
- Down R.E., L. Ford, S.D. Woodhouse, R.J.M. Raemaekers, B. Leitch, J.A. Gatehouse & A.M.R. Gatehouse. 2000. Snowdrop lectin (GNA) has no acute toxic effects on a beneficial insect predator, the 2-spot ladybird (*Adalia bipunctata* L.). J. Insect Physiol. 46:379-391.
- Ellstrand N.C., H.C. Prentice & J.F. Hancock. 1999. Gene flow and introgression from domesticated plants into their wild relatives. Ann. Rev. Ecol. System. 30:539-563.
- Ellstrand N.C. 2003. Current knowledge of gene flow in plants: implications for transgene flow. Philosoph. Transactions Royal Soc. London.; Biol. Sci. 358:1163-1170.
- European Commission, DG for the Environment, Joint Research Centre, website on Biotechnology & GMOs: http://gmoinfo.jrc.it/default.asp
- European Commission, DG Health and Consumer Protection/ Plant Health, GM web-site: http://europa.eu.int/comm/food/plant/gmplants/index_en.htm
- EFSA. 2004. Opinion of the scientific panel on genetically modified organisms on a request from the Commission related to the notification procedure (reference C/NL/98/11) for placing on the market of herbicide-tolerant oilseed rape GT73, for import and processing, under part C of Directive 2001/18/EC from Monsanto. EFSA Journal 29:1-19.
- Ewen S.W.B. & A. Pusztai. 1999. Effect of diets containing genetically modified potatoes expressing *Galanthus nivalis* lectin on rat small intestine. The Lancet 354:1353-1354.
- Faber F. & J.D. Van Elsas. 2005. COGEM rapportnr. 2005-02 . Transfer of DNA from genetically modified plants to bacteria.
- Franke R. & A. Meinel. 1990. History of the first fertile amphidiploid wheat x rye hybrid – W. Rimpau's triticale. Cereal Res. Commun. 18:103-109.
- Forsbach A., D. Schubert, B. Lechtenberg, M. Gils & R. Schmidt. 2003. A comprehensive characterization of single-copy T-DANN insertions in the *Arabidopsis thaliana* genome. Plant Mol. Biol. 52:161-176.
- Genetically modified crops in the EU: food safety assessment, regulation and public concerns. 2003. Overarching report Entransfood, the European network on safety assessment of genetically modified food crops. www.entransfood.com
- Girard C., A.L. Picard-Nizou, E. Grallien, B. Zaccomer, L. Jouanin & M.H. Pham-Delègue. 1998. Effects of proteinase inhibitor ingestion on survival learning abilities and digestive proteinases of the honeybee. Transgen. Res. 7:239-246.

- Glandorf D.C.M., P.A.H.M. Bakker & L.C. van Loon. 1997. Influence of the production of antibacterial and antifungal proteins by transgenic plants on the saprophytic soil microflora. Acta Bot. Neerl. 46:85-104.
- Glare T.R. & M. O'Callaghan. 2000. Bacillus thuringiensis: biology, ecology and safety. Chichester, UK: John Wiley and Sons.
- Goff S.A. et al. (2002). A Draft Sequence of the Rice Genome (*Oryza sativa* L. ssp. *japonica*) Science 296:92-100.
- Hails R.S. & K. Morley. 2005. Genes invading new populations: a risk assessment perspective. Trends in Ecol. Evolution 20:245-252.
- Heath M.C. 2000. Nonhost resistance and nonspecific plant defenses. Curr. Opinion Plant Biol. 3:315-319
- Heijbroek W., R.G. Munning & A.C.P.M. van Swaaij. 2002. The effect of different levels of beet cyst nematodes (*Heterodera schachtii*) and beet necrotic yellow vein virus (BNYVV) on single and double resistant sugar beet cultivars. Eur. J. Plant Pathol. 108:735-744.
- Hoffmann T., C. Golz & O. Schieder. 1994. Foreign DANN sequences are received by a wild-type strain of *Aspergillus niger* after co-culture with transgenic higher plants. Curr. Genet. 27:70-76.
- Integrale Beleidsnota Biotechnologie. 2000. Ministeries van VROM, VWS en LNV.
- Islam-Faridi M.N. & A. Mujeeb-Kazi. 1995. Visualization of *Secale cereale* DNA in wheat germ plasm by fluorescent in situ hybridization. Theor. Appl. Genet. 90:595-600.
- James C. 2004. Global status of commercialized biotech/GM crops: 2004. ISAAA Briefs no.32
- Jenczewski E., J. Ronfort & A.M. Chevre. 2003. Crop-to-wild gene flow, introgression and possible fitness effects of transgenes. Environm. Biosafety Res. 2:9-24.
- Jouanin L., C. Girard, M. Bonadé-Bottino, M. Le Metayer, A. Picard-Nizou, J. Lerin & M. Pham-Delègue. 1998. Impact of oilseed rape expressing proteinase inhibitors on coleopteran pests and honeybees. Cahiers Agri. 7:531-536.
- Kowalchuk G.A., W. de Boer & J.A. van Veen. 2003. COGEM *Rapportnr. 2003-03.* Knowledge gaps with respect to the effects of genetically modified crops on the functioning of soil ecosystems.
- Krens F.A., K.T.B. Pelgrom, J.G. Schaart, A.P.M. den Nijs & G.J.A. Rouwendal. 2004. Clean vector technology for marker-free transgenic fruit crops. Acta Horticulturae 663:431-435.
- Kumar S. & M. Fladung. 2002. Transgene integration in aspen: structures of integration sites and mechanism of T-DNA integration. The Plant J. 31:543-551.
- Lai J., Y. Li, J. Messing & H.K. Dooner. 2005. Gene movement by *Helitron* transposons contributes to the haplotype variability of maize. Proc. Natl. Acad. Sci. USA 102:9068-9073.
- Lehesranta S.J., H.V. Davies, L.V.T. Shepherd, N. Nunan, J.W. McNicol, S. Auriola, K.M. Koistinen, S. Suomalainen, H.I. Kokko & S.O. Kärenlampi. 2005. Comparison of tuber proteosomes of potato varieties, landraces and genetically modified lines. Plant Physiol. 138:1690-1699.
- Losey J.E., L.S. Rayor & M.E. Carter. 1999. Transgenic pollen harms monarch larvae. Nature 399:214.

- Madlung A. & L. Comai. 2004. The effect of stress on genome regulation and structure. Ann. Bot. 94:481-495.
- Malone L.A. & M.H. Pham-Delègue. 2001. Effects of transgene products on honey bees (*Apis mellifera*) and bumblebees (*Bombus* sp.) Apidologie 32:278-304.
- McDonald B.A. & C. Linde. 2002. Pathogen population genetics, evolutionary potential and durable resistance. Ann. Rev. Phytopathol. 40:349-379.
- Milling A., K. Smalla, F.X. Maidl, M. Schloter & J.C. Munch. 2004. Effects of transgenic potatoes with an altered starch composition on the diversity of soil and rhizosphere bacteria and fungi. Plant and Soil 266:23-39.
- Nap J.-P., J. Bijvoet & W.J. Stiekema. 1992. Biosafety of kanamycin-resistant transgenic plants. Transgen. Res. 1:239-249.
- Nap J.-P., P.L.J. Metz, M. Escaler & A.J. Conner. 2003. The release of genetically modified crops into the environment. Part I. Overview of current status and regulations. The Plant J. 33:1-18.
- Nielsen K.M., A.M. Bones, K. Smalla & J.D. van Elsas. 1998. Horizontal gene transfer from transgenic plants to terrestrial bacteria – rare events. FEMS Microbiol. Res. 22:79-103.
- Nielsen K.M. 2003. Transgenic organisms – time for conceptual diversification? Nature Biotechnol. 21:227-228.
- Ochman H., J.G. Lawrence & E.A. Groisman. 2000. Lateral gene transfer and the nature of bacterial innovation. Nature 405:299-304.
- Odjakova M. & C. Hadjiivanova. 2001. The complexity of pathogen defense in plants. Bulg. J. Plant Physiol. 27:101-109.
- Ramanna M.S. & E. Jacobsen. 1999. Introduction to Plant Breeding II: Genetic variation. Part I: Genetic modification in vivo. Wageningen UR.
- Regulation (EC) No. 1829/2003 of the European Parliament and of the Council
- Regulation (EC) No. 178/2002 of the European Parliament and of the Council
- Royal Society. 1999. Review of data on possible toxicityof GM potatoes. www.royalsoc.ac.uk/displaypagedoc.asp?id=6170
- Rufener Al Mazyad P. & K. Ammann. 1999. The *Medicago falcata/sativa* complex, crop-wild relative introgression in Switzerland. In: Proceedings VIIth Internatl. IOPB symposium, Amsterdam 10-15 August 1998. L.W.D. van Raamsdonk & J.C.M. den Nijs (eds.). Hugo de Vries Laboratory, Amsterdam pp 271-286.
- Schaart J.G., F.A. Krens, K.T.B. Pelgrom, O. Mendes & G.J.A. Rouwendal. 2004. Effective production of marker-free transgenic strawberry plants using inducible site-specific recombination and a bifunctional selectable marker gene. Plant Biotechnol. J. 2:233-240
- Schachermayr G.M., M.M. Messmer, C. Feuillet, H. Winzeler, M. Winzeler & B. Keller. 1995. Identification of molecular markers linked to the *Agropyron elongatum*-derived leaf rust resistance gene Lr24 in wheat. Theor. Appl. Genet. 90:982-990.
- Shirai Y. 2004. Influence of transgenic insecticidal crops on non-target arthropods: a review. Jap. J. Ecol. 54:47-65.
- Simmonds N.W. & J. Smartt. 1999. Principles of Crop Improvement. Blackwell Sciences Ltd, Oxford, U.K.

- Snow A.A., D. Pilson, L.H. Rieseberg, M.J. Paulsen, N. Pleskac, M.R. Reagon, D.E. Wolf & S.M. Selbo. 2003. A Bt transgene reduces herbivory and enhances fecundity in wild sunflowers. Ecol. Applications 13:279-286.
- Tang Q.L., T.Z. Rong, Y.C. Song, J.P. Yang, G.T. Pan, W.C. Li, Y. Huang & M Cao. 2005. Introgression of perennial teosinte genome into maize and identification of genomic in situ hybridization and microsatellite markers. Crop Sci. 45:717-721.
- Tepfer M. 1993. Viral genes and transgenic plants. What are the potential environmental risks? Bio/Technol. 11:1125-1132.
- Wiel C.C.M. van de. 2003. An exploration of the scientific literature on two aspects of GM crop biosafety. Botanical Files 2003. Note 292.
- Yu J. et al. 2002. A draft sequence of the rice genome (*Oryza sativa* L. ssp. *indica*). Science 296:79-92
- Zeven A.C. & J.M.J. de Wet. 1982. Dictionary of Cultivated Plants and their Regions of Diversity, 2nd edn. Wageningen, the Netherlands: Centre for Agricultural Publishing and Documentation.
- Zhu Y.Z., D. Li, F.L. Wang, J.D. Yin & H. Jin. 2004. Nutritional assessment and fate of DNA of soybean meal from roundup ready or traditional soybeans using rats. Arch. Animal Nutrit. 58:295-310.

Appendix A

Directive 2001/18/EC

I

(Acts whose publication is obligatory)

DIRECTIVE 2001/18/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 12 March 2001

on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission ([1]),

Having regard to the opinion of the Economic and Social Committee ([2]),

Acting in accordance with the procedure laid down in Article 251 of the Treaty, in the light of the joint text approved by the Conciliation Committee on 20 December 2000 ([3]),

Whereas:

(1) The Report of the Commission on the Review of Council Directive 90/220/EEC of 23 April 1990 on the deliberate release into the environment of genetically modified organisms ([4]), adopted on 10 December 1996, identified a number of areas where improvement is needed.

(2) There is a need for clarification of the scope of Directive 90/220/EEC and of the definitions therein.

(3) Directive 90/220/EEC has been amended. Now that new amendments are being made to the Directive, it is desirable, for reasons of clarity and rationalisation, that the provisions in question should be recast.

(4) Living organisms, whether released into the environment in large or small amounts for experimental purposes or as commercial products, may reproduce in the environment and cross national frontiers thereby affecting other Member States. The effects of such releases on the environment may be irreversible.

(5) The protection of human health and the environment requires that due attention be given to controlling risks from the deliberate release into the environment of genetically modified organisms (GMOs).

(6) Under the Treaty, action by the Community relating to the environment should be based on the principle that preventive action should be taken.

(7) It is necessary to approximate the laws of the Member States concerning the deliberate release into the environment of GMOs and to ensure the safe development of industrial products utilising GMOs.

(8) The precautionary principle has been taken into account in the drafting of this Directive and must be taken into account when implementing it.

(9) Respect for ethical principles recognised in a Member State is particularly important. Member States may take into consideration ethical aspects when GMOs are deliberately released or placed on the market as or in products.

(10) For a comprehensive and transparent legislative framework, it is necessary to ensure that the public is consulted by either the Commission or the Member States during the preparation of measures and that they are informed of the measures taken during the implementation of this Directive.

(11) Placing on the market also covers import. Products containing and/or consisting of GMOs covered by this Directive cannot be imported into the Community if they do not comply with its provisions.

(12) Making GMOs available to be imported or handled in bulk quantities, such as agricultural commodities, should be regarded as placing on the market for the purpose of this Directive.

(13) The content of this Directive duly takes into account international experience in this field and international

([1]) OJ C 139, 4.5.1998, p. 1.
([2]) OJ C 407, 28.12.1998, p. 1.
([3]) Opinion of the European Parliament of 11 February 1999 (OJ C 150, 28.5.1999, p. 363), Council Common Position of 9 December 1999 (OJ C 64, 6.3.2000, p. 1) and Decision of the European Parliament of 12 April 2000 (OJ C 40, 7.2.2001, p. 123). Decision of the European Parliament of 14 February 2001 and Decision of the Council of 15 February 2001.
([4]) OJ L 117, 8.5.1990, p. 15. Directive as last amended by Commission Directive 97/35/EC (OJ L 169, 27.6.1997, p. 72).

trade commitments and should respect the requirements of the Cartagena Protocol on Biosafety to the Convention on Biological Diversity. As soon as possible, and in any case before July 2001, the Commission should, in the context of the ratification of the Protocol, submit the appropriate proposals for its implementation.

(14) Guidance on the implementation of provisions related to the definition of the placing on the market in this Directive should be provided by the Regulatory Committee.

(15) When defining 'genetically modified organism' for the purpose of this Directive, human beings should not be considered as organisms.

(16) The provisions of this Directive should be without prejudice to national legislation in the field of environmental liability, while Community legislation in this field needs to be complemented by rules covering liability for different types of environmental damage in all areas of the European Union. To this end the Commission has undertaken to bring forward a legislative proposal on environmental liability before the end of 2001, which will also cover damage from GMOs.

(17) This Directive should not apply to organisms obtained through certain techniques of genetic modification which have conventionally been used in a number of applications and have a long safety record.

(18) It is necessary to establish harmonised procedures and criteria for the case-by-case evaluation of the potential risks arising from the deliberate release of GMOs into the environment.

(19) A case-by-case environmental risk assessment should always be carried out prior to a release. It should also take due account of potential cumulative long-term effects associated with the interaction with other GMOs and the environment.

(20) It is necessary to establish a common methodology to carry out the environmental risk assessment based on independent scientific advice. It is also necessary to establish common objectives for the monitoring of GMOs after their deliberate release or placing on the market as or in products. Monitoring of potential cumulative long-term effects should be considered as a compulsory part of the monitoring plan.

(21) Member States and the Commission should ensure that systematic and independent research on the potential risks involved in the deliberate release or the placing on the market of GMOs is conducted. The necessary resources should be secured for such research by Member States and the Community in accordance with their budgetary procedures and independent researchers should be given access to all relevant material, while respecting intellectual property rights.

(22) The issue of antibiotic-resistance genes should be taken into particular consideration when conducting the risk assessment of GMOs containing such genes.

(23) The deliberate release of GMOs at the research stage is in most cases a necessary step in the development of new products derived from, or containing GMOs.

(24) The introduction of GMOs into the environment should be carried out according to the 'step by step' principle. This means that the containment of GMOs is reduced and the scale of release increased gradually, step by step, but only if evaluation of the earlier steps in terms of protection of human health and the environment indicates that the next step can be taken.

(25) No GMOs, as or in products, intended for deliberate release are to be considered for placing on the market without first having been subjected to satisfactory field testing at the research and development stage in ecosystems which could be affected by their use.

(26) The implementation of this Directive should be carried out in close liaison with the implementation of other relevant instruments such as Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market [1]. In this context the competent authorities concerned with the implementation of this Directive and of those instruments, within the Commission and at national level, should coordinate their action as far as possible.

(27) Concerning the environmental risk assessment for part C, risk management, labelling, monitoring, information to the public and safeguard clause, this Directive should be a point of reference for GMOs as or in products authorised by other Community legislation which should therefore provide for a specific environmental risk assessment, to be carried out in accordance with the principles set out in Annex II and on the basis of information specified in Annex III without prejudice to additional requirements laid down by the Community legislation mentioned above, and for requirements as regards risk management, labelling, monitoring as appropriate, information to the public and safeguard clause at least equivalent to that laid down in this Directive. To this end it is necessary to provide for cooperation with the Community and Member State bodies mentioned in this Directive for the purpose of its implementation.

[1] OJ L 230, 19.8.1991, p. 1. Directive as last amended by Commission Directive 1999/80/EC (OJ L 210, 10.8.1999, p. 13).

(28) It is necessary to establish a Community authorisation procedure for the placing on the market of GMOs, as or in products, where the intended use of the product involves the deliberate release of the organism(s) into the environment.

(29) The Commission is invited to conduct a study which should contain an assessment of various options to improve further the consistency and efficiency of this framework, particularly focusing on a centralised authorisation procedure for the placing on the market of GMOs within the Community.

(30) For sectoral legislation, monitoring requirements may have to be adapted to the product concerned.

(31) Part C of this Directive does not apply to products covered by Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products ([1]), provided that it includes an environmental risk assessment equivalent to that provided for by this Directive.

(32) Any person, before undertaking a deliberate release into the environment of a GMO, or the placing on the market of GMOs, as or in products, where the intended use of the product involves its deliberate release into the environment, is to submit a notification to the national competent authority.

(33) That notification should contain a technical dossier of information including a full environmental risk assessment, appropriate safety and emergency response, and, in the case of products, precise instructions and conditions for use, and proposed labelling and packaging.

(34) After notification, no deliberate release of GMOs should be carried out unless the consent of the competent authority has been obtained.

(35) A notifier should be able to withdraw his dossier at any stage of the administrative procedures laid down in this Directive. The administrative procedure should come to an end when a dossier is withdrawn.

(36) Rejection of a notification for the placing on the market of a GMO as or in products by a competent authority should be without prejudice to the submission of a notification of the same GMO to another competent authority.

(37) An agreement should be reached at the end of the mediation period when no objections remain.

(38) Rejection of a notification following a confirmed negative assessment report should be without prejudice to future decisions based on the notification of the same GMO to another competent authority.

(39) In the interests of the smooth functioning of this Directive, Member States should be able to avail themselves of the various provisions for the exchange of information and experience before having recourse to the safeguard clause in this Directive.

(40) In order to ensure that the presence of GMOs in products containing, or consisting of, genetically modified organisms is appropriately identified, the words 'This product contains genetically modified organisms' should appear clearly either on a label or in an accompanying document.

(41) A system should be designed using the appropriate committee procedure, for the assignment of a unique identifier to GMOs, taking into account relevant developments in international fora.

(42) It is necessary to ensure traceability at all stages of the placing on the market of GMOs as or in products authorised under part C of this Directive.

(43) It is necessary to introduce into this Directive an obligation to implement a monitoring plan in order to trace and identify any direct or indirect, immediate, delayed or unforeseen effects on human health or the environment of GMOs as or in products after they have been placed on the market.

(44) Member States should be able, in accordance with the Treaty, to take further measures for monitoring and inspection, for example by official services, of the GMOs as or in products placed on the market.

(45) Means should be sought for providing possibilities for facilitating the control of GMOs or their retrieval in the event of severe risk.

(46) Comments by the public should be taken into consideration in the drafts of measures submitted to the Regulatory Committee.

(47) The competent authority should give its consent only after it has been satisfied that the release will be safe for human health and the environment.

(48) The administrative procedure for granting consents for the placing on the market of GMOs as or in products should be made more efficient and more transparent and first-time consent should be granted for a fixed period.

(49) For products for which consent has been granted for a fixed period a streamlined procedure should apply as regards the renewal of consent.

([1]) OJ L 214, 24.8.1993, p. 1. Regulation as amended by Commission Regulation (EC) No 649/98 (OJ L 88, 24.3.1998, p. 7).

(50) The existing consents granted under Directive 90/220/EEC have to be renewed in order to avoid disparities between consents granted under that Directive and those pursuant to this Directive and in order to take full account of the conditions of consent under this Directive.

(51) Such renewal requires a transitional period during which existing consents granted under Directive 90/220/EEC remain unaffected.

(52) When a consent is renewed, it should be possible to revise all the conditions of the original consent, including those related to monitoring and the time limitation of the consent.

(53) Provision should be made for consultation of the relevant Scientific Committee(s) established by Commission Decision 97/579/EC ([1]) on matters which are likely to have an impact on human health and/or the environment.

(54) The system of exchange of information contained in notifications, established under Directive 90/220/EEC, has been useful and should be continued.

(55) It is important to follow closely the development and use of GMOs.

(56) When a product containing a GMO, as or in products, is placed on the market, and where such a product has been properly authorised under this Directive, a Member State may not prohibit, restrict or impede the placing on the market of GMOs, as or in products, which comply with the requirements of this Directive. A safeguard procedure should be provided in case of risk to human health or the environment.

(57) The Commission's European Group on Ethics in Science and New Technologies should be consulted with a view to obtaining advice on ethical issues of a general nature regarding the deliberate release or placing on the market of GMOs. Such consultations should be without prejudice to the competence of Member States as regards ethical issues.

(58) Member States should be able to consult any committee they have established with a view to obtaining advice on the ethical implications of biotechnology.

(59) The measures necessary for the implementation of this Directive are to be adopted in accordance with Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission ([2]).

(60) The information exchange set up under this Directive should also cover experience gained with the consideration of ethical aspects.

(61) In order to increase the effective implementation of the provisions adopted under this Directive it is appropriate to provide for penalties to be applied by Member States, including in the event of release or placing on the market contrary to the provisions of this Directive, particularly as a result of negligence.

(62) A report to be issued every three years by the Commission, taking into account the information provided by Member States, should contain a separate chapter regarding the socioeconomic advantages and disadvantages of each category of GMOs authorised for placing on the market, which will take due account of the interest of farmers and consumers.

(63) The regulatory framework for biotechnology should be reviewed so as to identify the feasibility of improving further the consistency and efficiency of that framework. Procedures may need to be adapted so as to optimise efficiency, and all options which might achieve that should be considered,

HAVE ADOPTED THIS DIRECTIVE:

PART A

GENERAL PROVISIONS

Article 1

Objective

In accordance with the precautionary principle, the objective of this Directive is to approximate the laws, regulations and administrative provisions of the Member States and to protect human health and the environment when:

— carrying out the deliberate release into the environment of genetically modified organisms for any other purposes than placing on the market within the Community,

— placing on the market genetically modified organisms as or in products within the Community.

Article 2

Definitions

For the purposes of this Directive:

(1) 'organism' means any biological entity capable of replication or of transferring genetic material;

(2) 'genetically modified organism (GMO)' means an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination;

([1]) OJ L 237, 28.8.1997, p. 18.
([2]) OJ L 184, 17.7.1999, p. 23.

Within the terms of this definition:

(a) genetic modification occurs at least through the use of the techniques listed in Annex I A, part 1;

(b) the techniques listed in Annex I A, part 2, are not considered to result in genetic modification;

(3) 'deliberate release' means any intentional introduction into the environment of a GMO or a combination of GMOs for which no specific containment measures are used to limit their contact with and to provide a high level of safety for the general population and the environment;

(4) 'placing on the market' means making available to third parties, whether in return for payment or free of charge;

The following operations shall not be regarded as placing on the market:

— making available genetically modified microorganisms for activities regulated under Council Directive 90/219/EEC of 23 April 1990 on the contained use of genetically modified microorganisms [1] including culture collections,

— making available GMOs other than microorganisms referred to in the first indent, to be used exclusively for activities where appropriate stringent containment measures are used to limit their contact with and to provide a high level of safety for the general population and the environment, the measures should be based on the same principles of containment as laid down in Directive 90/219/EEC,

— making available GMOs to be used exclusively for deliberate releases complying with the requirements laid down in part B of this Directive;

(5) 'notification' means the submission of the information required under this Directive to the competent authority of a Member State;

(6) 'notifier' means the person submitting the notification;

(7) 'product' means a preparation consisting of, or containing, a GMO or a combination of GMOs, which is placed on the market;

(8) 'environmental risk assessment' means the evaluation of risks to human health and the environment, whether direct or indirect, immediate or delayed, which the deliberate release or the placing on the market of GMOs may pose and carried out in accordance with Annex II.

[1] OJ L 117, 8.5.1990, p. 1. Directive as amended by Directive 98/81/EC (OJ L 330 5.12.1998, p. 13).

Article 3

Exemptions

1. This Directive shall not apply to organisms obtained through the techniques of genetic modification listed in Annex I B.

2. This Directive shall not apply to the carriage of genetically modified organisms by rail, road, inland waterway, sea or air.

Article 4

General obligations

1. Member States shall, in accordance with the precautionary principle, ensure that all appropriate measures are taken to avoid adverse effects on human health and the environment which might arise from the deliberate release or the placing on the market of GMOs. GMOs may only be deliberately released or placed on the market in conformity with part B or part C respectively.

2. Any person shall, before submitting a notification under part B or part C, carry out an environmental risk assessment. The information which may be necessary to carry out the environmental risk assessment is laid down in Annex III. Member States and the Commission shall ensure that GMOs which contain genes expressing resistance to antibiotics in use for medical or veterinary treatment are taken into particular consideration when carrying out an environmental risk assessment, with a view to identifying and phasing out antibiotic resistance markers in GMOs which may have adverse effects on human health and the environment. This phasing out shall take place by the 31 December 2004 in the case of GMOs placed on the market according to part C and by 31 December 2008 in the case of GMOs authorised under part B.

3. Member States and where appropriate the Commission shall ensure that potential adverse effects on human health and the environment, which may occur directly or indirectly through gene transfer from GMOs to other organisms, are accurately assessed on a case-by-case basis. This assessment shall be conducted in accordance with Annex II taking into account the environmental impact according to the nature of the organism introduced and the receiving environment.

4. Member States shall designate the competent authority or authorities responsible for complying with the requirements of this Directive. The competent authority shall examine notifications under part B and part C for compliance with the requirements of this Directive and whether the assessment provided for in paragraph 2 is appropriate.

5. Member States shall ensure that the competent authority organises inspections and other control measures as appropriate, to ensure compliance with this Directive. In the event of a release of GMO(s) or placing on the market as or in products for which no authorisation was given, the Member

State concerned shall ensure that necessary measures are taken to terminate the release or placing on the market, to initiate remedial action if necessary, and to inform its public, the Commission and other Member States.

6. Member States shall take measures to ensure traceability, in line with the requirements laid down in Annex IV, at all stages of the placing on the market of GMOs authorised under part C.

PART B

DELIBERATE RELASE OF GMOs FOR ANY OTHER PURPOSE THAN FOR PLACING ON THE MARKET

Article 5

1. Articles 6 to 11 shall not apply to medicinal substances and compunds for human use consisting of, or containing, a GMO or combination of GMOs provided that their deliberate release for any purpose other than that of being placed on the market is authorised by Community legislation which provides:

(a) for a specific environmental risk assessment in accordance with Annex II and on the basis of the type of information specified in Annex III without prejudice to additional requirements provided for by the said legislation;

(b) for explicit consent prior to release;

(c) for a monitoring plan in accordance with the relevant parts of Annex III, with a view to detecting the effects of the GMO or GMOs on human health or the environment;

(d) in an appropriate manner for requirements relating to treatment of new items of information, information to the public, information on the results of releases, and exchanges of information at least equivalent to those contained in this Directive and in the measures taken in accordance therewith.

2. Assessment of the risks to the environment presented by such substances and compounds shall be carried out in coordination with the national and Community authorities mentioned in this Directive.

3. Procedures ensuring conformity of the specific environmental risk assessment and equivalence with the provisions of this Directive must be provided for by the said legislation, which must refer to this Directive.

Article 6

Standard authorisation procedure

1. Without prejudice to Article 5, any person must, before undertaking a deliberate release of a GMO or of a combination of GMOs, submit a notification to the competent authority of the Member State within whose territory the release is to take place.

2. The notification referred to in paragraph 1 shall include:

(a) a technical dossier supplying the information specified in Annex III necessary for carrying out the environmental risk assessment of the deliberate release of a GMO or combination of GMOs, in particular:

(i) general information including information on personnel and training,

(ii) information relating to the GMO(s),

(iii) information relating to the conditions of release and the potential receiving environment,

(iv) information on the interactions between the GMO(s) and the environment,

(v) a plan for monitoring in accordance with the relevant parts of Annex III in order to identify effects of the GMO(s) on human health or the environment,

(vi) information on control, remediation methods, waste treatment and emergency response plans,

(vii) a summary of the dossier;

(b) the environmental risk assessment and the conclusions required in Annex II, section D, together with any bibliographic reference and indications of the methods used.

3. The notifier may refer to data or results from notifications previously submitted by other notifiers, provided that the information, data and results are non confidential or these notifiers have given their agreement in writing, or may submit additional information he considers relevant.

4. The competent authority may accept that releases of the same GMO or of a combination of GMOs on the same site or on different sites for the same purpose and within a defined period may be notified in a single notification.

5. The competent authority shall acknowledge the date of receipt of the notification and, having considered, where appropriate, any observations by other Member States made in accordance with Article 11, shall respond in writing to the notifier within 90 days of receipt of the notification by either:

(a) indicating that it is satisfied that the notification is in compliance with this Directive and that the release may proceed; or

(b) indicating that the release does not fulfil the conditions of this Directive and that notification is therefore rejected.

6. For the purpose of calculating the 90 day period referred to in paragraph 5, no account shall be taken of any periods of time during which the competent authority:

(a) is awaiting further information which it may have requested from the notifier, or

(b) is carrying out a public inquiry or consultation in accordance with Article 9; this public inquiry or consultation shall not prolong the 90 day period referred to in paragraph 5 by more than 30 days.

7. If the competent authority requests new information it must simultaneously give its reasons for so doing.

8. The notifier may proceed with the release only when he has received the written consent of the competent authority, and in conformity with any conditions required in this consent.

9. Member States shall ensure that no material derived from GMOs which are deliberately released in accordance with part B is placed on the market, unless in accordance with part C.

Article 7

Differentiated procedures

1. If sufficient experience has been obtained of releases of certain GMOs in certain ecosystems and the GMOs concerned meet the criteria set out in Annex V, a competent authority may submit to the Commission a reasoned proposal for the application of differentiated procedures to such types of GMOs.

2. Following its own initiative or at the latest 30 days following the receipt of a competent authority's proposal, the Commission shall,

(a) forward the proposal to the competent authorities, which may, within 60 days, present observations and at the same time;

(b) make available the proposal to the public which may, within 60 days, make comments; and

(c) consult the relevant Scientific Committee(s) which may, within 60 days give an opinion.

3. A decision shall be taken on each proposal in accordance with the procedure laid down in Article 30(2). This decision shall establish the minimum amount of technical information from Annex III necessary for evaluating any foreseeable risks from the release, in particular:

(a) information relating to the GMO(s);

(b) information relating to the conditions of release and the potential receiving environment;

(c) information on the interactions between the GMO(s) and the environment;

(d) the environmental risk assessment.

4. This decision shall be taken within 90 days of the date of the Commission's proposal or of receipt of the competent authority's proposal. This 90 day period shall not take into account the period of time during which the Commission is awaiting the observations of competent authorities, the comments of the public or the opinion of Scientific Committees, as provided for in paragraph 2.

5. The decision taken under paragraphs 3 and 4 shall provide that the notifier may proceed with the release only when he has received the written consent of the competent authority. The notifier shall proceed with the release in conformity with any conditions required in this consent.

The decision taken under paragraphs 3 and 4 may provide that releases of a GMO or of a combination of GMOs on the same site or on different sites for the same purpose and within a defined period may be notified in a single notification.

6. Without prejudice to paragraphs 1 to 5, Commission Decision 94/730/EC of 4 November 1994 establishing simplified procedures concerning the deliberate release into the environment of genetically modified plants pursuant to Article 6(5) of Council Directive 90/220/EEC [1] shall continue to apply.

7. Where a Member State decides to make use or not of a procedure established in a decision taken in accordance with paragraphs 3 and 4 for releases of GMOs within its territory, it shall inform the Commission thereof.

Article 8

Handling of modifications and new information

1. In the event of any modification of, or unintended change to, the deliberate release of a GMO or of a combination of GMOs which could have consequences with regard to risks for human health and the environment after the competent authority has given its written consent, or if new information has become available on such risks, either while the notification is being examined by the competent authority of a Member State or after that authority has given its written consent, the notifier shall immediately:

[1] OJ L 292, 12.11.1994, p. 31.

(a) take the measures necessary to protect human health and the environment;

(b) inform the competent authority in advance of any modification or as soon as the unintended change is known or the new information is available;

(c) revise the measures specified in the notification.

2. If information becomes available to the competent authority referred to in paragraph 1 which could have significant consequences with regard to risks for human health and the environment or under the circumstances described in paragraph 1, the competent authority shall evaluate such information and make it available to the public. It may require the notifier to modify the conditions of, suspend or terminate the deliberate release and shall inform the public thereof.

Article 9

Consultation of and information to the public

1. Member States shall, without prejudice to the provisions of Articles 7 and 25, consult the public and, where appropriate, groups on the proposed deliberate release. In doing so, Member States shall lay down arrangements for this consultation, including a reasonable time-period, in order to give the public or groups the opportunity to express an opinion.

2. Without prejudice to the provisions of Article 25:

— Member States shall make available to the public information on all part B releases of GMOs in their territory;

— the Commission shall make available to the public the information contained in the system of exchange of information pursuant to Article 11.

Article 10

Reporting by notifiers on releases

After completion of a release, and thereafter, at any intervals laid down in the consent on the basis of the results of the environmental risk assessment, the notifier shall send to the competent authority the result of the release in respect of any risk to human health or the environment, with, where appropriate, particular reference to any kind of product that the notifier intends to notify at a later stage. The format for the presentation of this result shall be established in accordance with the procedure laid down in Article 30(2).

Article 11

Exchange of information between competent authorities and the Commission

1. The Commission shall set up a system of exchange of the information contained in the notifications. The competent authorities shall send to the Commission, within 30 days of its receipt, a summary of each notification received under Article 6. The format of this summary shall be established and modified if appropriate in accordance with the procedure laid down in Article 30(2).

2. The Commission shall, at the latest 30 days following their receipt, forward these summaries to the other Member States, which may, within 30 days, present observations through the Commission or directly. At its request, a Member State shall be permitted to receive a copy of the full notification from the competent authority of the relevant Member State.

3. The competent authorities shall inform the Commission of the final decisions taken in compliance with Article 6(5), including where relevant the reasons for rejecting a notification, and of the results of the releases received in accordance with Article 10.

4. For the releases of GMOs referred to in Article 7, once a year Member States shall send a list of GMOs which have been released on their territory and a list of notifications that were rejected to the Commission, which shall forward them to the competent authorities of the other Member States.

PART C

PLACING ON THE MARKET OF GMOs AS OR IN PRODUCTS

Article 12

Sectoral legislation

1. Articles 13 to 24 shall not apply to any GMO as or in products as far as they are authorised by Community legislation which provides for a specific environmental risk assessment carried out in accordance with the principles set out in Annex II and on the basis of information specified in Annex III without prejudice to additional requirements provided for by the Community legislation mentioned above, and for requirements as regards risk management, labelling, monitoring as appropriate, information to the public and safeguard clause at least equivalent to that laid down in this Directive.

2. As far as Council Regulation (EEC) No 2309/93 is concerned, Articles 13 to 24 of this Directive shall not apply to any GMO as or in products as far as they are authorised by that Regulation provided that a specific environmental risk assessment is carried out in accordance with the principles set out in Annex II to this Directive and on the basis of the type of information specified in Annex III to this Directive without prejudice to other relevant requirements as regards risk assessment, risk management, labelling, monitoring as appropriate, information to the public and safeguard clause provided by Community legislation concerning medicinal products for human and veterinary use.

3. Procedures ensuring that the risk assessment, requirements regarding risk management, labelling, monitoring as appropriate, information to the public and safeguard clause are equivalent to those laid down in this Directive shall be

introduced, in a Regulation of the European Parliament and of the Council. Future sectoral legislation based on the provisions of that Regulation shall make a reference to this Directive. Until the Regulation enters into force, any GMO as or in products as far as they are authorised by other Community legislation shall only be placed on the market after having been accepted for placing on the market in accordance with this Directive.

4. During evaluation of the requests for the placing on the market of the GMOs referred to in paragraph 1, the bodies established by the Community under this Directive and by Member States for the purpose of implementing this Directive shall be consulted.

Article 13

Notification procedure

1. Before a GMO or a combination of GMOs as or in products is placed on the market, a notification shall be submitted to the competent authority of the Member State where such a GMO is to be placed on the market for the first time. The competent authority shall acknowledge the date of receipt of the notification and immediately forward the summary of the dossier referred to in paragraph 2(h) to the competent authorities of the other Member States and the Commission.

The competent authority shall without delay examine whether the notification is in accordance with paragraph 2 and shall, if necessary, ask the notifier for additional information.

When the notification is in accordance with paragraph 2, and at the latest when it sends its assessment report in accordance with Article 14(2), the competent authority shall forward a copy of the notification to the Commission which shall, within 30 days of its receipt, forward it to the competent authorities of the other Member States.

2. The notification shall contain:

(a) the information required in Annexes III and IV. This information shall take into account the diversity of sites of use of the GMO as or in a product and shall include information on data and results obtained from research and developmental releases concerning the impact of the release on human health and the environment;

(b) the environmental risk assessment and the conclusions required in Annex II, section D;

(c) the conditions for the placing on the market of the product, including specific conditions of use and handling;

(d) with reference to Article 15(4), a proposed period for the consent which should not exceed ten years;

(e) a plan for monitoring in accordance with Annex VII, including a proposal for the time-period of the monitoring plan; this time-period may be different from the proposed period for the consent;

(f) a proposal for labelling which shall comply with the requirements laid down in Annex IV. The labelling shall clearly state that a GMO is present. The words 'this product contains genetically modified organisms' shall appear either on a label or in an accompanying document;

(g) a proposal for packaging which shall comprise the requirements laid down in Annex IV;

(h) a summary of the dossier. The format of the summary shall be established in accordance with the procedure laid down in Article 30(2).

If on the basis of the results of any release notified under part B, or on other substantive, reasoned scientific grounds, a notifier considers that the placing on the market and use of a GMO as or in a product do not pose a risk to human health and the environment, he may propose to the competent authority not to provide part or all of the information required in Annex IV, section B.

3. The notifier shall include in this notification information on data or results from releases of the same GMOs or the same combination of GMOs previously or currently notified and/or carried out by the notifier either inside or outside the Community.

4. The notifier may also refer to data or results from notifications previously submitted by other notifiers or submit additional information he considers relevant, provided that the information, data and results are non-confidential or these notifiers have given their agreement in writing.

5. In order for a GMO or combination of GMOs to be used for a purpose different from that already specified in a notification, a separate notification shall be submitted.

6. If new information has become available with regard to the risks of the GMO to human health or the environment, before the written consent is granted, the notifier shall immediately take the measures necessary to protect human health and the environment, and inform the competent authority thereof. In addition, the notifier shall revise the information and conditions specified in the notification.

Article 14

Assessment report

1. On receipt and after acknowledgement of the notification in accordance with Article 13(2), the competent authority shall examine it for compliance with this Directive.

2. Within 90 days after receipt of the notification the competent authority shall:

— prepare an assessment report and send it to the notifier. A subsequent withdrawal by the notifier shall be without prejudice to any further submission of the notification to another competent authority;

— in the case referred to in paragraph 3(a), send its report, together with the information referred to in paragraph 4 and any other information on which it has based its report, to the Commission which shall, within 30 days of its receipt, forward it to the competent authorities of the other Member States.

In the case referred to paragraph 3(b), the competent authority shall send its report, together with the information referred to in paragraph 4 and any other information on which it has based its report, to the Commission no earlier than 15 days after sending the assessment report to the notifier and no later than 105 days after receipt of the notification. The Commission shall, within 30 days of its receipt, forward the report to the competent authorities of the other Member States.

3. The assessment report shall indicate whether:

(a) the GMO(s) in question should be placed on the market and under which conditions; or

(b) the GMO(s) in question should not be placed on the market.

The assessment reports shall be established in accordance with the guidelines laid down in Annex VI.

4. For the purpose of calculating the 90 day period referred to in paragraph 2, any periods of time during which the competent authority is awaiting further information which it may have requested from the notifier shall not be taken into account. The competent authority shall state the reasons in any request for further information.

Article 15

Standard procedure

1. In the cases referred to in Article 14(3), a competent authority or the Commission may ask for further information, make comments or present reasoned objections to the placing on the market of the GMO(s) in question within a period of 60 days from the date of circulation of the assessment report.

Comments or reasoned objections and replies shall be forwarded to the Commission which shall immediately circulate them to all competent authorities.

The competent authorities and the Commission may discuss any outstanding issues with the aim of arriving at an agreement within 105 days from the date of circulation of the assessment report.

Any periods of time during which further information from the notifier is awaited shall not be taken into account for the purpose of calculating the final 45 day period for arriving at an agreement. Reasons shall be stated in any request for further information.

2. In the case referred to in Article 14(3)(b), if the competent authority which prepared the report decides that the GMO(s) should not be placed on the market, the notification shall be rejected. This decision shall state the reasons.

3. If the competent authority which prepared the report decides that the product may be placed on the market, in the absence of any reasoned objection from a Member State or the Commission within 60 days following the date of circulation of the assessment report referred to in Article 14(3)(a) or if outstanding issues are resolved within the 105 day period referred to in paragraph 1, the competent authority which prepared the report shall give consent in writing for placing on the market, shall transmit it to the notifier and shall inform the other Member States and the Commission thereof within 30 days.

4. The consent shall be given for a maximum period of ten years starting from the date on which the consent is issued.

For the purpose of approval of a GMO or a progeny of that GMO intended only for the marketing of their seeds under the relevant Community provisions, the period of the first consent shall end at the latest ten years after the date of the first inclusion of the first plant variety containing the GMO on an official national catalogue of plant varieties in accordance with Council Directives 70/457/EEC [1] and 70/458/EEC [2].

In the case of forest reproductive material, the period of the first consent shall end at the latest ten years after the date of the first inclusion of basic material containing the GMO on an official national register of basic material in accordance with Council Directive 1999/105/EC [3].

Article 16

Criteria and information for specified GMOs

1. A competent authority, or the Commission on its own initiative, may make a proposal on criteria and information requirements to be met for the notification, by way of derogation from Article 13, for the placing on the market of certain types of GMOs as or in products.

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[1] Council Directive 70/457/EEC of 29 September 1970 on the common catalogue of varieties of agricultural plant species (OJ L 225, 12.10.1970, p. 1). Directive as last amended by Directive 98/96/EC (OJ L 25, 1.2.1999, p. 27).

[2] Council Directive 70/458/EEC of 29 September 1970 on the marketing of vegetable seed (OJ L 225, 12.10.1970, p. 7). Directive as last amended by Directive 98/96/EC.

[3] Council Directive 1999/105/EC of 22 December 1999 on the marketing of forest reproductive material (OJ L 11, 15.1.2000, p. 17).

2. These criteria and information requirements as well as any appropriate requirements for a summary shall be adopted, after consultation of the relevant Scientific Committee(s), in accordance with the procedure laid down in Article 30(2). The criteria and the information requirements shall be such as to ensure a high level of safety to human health and the environment and be based on the scientific evidence available on such safety and on the experience gained from the release of comparable GMOs.

The requirements set out in Article 13(2) shall be replaced by those adopted above, and the procedure set out in Article 13(3), (4), (5) and (6) and Articles 14 and 15 shall apply.

3. Before the procedure laid down in Article 30(2) for a decision on criteria and information requirements referred to in paragraph 1 is initiated, the Commission shall make the proposal available to the public. The public may make comments to the Commission within 60 days. The Commission shall forward any such comments, together with an analysis, to the Committee set up pursuant to Article 30.

Article 17

Renewal of consent

1. By way of derogation from Articles 13, 14 and 15, the procedure set out in paragraphs 2 to 9 shall be applied to the renewal of:

(a) consents granted under part C; and

(b) before 17 October 2006 of consents granted under Directive 90/220/EEC for placing on the market of GMOs as or in products before 17 October 2002,

2. At the latest nine months before the expiry of the consent, for the consents referred to in paragraph 1(a), and before 17 October 2006, for the consents referred to in paragraph 1(b), the notifier under this Article shall submit a notification to the competent authority which received the original notification, which shall contain:

(a) a copy of the consent to the placing on the market of the GMOs;

(b) a report on the results of the monitoring which was carried out according to Article 20. In the case of consents referred to in paragraph 1(b), this report shall be submitted when the monitoring was carried out;

(c) any other new information which has become available with regard to the risks of the product to human health and/or the environment; and

(d) as appropriate, a proposal for amending or complementing the conditions of the original consent, *inter alia* the conditions concerning future monitoring and the time limitation of the consent.

The competent authority shall acknowledge the date of receipt of the notification and when the notification is in accordance with this paragraph it shall without delay forward a copy of the notification and its assessment report to the Commission, which shall, within 30 days of their receipt, forward them to the competent authorities of the other Member States. It shall also send its assessment report to the notifier.

3. The assessment report shall indicate whether:

(a) the GMO(s) should remain on the market and under which conditions; or

(b) the GMO(s) should not remain on the market.

4. The other competent authorities or the Commission may ask for further information, make comments, or present reasoned objections within a period of 60 days from the date of circulation of the assessment report.

5. All comments, reasoned objections and replies shall be forwarded to the Commission which shall immediately circulate them to all competent authorities.

6. In the case of paragraph 3(a) and in the absence of any reasoned objection from a Member State or the Commission within 60 days from the date of circulation of the assessment report, the competent authority which prepared the report shall transmit to the notifier the final decision in writing and shall inform the other Member States and the Commission thereof within 30 days. The validity of the consent should not, as a general rule, exceed ten years and may be limited or extended as appropriate for specific reasons.

7. The competent authorities and the Commission may discuss any outstanding issues with the aim of arriving at an agreement within 75 days from the date of circulation of the assessment report.

8. If outstanding issues are resolved within the 75 day period referred to in paragraph 7, the competent authority which prepared the report shall transmit to the notifier its final decision in writing and shall inform the other Member States and the Commission thereof within 30 days. The validity of the consent may be limited as appropriate.

9. Following a notification for the renewal of a consent in accordance with paragraph 2, the notifier may continue to place the GMOs on the market under the conditions specified in that consent until a final decision has been taken on the notification.

Article 18

Community procedure in case of objections

1. In cases where an objection is raised and maintained by a competent authority or the Commission in accordance with Articles 15, 17 and 20, a decision shall be adopted and published within 120 days in accordance with the procedure laid down in Article 30(2). This decision shall contain the same information as in Article 19(3).

For the purpose of calculating the 120 day period, any period of time during which the Commission is awaiting further information which it may have requested from the notifier or is seeking the opinion of the Scientific Committee which has been consulted in accordance with Article 28 shall not be taken into account. The Commission shall state reasons in any request for further information and inform the competent authorities of its requests to the notifier. The period of time during which the Commission is awaiting the opinion of the Scientific Committee shall not exceed 90 days.

The period of time that the Council takes to act in accordance with the procedure laid down in Article 30(2) shall not be taken into account.

2. Where a favourable decision has been taken, the competent authority which prepared the report shall give consent in writing to the placing on the market or to the renewal of the consent, shall transmit it to the notifier and shall inform the other Member States and the Commission thereof within 30 days following the publication or notification of the decision.

Article 19

Consent

1. Without prejudice to requirements under other Community legislation, only if a written consent has been given for the placing on the market of a GMO as or in a product may that product be used without further notification throughout the Community in so far as the specific conditions of use and the environments and/or geographical areas stipulated in these conditions are strictly adhered to.

2. The notifier may proceed with the placing on the market only when he has received the written consent of the competent authority in accordance with Articles 15, 17 and 18, and in conformity with any conditions required in that consent.

3. The written consent referred to in Articles 15, 17 and 18 shall, in all cases, explicitly specify:

(a) the scope of the consent, including the identity of the GMO(s) to be placed on the market as or in products, and their unique identifier;

(b) the period of validity of the consent;

(c) the conditions for the placing on the market of the product, including any specific condition of use, handling and packaging of the GMO(s) as or in products, and conditions for the protection of particular ecosystems/environments and/or geographical areas;

(d) that, without prejudice to Article 25, the notifier shall make control samples available to the competent authority on request;

(e) the labelling requirements, in compliance with the requirements laid down in Annex IV. The labelling shall clearly state that a GMO is present. The words 'This product contains genetically modified organisms' shall appear either on a label or in a document accompanying the product or other products containing the GMO(s);

(f) monitoring requirements in accordance with Annex VII, including obligations to report to the Commission and competent authorities, the time period of the monitoring plan and, where appropriate, any obligations on any person selling the product or any user of it, *inter alia*, in the case of GMOs grown, concerning a level of information deemed appropriate on their location.

4. Member States shall take all necessary measures to ensure that the written consent and the decision referred to in Article 18, where applicable, are made accessible to the public and that the conditions specified in the written consent and the decision, where applicable, are complied with.

Article 20

Monitoring and handling of new information

1. Following the placing on the market of a GMO as or in a product, the notifier shall ensure that monitoring and reporting on it are carried out according to the conditions specified in the consent. The reports of this monitoring shall be submitted to the Commission and the competent authorities of the Member States. On the basis of these reports, in accordance with the consent and within the framework for the monitoring plan specified in the consent, the competent authority which received the original notification may adapt the monitoring plan after the first monitoring period.

2. If new information has become available, from the users or other sources, with regard to the risks of the GMO(s) to human health or the environment after the written consent has been given, the notifier shall immediately take the measures necessary to protect human health and the environment, and inform the competent authority thereof.

In addition, the notifier shall revise the information and conditions specified in the notification.

3. If information becomes available to the competent authority which could have consequences for the risks of the GMO(s) to human health or the environment, or under the circumstances described in paragraph 2, it shall immediately forward the information to the Commission and the competent authorities of the other Member States and may avail itself of the provisions in Articles 15(1) and 17(7) where appropriate, when the information has become available before the written consent.

When the information has become available after the consent has been given, the competent authority shall within 60 days after receipt of the new information, forward its assessment report indicating whether and how the conditions of the consent should be amended or the consent should be terminated to the Commission which shall, within 30 days of its receipt, forward it to the competent authorities of the other Member States.

Comments or reasoned objections to further placing on the market of the GMO or on the proposal for amending the conditions of the consent shall, within 60 days following the circulation of the assessment report, be forwarded to the Commission which shall immediately forward them to all competent authorities.

The competent authorities and the Commission may discuss any outstanding issues with the aim of arriving at an agreement within 75 days from the date of circulation of the assessment report.

In the absence of any reasoned objection from a Member State or the Commission within 60 days following the date of circulation of the new information or if outstanding issues are resolved within 75 days, the competent authority which prepared the report shall amend the consent as proposed, shall transmit the amended consent to the notifier and shall inform the other Member States and the Commission thereof within 30 days.

4. So as to ensure its transparency, the results of the monitoring carried out under part C of the Directive shall be made publicly available.

Article 21

Labelling

1. Member States shall take all necessary measures to ensure that at all stages of the placing on the market, the labelling and packaging of GMOs placed on the market as or in products comply with the relevant requirements specified in the written consent referred to in Articles 15(3), 17(5) and (8), 18(2) and 19(3).

2. For products where adventitious or technically unavoidable traces of authorised GMOs cannot be excluded, a minimum threshold may be established below which these products shall not have to be labelled according to the provision in paragraph 1. The threshold levels shall be established according to the product concerned, under the procedure laid down in Article 30(2).

Article 22

Free circulation

Without prejudice to Article 23, Member States may not prohibit, restrict or impede the placing on the market of GMOs, as or in products, which comply with the requirements of this Directive.

Article 23

Safeguard clause

1. Where a Member State, as a result of new or additional information made available since the date of the consent and affecting the environmental risk assessment or reassessment of existing information on the basis of new or additional scientific knowledge, has detailed grounds for considering that a GMO as or in a product which has been properly notified and has received written consent under this Directive constitutes a risk to human health or the environment, that Member State may provisionally restrict or prohibit the use and/or sale of that GMO as or in a product on its territory.

The Member State shall ensure that in the event of a severe risk, emergency measures, such as suspension or termination of the placing on the market, shall be applied, including information to the public.

The Member State shall immediately inform the Commission and the other Member States of actions taken under this Article and give reasons for its decision, supplying its review of the environmental risk assessment, indicating whether and how the conditions of the consent should be amended or the consent should be terminated, and, where appropriate, the new or additional information on which its decision is based.

2. A decision shall be taken on the matter within 60 days in accordance with the procedure laid down in Article 30(2). For the purpose of calculating the 60 day period, any period of time during which the Commission is awaiting further information which it may have requested from the notifier or is seeking the opinion of the Scientific Committee(s) which has/have been consulted shall not be taken into account. The period of time during which the Commission is awaiting the opinion of the Scientific Committee(s) consulted shall not exceed 60 days.

Likewise, the period of time the Council takes to act in accordance with the procedure laid down in Article 30(2) shall not be taken into account.

Article 24

Information to the public

1. Without prejudice to Article 25, upon receipt of a notification in accordance with Article 13(1), the Commission shall immediately make available to the public the summary referred to in Article 13(2)(h). The Commission shall also make available to the public assessment reports in the case referred to in Article 14(3)(a). The public may make comments to the Commission within 30 days. The Commission shall immediately forward the comments to the competent authorities.

2. Without prejudice to Article 25, for all GMOs which have received written consent for placing on the market or whose placing on the market was rejected as or in products under this Directive, the assessment reports carried out for these GMOs and the opinion(s) of the Scientific Committees consulted shall be made available to the public. For each product, the GMO or GMOs contained therein and the use or uses shall be clearly specified.

PART D

FINAL PROVISIONS

Article 25

Confidentiality

1. The Commission and the competent authorities shall not divulge to third parties any confidential information notified or exchanged under this Directive and shall protect intellectual property rights relating to the data received.

2. The notifier may indicate the information in the notification submitted under this Directive, the disclosure of which might harm his competitive positionand which should therefore be treated as confidential. Verifiable justification must be given in such cases.

3. The competent authority shall, after consultation with the notifier, decide which information will be kept confidential and shall inform the notifier of its decisions.

4. In no case may the following information when submitted according to Articles 6, 7, 8, 13, 17, 20 or 23 be kept confidential:

— general description of the GMO or GMOs, name and address of the notifier, purpose of the release, location of release and intended uses;

— methods and plans for monitoring of the GMO or GMOs and for emergency response;

— environmental risk assessment.

5. If, for whatever reasons, the notifier withdraws the notification, the competent authorities and the Commission must respect the confidentiality of the information supplied.

Article 26

Labelling of GMOs referred to in Article 2(4), second subparagraph

1. The GMOs to be made available for operations referred to under Article 2(4), second subparagraph, shall be subject to adequate labelling requirements in accordance with the relevant sections of Annex IV in order to provide for clear information, on a label or in an accompanying document, on the presence of GMOs. To that effect the words 'This product contains genetically modified organisms' shall appear either on a label or in an accompanying document.

2. The conditions for the implementation of paragraph 1 shall, without duplicating or creating inconsistencies with existing labelling provisions laid down in existing Community legislation, be determined in accordance with the procedure laid down in Article 30(2). In doing so, account should be taken, as appropriate, of labelling provisions established by Member States in accordance with Community legislation.

Article 27

Adaptation of Annexes to technical progress

Sections C and D of Annex II, Annexes III to VI, and section C of Annex VII shall be adapted to technical progress in accordance with the procedure laid down in Article 30(2).

Article 28

Consultation of Scientific Committee(s)

1. In cases where an objection as regards the risks of GMOs to human health or to the environment is raised by a competent authority or the Commission and maintained in accordance with Article 15(1), 17(4), 20(3) or 23, or where the assessment report referred to in Article 14 indicates that the GMO should not be placed on the market, the relevant Scientific Committee(s) shall be consulted by the Commission, on its own initiative or at the request of a Member State, on the objection.

2. The relevant Scientific Committee(s) may also be consulted by the Commission, on its own initiative or at the request of a Member State, on any matter under this Directive that may have an adverse effect on human health and the environment.

3. The administrative procedures laid down in this Directive shall not be affected by paragraph 2.

Article 29

Consultation of Committee(s) on Ethics

1. Without prejudice to the competence of Member States as regards ethical issues, the Commission shall, on its own initiative or at the request of the European Parliament or the Council, consult any committee it has created with a view to obtaining its advice on the ethical implications of biotechnology, such as the European Group on Ethics in Science and New Technologies, on ethical issues of a general nature.

This consultation may also take place at the request of a Member State.

2. This consultation is conducted under clear rules of openness, transparency and public accessibility. Its outcome shall be accessible to the public.

3. The administrative procedures provided for in this Directive shall not be affected by paragraph 1.

Article 30

Committee procedure

1. The Commission shall be assisted by a committee.

2. Where reference is made to this paragraph, Articles 5 and 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

The period laid down in Article 5(6) of Decision 1999/468/EC shall be set at three months.

3. The committee shall adopt its own rules of procedure.

Article 31

Exchange of information and reporting

1. Member States and the Commission shall meet regularly and exchange information on the experience acquired with regard to the prevention of risks related to the release and the placing on the market of GMOs. This information exchange shall also cover experience gained from the implementation of Article 2(4), second subparagraph, environmental risk assessment, monitoring and the issue of consultation and information of the public.

Where necessary, guidance on the implementation of Article 2(4), second subparagraph, may be provided by the committee established under Article 30(1).

2. The Commission shall establish one or several register(s) for the purpose of recording the information on genetic modifications in GMOs mentioned in point A No 7 of Annex IV. Without prejudice to Article 25, the register(s) shall include a part which is accessible to the public. The detailed arrangements for the operation of the register(s) shall be decided in accordance with the procedure laid down in Article 30(2).

3. Without prejudice to paragraph 2 and point A No 7 of Annex IV,

(a) Member States shall establish public registers in which the location of the release of the GMOs under part B is recorded.

(b) Member States shall also establish registers for recording the location of GMOs grown under part C, *inter alia* so that the possible effects of such GMOs on the environment may be monitored in accordance with the provisions of Articles 19(3)(f) and 20(1). Without prejudice to such provisions in Articles 19 and 20, the said locations shall:

— be notified to the competent authorities, and

— be made known to the public

in the manner deemed appropriate by the competent authorities and in accordance with national provisions.

4. Every three years, Member States shall send the Commission a report on the measures taken to implement the provisions of this Directive. This report shall include a brief factual report on their experience with GMOs placed on the market in or as products under this Directive.

5. Every three years, the Commission shall publish a summary based on the reports referred to in paragraph 4.

6. The Commission shall send to the European Parliament and the Council, in 2003 and thereafter every three years, a report on the experience of Member States with GMOs placed on the market under this Directive.

7. When submitting this report in 2003, the Commission shall at the same time submit a specific report on the operation of part B and part C including an assessment of:

(a) all its implications, particularly to take account of the diversity of European ecosystems and the need to complement the regulatory framework in this field;

(b) the feasibility of various options to improve further the consistency and efficiency of this framework, including a centralised Community authorisation procedure and the arrangements for the final decision making by the Commission;

(c) whether sufficient experience has accumulated on the implementation of part B differentiated procedures to justify a provision on implicit consent in these procedures

and on part C to justify the application of differentiated procedures; and

(d) the socioeconomic implications of deliberate releases and placing on the market of GMOs.

8. The Commission shall send to the European Parliament and the Council every year, a report on the ethical issues referred to in Article 29(1); this report may be accompanied, if appropriate, by a proposal with a view to amending this Directive.

Article 32

Implementation of the Cartagena Protocol on biosafety

1. The Commission is invited to bring forward as soon as possible and in any case before July 2001 a legislative proposal for implementing in detail the Cartagena Protocol on biosafety. The proposal shall complement and, if necessary, amend the provisions of this Directive.

2. This proposal shall, in particular, include appropriate measures to implement the procedures laid down in the Cartagena Protocol and, in accordance with the Protocol, require Community exporters to ensure that all requirements of the Advance Informed Agreement Procedure, as set out in Articles 7 to 10, 12 and 14 of the Cartagena Protocol, are fulfilled.

Article 33

Penalties

Member States shall determine the penalties applicable to breaches of the national provisions adopted pursuant to this Directive. Those penalties shall be effective, proportionate and dissuasive.

Article 34

Transposition

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by 17 October 2002. They shall forthwith inform the Commission thereof.

When Member States adopt these measures they shall contain a reference to this Directive or shall be accompanied by such reference on the occasion of their official publication. The methods of making such a reference shall be laid down by the Member States.

2. Member States shall communicate to the Commission the texts of the main provisions of domestic law which they adopt in the field covered by this Directive.

Article 35

Pending notifications

1. Notifications concerning placing on the market of GMOs as or in products received pursuant to Directive 90/220/EEC, and in respect of which the procedures of that Directive have not been completed by 17 October 2002 shall be subject to the provisions of this Directive.

2. By 17 January 2003 notifiers shall have complemented their notification in accordance with this Directive.

Article 36

Repeal

1. Directive 90/220/EEC shall be repealed on 17 October 2002.

2. References made to the repealed Directive shall be construed as being made to this Directive and should be read in accordance with the correlation table in Annex VIII.

Article 37

This Directive shall enter into force on the day of its publication in the *Official Journal of the European Communities*.

Article 38

This Directive is addressed to the Member States.

Done at Brussels, 12 March 2001.

For the European Parliament	*For the Council*
N. FONTAINE	L. PAGROTSKY
The President	*The President*

ANNEX I A

TECHNIQUES REFERRED TO IN ARTICLE 2(2)

PART 1

Techniques of genetic modification referred to in Article 2(2)(a) are *inter alia:*

(1) recombinant nucleic acid techniques involving the formation of new combinations of genetic material by the insertion of nucleic acid molecules produced by whatever means outside an organism, into any virus, bacterial plasmid or other vector system and their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation;

(2) techniques involving the direct introduction into an organism of heritable material prepared outside the organism including micro-injection, macro-injection and micro-encapsulation;

(3) cell fusion (including protoplast fusion) or hybridisation techniques where live cells with new combinations of heritable genetic material are formed through the fusion of two or more cells by means of methods that do not occur naturally.

PART 2

Techniques referred to in Article 2(2)(b) which are not considered to result in genetic modification, on condition that they do not involve the use of recombinant nucleic acid molecules or genetically modified organisms made by techniques/methods other than those excluded by Annex I B:

(1) in vitro fertilisation,

(2) natural processes such as: conjugation, transduction, transformation,

(3) polyploidy induction.

ANNEX I B

TECHNIQUES REFERRED TO IN ARTICLE 3

Techniques/methods of genetic modification yielding organisms to be excluded from the Directive, on the condition that they do not involve the use of recombinant nucleic acid molecules or genetically modified organisms other than those produced by one or more of the techniques/methods listed below are:

(1) mutagenesis,

(2) cell fusion (including protoplast fusion) of plant cells of organisms which can exchange genetic material through traditional breeding methods.

ANNEX II

PRINCIPLES FOR THE ENVIRONMENTAL RISK ASSESSMENT

This Annex describes in general terms the objective to be achieved, the elements to be considered and the general principles and methodology to be followed to perform the environmental risk assessment (e.r.a.) referred to in Articles 4 and 13. It will be supplemented by guidance notes to be developed in accordance with the procedure laid down in Article 30(2). These guidance notes shall be completed by 17 October 2002.

With a view to contributing to a common understanding of the terms 'direct, indirect, immediate and delayed' when implementing this Annex, without prejudice to further guidance in this respect and in particular as regards the extent to which indirect effects can and should be taken into account, these terms are described as follows:

— 'direct effects' refers to primary effects on human health or the environment which are a result of the GMO itself and which do not occur through a causal chain of events;

— 'indirect effects' refers to effects on human health or the environment occurring through a causal chain of events, through mechanisms such as interactions with other organisms, transfer of genetic material, or changes in use or management.

Observations of indirect effects are likely to be delayed;

— 'immediate effects' refers to effects on human health or the environment which are observed during the period of the release of the GMO. Immediate effects may be direct or indirect;

— 'delayed effects' refers to effects on human health or the environment which may not be observed during the period of the release of the GMO, but become apparent as a direct or indirect effect either at a later stage or after termination of the release.

A general principle for environmental risk assessment is also that an analysis of the 'cumulative long-term effects' relevant to the release and the placing on the market is to be carried out. 'Cumulative long-term effects' refers to the accumulated effects of consents on human health and the environment, including *inter alia* flora and fauna, soil fertility, soil degradation of organic material, the feed/ food chain, biological diversity, animal health and resistance problems in relation to antibiotics.

A. **Objective**

The objective of an e.r.a. is, on a case by case basis, to identify and evaluate potential adverse effects of the GMO, either direct and indirect, immediate or delayed, on human health and the environment which the deliberate release or the placing on the market of GMOs may have. The e.r.a. should be conducted with a view to identifying if there is a need for risk management and if so, the most appropriate methods to be used.

B. **General Principles**

In accordance with the precautionary principle, the following general principles should be followed when performing the e.r.a.:

— identified characteristics of the GMO and its use which have the potential to cause adverse effects should be compared to those presented by the non-modified organism from which it is derived and its use under corresponding situations;

— the e.r.a. should be carried out in a scientifically sound and transparent manner based on available scientific and technical data;

— the e.r.a. should be carried out on a case by case basis, meaning that the required information may vary depending on the type of the GMOs concerned, their intended use and the potential receiving environment, taking into account, i.a., GMOs already in the environment;

— if new information on the GMO and its effects on human health or the environment becomes available, the e.r.a. may need to be readdressed in order to:

— determine whether the risk has changed;

— determine whether there is a need for amending the risk management accordingly.

C. **Methodology**

C.1. Characteristics of GMOs and releases

Depending on the case the e.r.a. has to take into account the relevant technical and scientific details regarding characteristics of:

— the recipient or parental organism(s);

— the genetic modification(s), be it inclusion or deletion of genetic material, and relevant information on the vector and the donor;

— the GMO;

— the intended release or use including its scale;

— the potential receiving environment; and

— the interaction between these.

Information from releases of similar organisms and organisms with similar traits and their interaction with similar environments can assist the e.r.a.

C.2. Steps in the e.r.a.

In drawing conclusions for the e.r.a. referred to in Articles 4, 6, 7 and 13 the following points should be addressed:

1. *Identification of characteristics which may cause adverse effects:*

Any characteristics of the GMOs linked to the genetic modification that may result in adverse effects on human health or the environment shall be identified. A comparison of the characteristics of the GMO(s) with those of the non-modified organism under corresponding conditions of the release or use, will assist in identifying the particular potential adverse effects arising from the genetic modification. It is important not to discount any potential adverse effect on the basis that it is unlikely to occur.

Potential adverse effects of GMOs will vary from case to case, and may include:

— disease to humans including allergenic or toxic effects (see for example items II.A.11. and II.C.2(i) in Annex III A, and B 7 in Annex III B);

— disease to animals and plants including toxic, and where appropriate, allergenic effects (see for example items II.A.11. and II.C.2(i) in Annex III A, and B 7 and D 8 in Annex III B);

— effects on the dynamics of populations of species in the receiving environment and the genetic diversity of each of these populations (see for example items IV B 8, 9 and 12 in Annex III A);

— altered susceptibility to pathogens facilitating the dissemination of infectious diseases and/or creating new reservoirs or vectors;

— compromising prophylactic or therapeutic medical, veterinary, or plant protection treatments, for example by transfer of genes conferring resistance to antibiotics used in human or veterinary medicine (see for example items II.A.11(e) and II.C.2(i)(iv) in Annex III A);

— effects on biogeochemistry(biogeochemical cycles), particularly carbon and nitrogen recycling through changes in soil decomposition of organic material (see for example items II.A.11(f) and IV.B.15 in Annex III A, and D 11 in Annex III B).

Adverse effects may occur directly or indirectly through mechanisms which may include:

— the spread of the GMO(s) in the environment,

— the transfer of the inserted genetic material to other organisms, or the same organism whether genetically modified or not,

— phenotypic and genetic instability,

— interactions with other organisms,

— changes in management, including, where applicable, in agricultural practices.

2. *Evaluation of the potential consequences of each adverse effect, if it occurs*

The magnitude of the consequences of each potential adverse effect should be evaluated.

This evaluation should assume that such an adverse effect will occur. The magnitude of the consequences is likely to be influenced by the environment into which the GMO(s) is (are) intended to be released and the manner of the release.

3. *Evaluation of the likelihood of the occurrence of each identified potential adverse effect*

A major factor in evaluating the likelihood or probability of adverse effects occurring is the characteristics of the environment into which the GMO(s) is intended to be released, and the manner of the release.

4. *Estimation of the risk posed by each identified characteristic of the GMO(s)*

An estimation of the risk to human health or the environment posed by each identified characteristic of the GMO which has the potential to cause adverse effects should be made as far as possible, given the state of the art, by combining the likelihood of the adverse effect occurring and the magnitude of the consequences, if it occurs.

5. *Application of management strategies for risks from the deliberate release or marketing of GMO(s)*

The risk assessment may identify risks that require management and how best to manage them, and a risk management strategy should be defined.

6. *Determination of the overall risk of the GMO(s)*

An evaluation of the overall risk of the GMO(s) should be made taking into account any risk management strategies which are proposed.

D. **Conclusions on the potential environmental impact from the release or the placing on the market of GMOs**

On the basis of an e.r.a. carried out in accordance with the principles and methodology outlined in sections B and C, information on the points listed in sections D1 or D2 should be included, as appropriate, in notifications with a view to assisting in drawing conclusions on the potential environmental impact from the release or the placing on the market of GMOs:

D.1. In the case of GMOs other than higher plants

1. Likelihood of the GMO to become persistent and invasive in natural habitats under the conditions of the proposed release(s).

2. Any selective advantage or disadvantage conferred to the GMO and the likelihood of this becoming realised under the conditions of the proposed release(s).

3. Potential for gene transfer to other species under conditions of the proposed release of the GMO and any selective advantage or disadvantage conferred to those species.

4. Potential immediate and/or delayed environmental impact of the direct and indirect interactions between the GMO and target organisms (if applicable).

5. Potential immediate and/or delayed environmental impact of the direct and indirect interactions between the GMO with non-target organisms, including impact on population levels of competitors, prey, hosts, symbionts, predators, parasites and pathogens.

6. Possible immediate and/or delayed effects on human health resulting from potential direct and indirect interactions of the GMO and persons working with, coming into contact with or in the vicinity of the GMO release(s).

7. Possible immediate and/or delayed effects on animal health and consequences for the feed/food chain resulting from consumption of the GMO and any product derived from it, if it is intended to be used as animal feed.

8. Possible immediate and/or delayed effects on biogeochemical processes resulting from potential direct and indirect interactions of the GMO and target and non-target organisms in the vicinity of the GMO release(s).

9. Possible immediate and/or delayed, direct and indirect environmental impacts of the specific techniques used for the management of the GMO where these are different from those used for non-GMOs.

D.2. In the case of genetically modified higher plants (GMHP)

1. Likelihood of the GMHP becoming more persistent than the recipient or parental plants in agricultural habitats or more invasive in natural habitats.

2. Any selective advantage or disadvantage conferred to the GMHP.

3. Potential for gene transfer to the same or other sexually compatible plant species under conditions of planting the GMHP and any selective advantage or disadvantage conferred to those plant species.

4. Potential immediate and/or delayed environmental impact resulting from direct and indirect interactions between the GMHP and target organisms, such as predators, parasitoids, and pathogens (if applicable).

5. Possible immediate and/or delayed environmental impact resulting from direct and indirect interactions of the GMHP with non-target organisms, (also taking into account organisms which interact with target organisms), including impact on population levels of competitors, herbivores, symbionts (where applicable), parasites and pathogens.

6. Possible immediate and/or delayed effects on human health resulting from potential direct and indirect interactions of the GMHP and persons working with, coming into contact with or in the vicinity of the GMHP release(s).

7. Possible immediate and/or delayed effects on animal health and consequences for the feed/food chain resulting from consumption of the GMO and any products derived from it, if it is intended to be used as animal feed.

8. Possible immediate and/or delayed effects on biogeochemical processes resulting from potential direct and indirect interactions of the GMO and target and non-target organisms in the vicinity of the GMO release(s).

9. Possible immediate and/or delayed, direct and indirect environmental impacts of the specific cultivation, management and harvesting techniques used for the GMHP where these are different from those used for non-GMHPs.

ANNEX III

INFORMATION REQUIRED IN THE NOTIFICATION

A notification referred to in part B or part C of the Directive is to include, as appropriate, the information set out below in the sub-Annexes.

Not all the points included will apply to every case. It is to be expected that individual notifications will address only the particular subset of considerations which is appropriate to individual situations.

The level of detail required in response to each subset of considerations is also likely to vary according to the nature and the scale of the proposed release.

Future developments in genetic modification may necessitate adapting this Annex to technical progress or developing guidance notes on this Annex. Further differentiation of information requirements for different types of GMOs, for example single celled organisms, fish or insects, or for particular use of GMOs like the development of vaccines, may be possible once sufficient experience with notifications for the release of particular GMOs has been gained in the Community.

The description of the methods used or the reference to standardised or internationally recognised methods shall also be mentioned in the dossier, together with the name of the body or bodies responsible for carrying out the studies.

Annex III A applies to releases of all types of genetically modified organisms other than higher plants. Annex III B applies to release of genetically modified higher plants.

The term 'higher plants' means plants which belong to the taxonomic group Spermatophytae (Gymnospermae and Angiospermae).

ANNEX III A

INFORMATION REQUIRED IN NOTIFICATIONS CONCERNING RELEASES OF GENETICALLY MODIFIED ORGANISMS OTHER THAN HIGHER PLANTS

I. GENERAL INFORMATION

A. Name and address of the notifier (company or institute)

B. Name, qualifications and experience of the responsible scientist(s)

C. Title of the project

II. INFORMATION RELATING TO THE GMO

A. **Characteristics of (a) the donor, (b) the recipient or (c) (where appropriate) parental organism(s):**

1. scientific name,
2. taxonomy,
3. other names (usual name, strain name, etc.),
4. phenotypic and genetic markers,
5. degree of relatedness between donor and recipient or between parental organisms,
6. description of identification and detection techniques,
7. sensitivity, reliability (in quantitative terms) and specificity of detection and identification techniques,
8. description of the geographic distribution and of the natural habitat of the organism including information on natural predators, preys, parasites and competitors, symbionts and hosts,
9. organisms with which transfer of genetic material is known to occur under natural conditions,
10. verification of the genetic stability of the organisms and factors affecting it,
11. pathological, ecological and physiological traits:
    (a) classification of hazard according to existing Community rules concerning the protection of human health and/or the environment;
    (b) generation time in natural ecosystems, sexual and asexual reproductive cycle;
    (c) information on survival, including seasonability and the ability to form survival structures;
    (d) pathogenicity: infectivity, toxigenicity, virulence, allergenicity, carrier (vector) of pathogen, possible vectors, host range including non-target organism. Possible activation of latent viruses (proviruses). Ability to colonise other organisms;
    (e) antibiotic resistance, and potential use of these antibiotics in humans and domestic organisms for prophylaxis and therapy;
    (f) involvement in environmental processes: primary production, nutrient turnover, decomposition of organic matter, respiration, etc.
12. Nature of indigenous vectors:
    (a) sequence;
    (b) frequency of mobilisation;
    (c) specificity;
    (d) presence of genes which confer resistance.
13. History of previous genetic modifications.

B. **Characteristics of the vector**

1. nature and source of the vector,

2. sequence of transposons, vectors and other non-coding genetic segments used to construct the GMO and to make the introduced vector and insert function in the GMO,

3. frequency of mobilisation of inserted vector and/or genetic transfer capabilities and methods of determination,

4. information on the degree to which the vector is limited to the DNA required to perform the intended function.

C. **Characteristics of the modified organism**

1. Information relating to the genetic modification:

   (a) methods used for the modification;

   (b) methods used to construct and introduce the insert(s) into the recipient or to delete a sequence;

   (c) description of the insert and/or vector construction;

   (d) purity of the insert from any unknown sequence and information on the degree to which the inserted sequence is limited to the DNA required to perform the intended function;

   (e) methods and criteria used for selection;

   (f) sequence, functional identity and location of the altered/inserted/deleted nucleic acid segment(s) in question with particular reference to any known harmful sequence.

2. Information on the final GMO:

   (a) description of genetic trait(s) or phenotypic characteristics and in particular any new traits and characteristics which may be expressed or no longer expressed;

   (b) structure and amount of any vector and/or donor nucleic acid remaining in the final construction of the modified organism;

   (c) stability of the organism in terms of genetic traits;

   (d) rate and level of expression of the new genetic material. Method and sensitivity of measurement;

   (e) activity of the expressed protein(s);

   (f) description of identification and detection techniques including techniques for the identification and detection of the inserted sequence and vector;

   (g) sensitivity, reliability (in quantitative terms) and specificity of detection and identification techniques;

   (h) history of previous releases or uses of the GMO;

   (i) considerations for human health and animal health, as well as plant health:

      (i) toxic or allergenic effects of the GMOs and/or their metabolic products;

      (ii) comparison of the modified organism to the donor, recipient or (where appropriate) parental organism regarding pathogenicity;

      (iii) capacity for colonisation;

(iv) if the organism is pathogenic to humans who are immunocompetent:

— diseases caused and mechanism of pathogenicity including invasiveness and virulence,

— communicability,

— infective dose,

— host range, possibility of alteration,

— possibility of survival outside of human host,

— presence of vectors or means of dissemination,

— biological stability,

— antibiotic resistance patterns,

— allergenicity,

— availability of appropriate therapies.

(v) other product hazards.

III. INFORMATION RELATING TO THE CONDITIONS OF RELEASE AND THE RECEIVING ENVIRONMENT

A. **Information on the release**

1. description of the proposed deliberate release, including the purpose(s) and foreseen products,
2. foreseen dates of the release and time planning of the experiment including frequency and duration of releases,
3. preparation of the site previous to the release,
4. size of the site,
5. method(s) to be used for the release,
6. quantities of GMOs to be released,
7. disturbance on the site (type and method of cultivation, mining, irrigation, or other activities),
8. worker protection measures taken during the release,
9. post-release treatment of the site,
10. techniques foreseen for elimination or inactivation of the GMOs at the end of the experiment,
11. information on, and results of, previous releases of the GMOs, especially at different scales and in different ecosystems.

B. **Information on the environment (both on the site and in the wider environment):**

1. geographical location and grid reference of the site(s) (in case of notifications under part C the site(s) of release will be the foreseen areas of use of the product),
2. physical or biological proximity to humans and other significant biota,
3. proximity to significant biotopes, protected areas, or drinking water supplies,
4. climatic characteristics of the region(s) likely to be affected,
5. geographical, geological and pedological characteristics,
6. flora and fauna, including crops, livestock and migratory species,
7. description of target and non-target ecosystems likely to be affected,

8. a comparison of the natural habitat of the recipient organism with the proposed site(s) of release,

9. any known planned developments or changes in land use in the region which could influence the environmental impact of the release.

IV. INFORMATION RELATING TO THE INTERACTIONS BETWEEN THE GMOs AND THE ENVIRONMENT

A. **Characteristics affecting survival, multiplication and dissemination**

1. biological features which affect survival, multiplication and dispersal,

2. known or predicted environmental conditions which may affect survival, multiplication and dissemination (wind, water, soil, temperature, pH, etc.),

3. sensitivity to specific agents.

B. **Interactions with the environment**

1. predicted habitat of the GMOs,

2. studies of the behaviour and characteristics of the GMOs and their ecological impact carried out in simulated natural environments, such as microcosms, growth rooms, greenhouses,

3. genetic transfer capability

   (a) postrelease transfer of genetic material from GMOs into organisms in affected ecosystems;

   (b) postrelease transfer of genetic material from indigenous organisms to the GMOs;

4. likelihood of postrelease selection leading to the expression of unexpected and/or undesirable traits in the modified organism,

5. measures employed to ensure and to verify genetic stability. Description of genetic traits which may prevent or minimise dispersal of genetic material. Methods to verify genetic stability,

6. routes of biological dispersal, known or potential modes of interaction with the disseminating agent, including inhalation, ingestion, surface contact, burrowing, etc.,

7. description of ecosystems to which the GMOs could be disseminated,

8. potential for excessive population increase in the environment,

9. competitive advantage of the GMOs in relation to the unmodified recipient or parental organism(s),

10. identification and description of the target organisms if applicable,

11. anticipated mechanism and result of interaction between the released GMOs and the target organism(s) if applicable,

12. identification and description of non-target organisms which may be adversely affected by the release of the GMO, and the anticipated mechanisms of any identified adverse interaction,

13. likelihood of postrelease shifts in biological interactions or in host range,

14. known or predicted interactions with non-target organisms in the environment, including competitors, preys, hosts, symbionts, predators, parasites and pathogens,

15. known or predicted involvement in biogeochemical processes,

16. other potential interactions with the environment.

V. INFORMATION ON MONITORING, CONTROL, WASTE TREATMENT AND EMERGENCY RESPONSE PLANS

A. **Monitoring techniques**

1. methods for tracing the GMOs, and for monitoring their effects,
2. specificity (to identify the GMOs, and to distinguish them from the donor, recipient or, where appropriate, the parental organisms), sensitivity and reliability of the monitoring techniques,
3. techniques for detecting transfer of the donated genetic material to other organisms,
4. duration and frequency of the monitoring.

B. **Control of the release**

1. methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of release or the designated area for use,
2. methods and procedures to protect the site from intrusion by unauthorised individuals,
3. methods and procedures to prevent other organisms from entering the site.

C. **Waste treatment**

1. type of waste generated,
2. expected amount of waste,
3. description of treatment envisaged.

D. **Emergency response plans**

1. methods and procedures for controlling the GMOs in case of unexpected spread,
2. methods for decontamination of the areas affected, for example eradication of the GMOs,
3. methods for disposal or sanitation of plants, animals, soils, etc., that were exposed during or after the spread,
4. methods for the isolation of the area affected by the spread,

5 plans for protecting human health and the environment in case of the occurrence of an undesirable effect.

ANNEX III B

INFORMATION REQUIRED IN NOTIFICATIONS CONCERNING RELEASES OF GENETICALLY MODIFIED HIGHER PLANTS (GMHPs) (GYMNOSPERMAE AND ANGIOSPERMAE)

A. GENERAL INFORMATION

1. Name and address of the notifier (company or institute),
2. Name, qualifications and experience of the responsible scientist(s),
3. Title of the project,

B. INFORMATION RELATING TO (A) THE RECIPIENT OR (B) (WHERE APPROPRIATE) PARENTAL PLANTS

1. Complete name:
   (a) family name
   (b) genus
   (c) species
   (d) subspecies
   (e) cultivar/breeding line
   (f) common name.
2. (a) Information concerning reproduction:
      (i) mode(s) of reproduction
      (ii) specific factors affecting reproduction, if any
      (iii) generation time.
   (b) Sexual compatibility with other cultivated or wild plant species, including the distribution in Europe of the compatible species.
3. Survivability:
   (a) ability to form structures for survival or dormancy
   (b) specific factors affecting survivability, if any.
4. Dissemination:
   (a) ways and extent (for example an estimation of how viable pollen and/or seeds declines with distance) of dissemination
   (b) specific factors affecting dissemination, if any.
5. Geographical distribution of the plant.
6. In the case of plant species not normally grown in the Member State(s), description of the natural habitat of the plant, including information on natural predators, parasites, competitors and symbionts.
7. Other potential interactions, relevant to the GMO, of the plant with organisms in the ecosystem where it is usually grown, or elsewhere, including information on toxic effects on humans, animals and other organisms.

C. INFORMATION RELATING TO THE GENETIC MODIFICATION

1. Description of the methods used for the genetic modification.
2. Nature and source of the vector used.
3. Size, source (name) of donor organism(s) and intended function of each constituent fragment of the region intended for insertion.

D. INFORMATION RELATING TO THE GENETICALLY MODIFIED PLANT

1. Description of the trait(s) and characteristics which have been introduced or modified.

2. Information on the sequences actually inserted/deleted:

   (a) size and structure of the insert and methods used for its characterisation, including information on any parts of the vector introduced in the GMHP or any carrier or foreign DNA remaining in the GMHP;

   (b) in case of deletion, size and function of the deleted region(s);

   (c) copy number of the insert;

   (d) location(s) of the insert(s) in the plant cells (integrated in the chromosome, chloroplasts, mitochondria, or maintained in a non-integrated form), and methods for its determination.

3. Information on the expression of the insert:

   (a) information on the developmental expression of the insert during the lifecycle of the plant and methods used for its characterisation;

   (b) parts of the plant where the insert is expressed (for example roots, stem, pollen, etc.).

4. Information on how the genetically modified plant differs from the recipient plant in:

   (a) mode(s) and/or rate of reproduction;

   (b) dissemination;

   (c) survivability.

5. Genetic stability of the insert and phenotypic stability of the GMHP.

6. Any change to the ability of the GMHP to transfer genetic material to other organisms.

7. Information on any toxic, allergenic or other harmful effects on human health arising from the genetic modification.

8. Information on the safety of the GMHP to animal health, particularly regarding any toxic, allergenic or other harmful effects arising from the genetic modification, where the GMHP is intended to be used in animal feedstuffs.

9. Mechanism of interaction between the genetically modified plant and target organisms (if applicable).

10. Potential changes in the interactions of the GMHP with non-target organisms resulting from the genetic modification.

11. Potential interactions with the abiotic environment.

12. Description of detection and identification techniques for the genetically modified plant.

13. Information about previous releases of the genetically modified plant, if applicable.

E. INFORMATION RELATING TO THE SITE OF RELEASE (ONLY FOR NOTIFICATIONS SUBMITTED PURSUANT TO ARTICLES 6 AND 7)

1. Location and size of the release site(s).

2. Description of the release site ecosystem, including climate, flora and fauna.

3. Presence of sexually compatible wild relatives or cultivated plant species.

4. Proximity to officially recognised biotopes or protected areas which may be affected.

F. INFORMATION RELATING TO THE RELEASE (ONLY FOR NOTIFICATIONS SUBMITTED PURSUANT TO ARTICLES 6 AND 7)

1. Purpose of the release.

2. Foreseen date(s) and duration of the release.

3. Method by which the genetically modified plants will be released.

4. Method for preparing and managing the release site, prior to, during and postrelease, including cultivation practices and harvesting methods.

5. Approximate number of plants (or plants per m^2).

G. INFORMATION ON CONTROL, MONITORING, POSTRELEASE AND WASTE TREATMENT PLANS (ONLY FOR NOTIFICATIONS SUBMITTED PURSUANT TO ARTICLES 6 AND 7)

1. Any precautions taken:

   (a) distance(s) from sexually compatible plant species, both wild relatives and crops

   (b) any measures to minimise/prevent dispersal of any reproductive organ of the GMHP (for example pollen, seeds, tuber).

2. Description of methods for postrelease treatment of the site.

3. Description of postrelease treatment methods for the genetically modified plant material including wastes.

4. Description of monitoring plans and techniques.

5. Description of any emergency plans.

6. Methods and procedures to protect the site.

ANNEX IV

ADDITIONAL INFORMATION

This Annex describes in general terms the additional information to be provided in the case of notification for placing on the market and information for labelling requirements regarding GMOs as or in product to be placed on the market, and GMO exempted under Article 2(4), second subparagraph. It will be supplemented by guidance notes, as regards i.a. the description of how the product is intended to be used, to be developed in accordance with the procedure laid down in Article 30(2). The labelling of exempted organisms as required by Article 26 shall be met by providing appropriate recommendations for, and restrictions on, use:

A. The following information shall be provided in the notification for placing on the market of GMOs as or in product in addition to that of Annex III:

1. proposed commercial names of the products and names of GMOs contained therein, and any specific identification, name or code used by the notifier to identify the GMO. After the consent any new commercial names should be provided to the competent authority,

2. name and full address of the person established in the Community who is responsible for the placing on the market, whether it be the manufacturer, the importer or the distributor,

3. name and full address of the supplier(s) of control samples,

4. description of how the product and the GMO as or in product are intended to be used. Differences in use or management of the GMO compared to similar non-genetically modified products should be highlighted,

5. description of the geographical area(s) and types of environment where the product is intended to be used within the Community, including, where possible, estimated scale of use in each area,

6. intended categories of users of the product e.g. industry, agriculture and skilled trades, consumer use by public at large,

7. information on the genetic modification for the purposes of placing on one or several registers modifications in organisms, which can be used for the detection and identification of particular GMO products to facilitate post-marketing control and inspection. This information should include where appropriate the lodging of samples of the GMO or its genetic material, with the competent authority and details of nucleotide sequences or other type of information which is necessary to identify the GMO product and its progeny, for example the methodology for detecting and identifying the GMO product, including experimental data demonstrating the specificity of the methodology. Information that cannot be placed, for confidentiality reasons, in the publicly accessible part of the register should be identified,

8. proposed labelling on a label or in an accompanying document. This must include, at least in summarised form, a commercial name of the product, a statement that 'This product contains genetically modified organisms', the name of the GMO and the information referred to in point 2, the labelling should indicate how to access the information in the publicly accessible part of the register.

B. The following information shall be provided in the notification, when relevant, in addition to that of point A, in accordance with Article 13 of this Directive:

1. measures to take in case of unintended release or misuse,

2. specific instructions or recommendations for storage and handling,

3. specific instructions for carrying out monitoring and reporting to the notifier and, if required, the competent authority, so that the competent authorities can be effectively informed of any adverse effect. These instructions should be consistent with Annex VII part C,

4. proposed restrictions in the approved use of the GMO, for example where the product may be used and for what purposes,

5. proposed packaging,

6. estimated production in and/or imports to the Community,

7. proposed additional labelling. This may include, at least in summarised form, the information referred to in points A 4, A 5, B 1, B 2, B 3 and B 4.

ANNEX V

CRITERIA FOR THE APPLICATION OF DIFFERENTIATED PROCEDURES (ARTICLE 7)

The criteria referred to in Article 7(1) are set out below.

1. The taxonomic status and the biology (for example mode of reproduction and pollination, ability to cross with related species, pathogenecity) of the non-modified (recipient) organism shall be well-known.

2. There shall be sufficient knowledge about the safety for human health and the environment of the parental, where appropriate, and recipient organisms in the environment of the release.

3. Information shall be available on any interaction of particular relevance for the risk assessment, involving the parental, where appropriate, and recipient organism and other organisms in the experimental release ecosystem.

4. Information shall be available to demonstrate that any inserted genetic material is well characterised. Information on the construction of any vector systems or sequences of genetic material used with the carrier DNA shall be available. Where a genetic modification involves the deletion of genetic material, the extent of the deletion shall be known. Sufficient information on the genetic modification shall also be available to enable identification of the GMO and its progeny during a release.

5. The GMO shall not present additional or increased risks to human health or the environment under the conditions of the experimental release that are not presented by releases of the corresponding parental, where appropriate, and recipient organisms. Any capacity to spread in the environment and invade other unrelated ecosystems and capacity to transfer genetic material to other organisms in the environment shall not result in adverse effects.

ANNEX VI

GUIDELINES FOR THE ASSESSMENT REPORTS

The assessment report provided for by Articles 13, 17, 19 and 20 should include in particular the following:

1. Identification of the characteristics of the recipient organism which are relevant to the assessment of the GMO(s) in question. Identification of any known risks to human health and the environment resulting from the release into the environment of the recipient non-modified organism.

2. Description of the result of the genetic modification in the modified organism.

3. Assessment of whether the genetic modification has been characterised sufficiently for the purpose of evaluating any risks to human health and the environment.

4. Identification of any new risks to human health and the environment that may arise from the release of the GMO(s) in question as compared to the release of the corresponding non-modified organism(s), based on the environmental risk assessment carried out in accordance with Annex II.

5. A conclusion on whether the GMO(s) in question should be placed on the market or as (a) product(s) and under which conditions, whether the GMOs in question shall not be placed on the market or whether the views of other competent authorities and the Commission are sought for on specific issues of the e.r.a.. These aspects should be specified. The conclusion should clearly address the use proposed, risk management and the monitoring plan proposed. In the case that it has been concluded that the GMOs should not be placed on the market, the competent authority shall give reasons for its conclusion.

ANNEX VII

MONITORING PLAN

This Annex describes in general terms the objective to be achieved and the general principles to be followed to design the monitoring plan referred to in Articles 13(2), 19(3) and 20. It will be supplemented by guidance notes to be developed in accordance with the procedure laid down in Article 30(2).

These guidance notes shall be completed by 17 October 2002.

A. **Objective**

The objective of a monitoring plan is to:

— confirm that any assumption regarding the occurrence and impact of potential adverse effects of the GMO or its use in the e.r.a. are correct, and

— identify the occurrence of adverse effects of the GMO or its use on human health or the environment which were not anticipated in the e.r.a.

B. **General principles**

Monitoring, as referred to in Articles 13, 19 and 20, takes place after the consent to the placing of a GMO on the market.

The interpretation of the data collected by monitoring should be considered in the light of other existing environmental conditions and activities. Where changes in the environment are observed, further assessment should be considered to establish whether they are a consequence of the GMO or its use, as such changes may be the result of environmental factors other than the placing of the GMO on the market.

Experience and data gained through the monitoring of experimental releases of GMOs may assist in designing the post marketing monitoring regime required for the placing on the market of GMOs as or in products.

C. **Design of the monitoring plan**

The design of the monitoring plan should:

1. be detailed on a case by case basis taking into account the e.r.a.,

2. take into account the characteristics of the GMO, the characteristics and scale of its intended use and the range of relevant environmental conditions where the GMO is expected to be released,

3. incorporate general surveillance for unanticipated adverse effects and, if necessary, (case-) specific monitoring focusing on adverse effects identified in the e.r.a.:

   3.1. whereas case-specific monitoring should be carried out for a sufficient time period to detect immediate and direct as well as, where appropriate, delayed or indirect effects which have been identified in the e.r.a.,

   3.2. whereas surveillance could, if appropriate, make use of already established routine surveillance practices such as the monitoring of agricultural cultivars, plant protection, or veterinary and medical products. An explanation as to how relevant information collected through established routine surveillance practices will be made available to the consent-holder should be provided.

4. facilitate the observation, in a systematic manner, of the release of a GMO in the receiving environment and the interpretation of these observations with respect to safety to human health or the environment.

5. identify who (notifier, users) will carry out the various tasks the monitoring plan requires and who is responsible for ensuring that the monitoring plan is set into place and carried out appropriately, and ensure that there is a route by which the consent holder and the competent authority will be informed on any observed adverse effects on human health and the environment. (Time points and intervals for reports on the results of the monitoring shall be indicated).

6. give consideration to the mechanisms for identifying and confirming any observed adverse effects on human health and environment and enable the consent holder or the competent authority, where appropriate, to take the measures necessary to protect human health and the environment.

ANNEX VIII

CORRELATION TABLE

Directive 90/220/EEC	This Directive
Article 1 (1)	Article 1
Article 1 (2)	Article 3 (2)
Article 2	Article 2
Article 3	Article 3 (1)
Article 4	Article 4
—	Article 5
Article 5	Article 6
Article 6 (1) to 4	
Article 6 (5)	Article 7
Article 6 (6)	Article 8
Article 7	Article 9
Article 8	Article 10
Article 9	Article 11
Article 10 (2)	Article 12
Article 11	Article 13
Article 12 (1) to (3) and (5)	Article 14
Article 13 (2)	Article 15 (3)
—	Article 15 (1), (2) and (4)
—	Article 16
—	Article 17
Article 13 (3) and (4)	Article 18
Article 13 (5) and (6)	Article 19 (1) and (4)
Article 12 (4)	Article 20 (3)
Article 14	Article 21
Article 15	Article 22
Article 16	Article 23
—	Article 24 (1)
Article 17	Article 24 (2)
Article 19	Article 25
—	Article 26
Article 20	Article 27
—	Article 28
—	Article 29
Article 21	Article 30
Article 22	Article 31 (1), (4) and (5)
Article 18 (2)	Article 31 (6)
Article 18 (3)	Article 31 (7)
—	Article 32
—	Article 33
Article 23	Article 34
—	Article 35
—	Article 36
—	Article 37
Article 24	Article 38
Annex I A	Annex I A
Annex I B	Annex I B
—	Annex II
Annex II	Annex III
Annex II A	Annex III A
Annex II B	Annex III B
Annex III	Annex IV
—	Annex V
—	Annex VI
—	Annex VII