Regulatory aspects of environmental applications of transgenic crops: from precaution to familiarity

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1. Precaution is preferred over remediation

The introduction of any new technology is accompanied with side-effects. Usually, they go unobserved in the enthusiasm of the positive forecast. Other side-effects only show up as the use is prolonged. Accordingly, safety requirements for products are generally introduced on a curative basis. It is only when an unsafe situation is recorded, that a new requirement is installed in order to prevent future, similar cases. All safety regulations on eg. pharmaceutical and agrochemical products have evolved in this way.

Since it is better to prevent than to cure, the precautionary approach was introduced. Before any development step or introduction of a product, an assessment of the potential impact has to be made. Upon the result of that assessment an evaluation of the overall risk/benefit ratio can guide the decision on adequate management practices. Typically such an approach is expected to impose a high regulatory burden in the first cases, gradually levelling off to focused safety evaluation.

The introduction of technology that alters the genetic basis of living organisms was deemed new enough to warrant precaution and careful evaluation of potential impacts on the environment and human health. While the potential of the technology to improve health care, diagnostics, agriculture, industrial processes and waste treatment are recognized, such improvements should not be accompanied by the introduction of side-effects.

Yet, the potential applications are so diverse, that an evaluation of generic impacts or the establishment of fixed norms would be non-realistic. Every application — usually defined by the organism, the introduced trait and the intended environment — has to be evaluated for its own impact. The case-by-case assessment was introduced enabling tailoring of the review to the appropriate detail.

Furthermore, it was not clear what type of new problems could be expected. In the case of pathogens or harmful organisms, questions were raised on increased harm. But for most applications, eg. in plants and animals, the understanding of potential negative impacts was very vague. Additionally, while scale increases, the amount of control and containment decreases. Therefore, in order to advance without missing the identification and prevention of any potential harm, a stepwise review was introduced. As one gradually learns more about the organism and gets confirmation on the "normal" behavior in the environment, less restrictions are needed and "standard" practices can be relied upon.

2. Regulatory measures supporting the precautionary approach

Several regulatory initiatives have been installed in order to secure a high level of protection for the environment and human health, while not limiting the progress of biotechnology. In the USA, Canada and Japan, a set of guidelines within existing regulatory frameworks, eg. on plant pests (USDA), were preferred. As such, a flexible tool is created, which is not only limited to genetically modified plants. In fact, in Canada the scope of the guidelines are broadened to "Plants with Novel Traits", which really focusses on the novelty of the product, irrespective of the method by which it is produced. Contrary, in Europe, a specific regulation for genetically modified organisms was preferred. In 1990, two European Directives were adapted dealing with environmental aspects of genetically modified organisms. While the stigmatization of one technique — genetic engineering — has been criticized repetitively, it has to be recognized that — so far — the same organisms have been subject to scrutiny whatever the approach of the regulatory system.

The European Directive 90/220 specifically addresses the requirements for releasing a GMO into the environment, being it for experimental or commercial reasons. During each experimental stage, a document describing the releases and their potential impact needs to be submitted to the national competent authority. A summary of that document is send to all EU member states for information. It is then up to the national authority to decide on the authorization of the release and on possible additional conditions for management and control.

When a submission is made for commercial release, the same type of procedure is followed, but upon agreement with the national authority the full file is send to all member states for their review and approval. Since an eventual clearance would mean the authorization for marketing within the entire EU, all member states have to come to an agreement on the acceptance of a product. So far, one product — an oxynil tolerant tobacco — has been cleared through the European system. Hybrid oilseed rape, insect tolerant corn, herbicide tolerant soybean and hybrid radicchio rosso are now under evaluation at the European level.

3. Drawbacks of the precautionary approach

3.1. The risk assessment process has its own limitations

Within the precautionary approach, one can not fully guarantee safety of an application. The quality of the predictive value is highly dependent on the status of our knowledge on the host organism, the modification and the environment. Ecological studies provide further fine-tuning of predictive models, making the risk assessment reliable for future cases. Based on the precautionary approach, a risk assessment process cannot be a normative instrument. The final decision on allowing a product needs to balance the assessment with the benefits of the product within a framework of what is acceptable today and in future.

3.2. Stepwise review neglects true product oriented assessments

The reviews and releases fit within development programs of products. While such developments do naturally occur in gradual steps of research, feasibility studies, small scale application, production, etc., it has to be highlighted that the overall approach between the developer and the reviewer is in most cases different. The developer works towards a specification of a product. During the development phase these specification are fine-tuned, but the global picture in terms of required quality and the steps to get there are settled from the early days of the development program. The step-by-step approach requires evaluation at each moment of the development. It combines the review of the product and the intended release. If specific potential harms are identified, management may be required. Yet, the immediate goal is to ensure safety of that limited application. There is in most cases no feeling for the future direction of the development. The fear of the developer is to find that suddenly, while advancing to a next stage, new questions are asked. This may be strengthened by some indications that something that may be tolerated at a small scale, may be rejected for larger scale applications. The important point is not as much that something may be rejected, but the uncertainty on what information to supply, at what moment, and on which topic. Ideally, a full indication on the type of topics to address for the product should be established as soon as the first release. The developer can then evaluate the incorporation of appropriate testing and documenting at the relevant stage towards commercialization.

3.3. One step can be important for a nation, but small in relation to global competence

As more trials are carried out, a serious discrepancy is arising between national authorities in terms of experience in the review process. While re-

cognizing the national sovereignty, the step-by-step procedure imposes most authorities to go through the learning process independently from other evolutions. While some differences in condition of a trial can be related to environmental differences, others are strictly related to the experience of a regulatory authority with the particular case.

3.4. Broader issues tend to interfere with the risk assessment process of the genetically modified organism

Applications of genetic modification are subject to all existing quality and safety regulations, relevant for the specific products. In some cases, this has led to broadening the safety debate to other aspects. For instance, the introduction of specific herbicide tolerances has stirred up the debate on the use of herbicides in today's agriculture, whereas plants — incorporating protection mechanisms against insects- raise concerns for the development of resistant pests. In general a call for better management strategies is heard. While the points raised definitely deserve thorough reflection and policy decisions, it is unrealistic to burden only the developments of genetic engineering with these broader questions. None of the issues is specifically linked to the genetic modification per se and therefore needs to be pictured against today's practice and the future developments.

4. Scientific approaches towards risk assessment

We will base our concept of risk on the general paradigm : Risk = Hazard x Likelihood (x Consequence). Hazard essentially refers to a potential event that requires attention (eg. an introduced gene can spread to a wild relative). Likelihood (or frequency) would merely give an indication on the probability for such an event to occur. With the evaluation of the "consequence" it should finally become clear whether a given event will have a harmful, neutral or positive effect.

At the European level, within the Biotechnology Action Program, several pan-European collaborations have been addressing assessment methodology, establishment ability and competitiveness and gene dispersal from genetically modified plants. Part of this research has been completed in the Biotechnology Research for Innovation, Development and Growth in Europe (BRIDGE) program "Safety Assessment of the Deliberate Release of Two Model Transgenic Crop Plants, Oilseed Rape and Sugarbeet", which explicitly takes up the design of protocols and predictive modelling. The aim of these projects included a model crop description, highlighting hazard identification, determination of likelihood and ecological consequences (as summarized in Tab. 1). Most of these studies are based on lines with herbicide tolerance obtained through genetic engineering. In fact, the oilseed rape plants contained the "bar" gene,

coding for tolerance to glufosinate-ammonium, the sugarbeet plants were either tolerant to glufosinate-ammonium or to glyphosate. These particular lines were chosen because of the ease of the herbicide marker system and the economic importance of the particular trait/crop combination.

TABLE 1
RESEARCH TOPICS OF THE BRIDGE PROGRAM: SAFETY ASSESSMENT OF THE DELIBERATE RELEASE OF TWO MODEL TRANSGENIC CROP PLANTS, OILSEED RAPE AND SUGARBEET

Research topics Oilseed Rape	Research topics Sugarbeet
* Dispersal of introduced genes	* Evaluation physiology
Large scale pollen dispersal	Reference systems
Evaluation of outcrossing	Evaluation system
Monitoring seed dispersal	* Dispersal of genes
* Outcrossing to relatives	Spread of pollen
Behavior of introduced gene	Spread to wild relatives
Analysis of position effect	* Behavior of plants/populations
* Behavior of plant/populations	Fate of hybrids
Fate of hybrids	Evolution of mixed populations
Evolution of mixed populations	
* Stability of a GM plant	
Population and generation	
* Computer modelling	

Other Pan-European initiatives, eg. by the Steering Committee for the Conservation and Management of the Environment and Natural Habitats, have looked at long term effects of introductions on genetic diversity and the presence of hazardous substances in the environment.

Complimentary studies are conducted at national level. A prominent one, joining the authorities, industry and research institutes in a multi-year evaluation in the UK, is known by the acronym PROSAMO (Planned Release Of Selected And Modified Organisms). But also smaller, sometimes desk-, reviews have been and are conducted in cooperations instigated by the Competent Authorities. Without being comprehensive, it is worth mentioning some early initiatives:

- A review on kanamycin tolerance commissioned by the Dutch Ministry of Environment, being the basis of a conclusive statement: "Therefore, it would seem to be out of the question that a kanamycin resistant transgenic plant would pose any more harm than the non-transgenic parent plant".
- An initiative supported by the Danish Environmental authorities (The National Forest and Nature Agency, The Danish Environmental Protection Agency and The National Environmental Research Institute), in order to

design a checklist of testing parameters and protocols to evaluate genetically modified organisms.

- A set of research projects addressing horizontal and vertical gene transfer, ecological research supporting the release of transgenic sugarbeet and potatoes, technology assessment and ethical problems, on behalf of the German Federal Ministry for Research and Technology.

In connection to the increasing number of field trials, authorities and applicants are communicating on biosafety aspects and results.

Unfortunately, the national approaches may to some extent represent a multiplication of the effort to address a specific issue. It is recognized that there is a need and an opportunity to bring the initiatives together and update the entire community on the progress.

In addition to the European and national initiatives, every commercial product development contains a number of biosafety aspects and as the first commercial applications are announced, more of the research conducted by companies will become available. With the comfortable background of a large number of releases of genetically modified plants worldwide, several working groups have focussed on the identification of the major hazard factors. The Group of National Experts on Safety in Biotechnology of the OECD (OECD, 1993, Safety considerations for biotechnology: scale up of crop plants), summarizes the safety issues:

Vector effects and material derived from pathogens: Is the transforming agent still present?

Most transformations of crop plants are based on the *Agrobacterium* vector system. If plants would not be free of the transforming vector organism, transformation could proceed on other plants susceptible to the *Agrobacterium* system. In crops, where development involves several generations and multiplication through seeds, the absence of the transforming agent can be assumed.

Variability (genetic and phenotypic): Are the introduced genes stably expressed?

The aim of introducing genes for agronomic or industrial applications would require stable expression of those traits. Instability is primarily a quality problem, monitored through proper checks in development, breeding and certification. Although fluctuations and silencing of genes have been reported, most of the transformed lines for commercial development have been selected very thoroughly on stable genotype and phenotype. Only when the expression level is key to the determination of safety (eg. in determining threshold levels of toxic compounds), unpredictable fluctuations in expression level could introduce a risk.

Changed weediness characteristics: Can the genetically modified oilseed rape be more invasive than oilseed rape grown today?

If there is one common understanding on weediness, it is probably that it is very hard — if not impossible — to define what makes a plant a weed. The introduced traits aim at changing the performance in a very specific way, yet now we also focus on possible changes in ecological performance. For instance in the case of oilseed rape, a crop perceived as having a weedy potential, such evaluation is of interest. Pioneering work has been conducted in the biosafety programs, showing that for the range of oilseed rape material under investigation (incorporating genes for kanamycin tolerance, phosphinotricin tolerance, male sterility and restoration of fertility, and/or changed oil composition) no significant change in ecological performance could be recorded.

Gene transfer to sexually related species.

When introduced in the environment, the newly introduced genes have to be considered as part of the natural gene pool. The possibility to obtain F1 interspecific hybrids is only the first step in the long way of introgression of a trait into a distant species. In fact, the performance of that hybrid and its progeny, the fertility at the different steps, the spatial distribution of parental lines and the selective pressure exerted on such introgression processes have also to be taken into account. Finally, the consequence of a potential introgression has to complete the assessment, most revealing no introduction of additional competitive behavior.

For all practical reasons, exchange with organisms by other than sexual transmission can be rated as extremely unlikely.

Are there other trait specific concerns?

Some traits could introduce specific concerns. In work on insect tolerance, one would obviously be interested in the effect on beneficiary insects. The broader the biochemical base of a trait, the more difficult it may prove to address these aspects. Testing will need to be tailored to the particular specifications of the trait.

The likelihood of such events will be largely crop/trait dependent but can be related to existing crop knowledge and experience. Management strategies could be applied to change the likelihood of a certain event (eg. isolation distances in order to reduce possibility of effective pollen spread). The consequence of an interaction is entirely dependent on the trait.

5. Simplification of the regulatory system based on the establishment of familiarity

As pointed out above, the precautionary approach was initially envisaged in order to cope with the "unknown" nature of potential risks. Based on the safety assessment programs as well as on the record of many field releases, it was concluded that "there have been no surprises in the behavior of the transgenic plants in relation to what might be expected from the charac-

teristics of the host and nature of the genetic insert" (OECD, 1993, Field releases of transgenic plants, 1986-1992 an analysis). In addition to "precaution" the concept of "familiarity" has been introduced: knowledge and experience with crop plants, the environment, traits and their interactions are gradually integrated during the developmental scale up in projects. This first level of familiarity being recognized, future scientific approaches will have to focus on the consequence of specific novel traits. Recently based on the experience with field releases of genetically modified higher plants the data requirements for such requests were adapted in Europe. In other cases, e.g. in the USA and in the UK, the requirements for certain crops were streamlined covering different traits.

The next challenge to the regulatory system will be to achieve international harmonization. While field experiments are confined to limited areas, products will be employed over larger, trans-national growing areas. Furthermore, the agrofood products derived from the application of these crops, will be handled in international trade as part of the global commodity market. While the products are gradually being introduced, several initiatives to share information among regulatory agencies are being established. Within Europe the exchange of SNIFs has been officially established. Regular meetings between authorities from Europe and North-America, or at a global scale within the framework of the OECD, target the harmonization in the evaluation and management of risks. Further initiatives for mutual acceptance of criteria, of data and of review should pave the introduction of GMOs on the global market.

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Summary

Based on the precautionary approach, new, unfamiliar products or processes are subject to a risk evaluation before carrying out any intended use. The behavior of GMO's was deemed to be new — therefore unpredictable — enough to warrant such careful evaluation in order to reduce the risk of harm to human health and the environment. Over the past years, several studies have focussed on environmental interactions of model transgenic crops, e.g. oilseed rape, *Brassica napus*, in different eco-systems in North-America and Europe. Based on the experience with field releases of genetically modified higher plants, the data requirements for such requests were adapted in Europe. In other cases, e.g. in the USA and in the UK, the requirements for certain crops were streamlined, covering different traits. In this respect, the step-by-step, case-by-case approach allowed to identify relevant environmental issues, thereby creating a comfort level of "familiarity". With the acquisition of familiarity, a basis is created for focussed risk analysis, which is now leading to the first commercial introductions of genetically modified crops.

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