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A conceptual framework for the design of environmental post-market monitoring of genetically modified plants

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Genetically modified plants (GMPs) may soon be cultivated commercially in several member countries of the European Union (EU). According to EU Directive 2001/18/EC, post-market monitoring (PMM) for commercial GMP cultivation must be implemented, in order to detect and prevent adverse effects on human health and the environment. However, no general PMM strategies for GMP cultivation have been established so far. We present a conceptual framework for the design of environmental PMM for GMP cultivation based on current EU legislation and common risk analysis procedures. We have established a comprehensive structure of the GMP approval process, consisting of pre-market risk assessment (PMRA) as well as PMM. Both programs can be distinguished conceptually due to principles inherent to risk analysis procedures. The design of PMM programs should take into account the knowledge gained during approval for commercialization of a specific GMP and the decisions made in the environmental risk assessments (ERAs). PMM is composed of case-specific monitoring (CSM) and general surveillance. CSM focuses on anticipated effects of a specific GMP. Selection of case-specific indicators for detection of ecological exposure and effects, as well as definition of effect sizes, are important for CSM. General surveillance is designed to detect unanticipated effects on general safeguard subjects, such as natural resources, which must not be adversely affected by human activities like GMP cultivation. We have identified clear conceptual differences between CSM and general surveillance, and propose to adopt separate frameworks when developing either of the two programs. Common to both programs is the need to put a value on possible ecological effects of GMP cultivation. The structure of PMM presented here will be of assistance to industry, researchers, and regulators, when assessing GMPs during commercialization.

Keywords: environmental monitoring / EU Directive 2001/18/EC / genetically modified plants / transgenic crops / post-market monitoring

Abbreviations: **CSM**: case-specific monitoring; **ERA**: environmental risk assessment; **GMP**: genetically modified plant; **PMM**: post-market monitoring; **PMRA**: pre-market risk assessment

INTRODUCTION

In 2004, the estimated global area of genetically modified plant (GMP) cultivation was more than 81 million hectares, with five countries, *i.e.* USA, Argentina, Canada, Brazil and China, growing 97 percent of these crops (James, 2004). None of these countries requires legally binding post-market monitoring (PMM) activities, or they limit them to very specific areas, such as insect resistance monitoring of *Bt* maize cultivation, as in the United States (Jaffe, 2004). The regulatory frameworks of these countries recognize that products that have received regulatory approval are judged to be substantially equivalent, and do not represent a greater risk than comparable products with a history of safe use. Environmental PMM or long-term population health surveillance are therefore not considered necessary. However, this principle is being questioned, since short-term experiments and general characterization of plant traits may not detect all environmental effects of GMPs (National Research Council, 2002). In the United States, PMM activities are being discussed in order to determine if pre-market testing protocols adequately

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assess risks. In Europe, the principle of substantial equivalence is not followed, and a precautionary approach is chosen instead. In the European Union (EU), the principles for regulating the release of GMPs into the environment are laid down in EU Directive 2001/18/EC (European Community, 2001). Everyone who intends to commercially introduce GMPs into the environment is obligated to present a PMM plan to identify possible adverse effects on human health and the environment, which could arise directly or indirectly from the released GMP. To date, no EU-wide consensus on how to design such PMM programs has been defined, although monitoring concepts are currently developed in several European countries. In addition, new EU regulations on approval, labeling, threshold values and traceability of GMPs have become effective in November 2003 (European Union, 2003a, b). In some EU member countries the commercial cultivation of GMPs could soon be approved, which results in an urgent need for conceptual frameworks and guidance on how PMM programs should be planned and performed. Despite the fact that the use of GMPs in Swiss agriculture seems unlikely in the near future, commercial releases of GMPs would, as in the EU, also have to be monitored in Switzerland. According to the EU Directive and to Swiss laws, the ultimate responsibility for a PMM program would lie with the companies holding the consent for commercial release of a specific GMP. However, there certainly is a need for governmental structures to coordinate PMM programs. For providing consistent and comparable results, consent holders would also have to design and run their PMM programs according to a general framework using standardized methods and protocols.

The aim of this study was to develop a conceptual framework that would propose structures and procedures that could be used to implement such PMM programs. The conceptual framework should represent a pragmatic approach to realistic and feasible PMM programs. We limited our study to GMPs and to potential adverse effects on the environment that could occur during their commercial cultivation. We took EU Directive 2001/18/EC and its respective guidance notes (European Commission, 2002; European Community, 2001; European Council, 2002) as a basis for our study, since Swiss legislation (FrSV, SR 814.911; GTG, SR 814.91) remains relatively unspecific with respect to aims, design and planning of PMM programs. The approach we chose was to analyze the basic requirements for effective environmental monitoring, and to determine whether such activities do meet the needs of a PMM according to EU Directive 2001/18/EC. Using this approach two specific principles had to be combined: (1) the approval process for GMPs in Europe and (2) general principles of environmental monitoring programs.

PRINCIPLES CONSIDERED FOR THE DEVELOPMENT OF THE CONCEPTUAL FRAMEWORK

Procedure for the approval to commercially cultivate GMPs in Europe

Each approval for commercial cultivation of a specific GMP has to be preceded by case-by-case risk assessments of potential adverse effects on human health and the environment. Furthermore, the introduction of GMPs into the environment should generally be performed according to the step-by-step principle, which means that the scale of GMP releases can only be increased if a risk assessment based on information of the preceding step has resulted in an estimation of an acceptable risk for the next step (European Community, 2001). Potential adverse effects of a GMP have to be investigated in a first step under containment in the laboratory and in the greenhouse. In a first environmental risk assessment (ERA I), it is decided whether a limited experimental release of the GMP under controlled conditions can be performed. Approval for commercial cultivation is only granted after a thorough second environmental risk assessment (ERA II), in which the characteristics of the GMP are compared to those of the corresponding non-modified plant under comparable conditions (European Commission, 2002). Due to the complexity of the issues addressed, ERA II may not always result in final answers. The resulting lack of data may be due to the spatial and temporal restrictions of the experiments performed during pre-market risk assessment (PMRA). For a final assessment of the long-term effects of GMP cultivation, data from PMRA may be limited. These data can only be provided by PMM. Case-specific monitoring (CSM) shall assess whether the decision based on ERA II regarding the occurrence and the impact of anticipated adverse effects is correct, whereas general surveillance shall detect unanticipated adverse effects (European Community, 2001). The consent for commercial cultivation is limited to ten years, after which the results of CSM, general surveillance and any other new information have to be presented in a third environmental risk assessment (ERA III) to the competent authority in order to allow renewal of the consent (European Community, 2001). The procedure used to decide whether a GMP meets the requirements for

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approval for commercial cultivation leads to conceptual differences between PMRA and PMM, which have to be considered when designing a PMM program.

Distinction between pre-market risk assessment and post-market monitoring

Even though PMM, according to Part C of EU Directive 2001/18/EC, covers commercial cultivation of GMPs, we noticed that activities belonging to a PMM program are not clearly distinguished from tasks performed during a PMRA. We found, however, that based on their different purposes, the two phases can be distinguished. Approval for commercial cultivation can be regarded as an important step during the evaluation process of GMPs, and is based on the knowledge gained from risk assessments in laboratory, greenhouse and field trials (ERA II). It therefore represents a consolidated risk conclusion by the competent authority. Since these PMRAs have been carried out in a scientifically sound manner and according to accepted risk assessment approaches (CBD, 2000; European Commission, 2002), it can be assumed that the risks related to the cultivation of the approved GMPs are judged to be acceptable, otherwise consent would not be given. However, risk assessments are always limited by some uncertainties (Hill and Sendashonga, 2003; Levidow, 2003). The Cartagena Protocol on Biosafety explicitly recognizes that these scientific uncertainties exist, and that decisions must be made recognizing that those uncertainties may not be resolved (CBD, 2000). This is also recognized by the European Commission, which states that the precautionary approach (Ammann, 2004) is particularly relevant to the management of risks (European Commission, 2000a), and risk management should control an identified risk but also cover possible uncertainties (European Commission, 2002). Activities like PMM programs therefore represent appropriate tools to address and reduce such uncertainties. It is interesting that EU Directive 2001/18/EC does not consider possible benefits for the approval of GMPs. Only possible adverse effects on human health and the environment are evaluated, although a risk/benefit assessment should be common practice in an approval process, as common for many other hazards (European Commission, 2000b). The approval process for commercial cultivation of a GMP should include a risk/benefit assessment where the benefits and the risks of a GMP are weighed by comparing positive and negative effects with current agricultural practice.

We established a scheme that clearly presents and distinguishes the different phases and activities during development and commercialization of a GMP (Fig. 1). PMRA is limited to the phase prior to approval for commercial cultivation, whereas PMM is limited to activities related to the commercial cultivation of GMPs. It is important to bear in mind that PMM programs are tools to provide decision-makers with science-based data on possible effects of GMP cultivation and to support decisions when corrective action will be needed in order to prevent ecological damage. Without reliable information on changes in the state of the environment, and on the causes of these changes, decision-making can not efficiently deal with these issues (Vos et al., 2000). In this context it is important to emphasize the difference between the terms change and damage. Damage is an adverse effect and is always linked to deterioration in quality of a particular subject (*e.g.* human health or the environment). Definition of a damage is based on a value judgment, and differs thus from a change, which is a neutral description. Unless there is an appropriate value judgment, change is not *per se* harmful and may represent a natural process. It is not possible to scientifically define ecological damage, as scientific methods are only capable of showing ecological changes. To put a value on these changes, scientific, social, ethical, and economic factors have to be considered.

Principles of environmental monitoring programs

We felt a strong need for a clear definition of the specific functions and differences of CSM and general surveillance, as well as for a definition of what tasks should be performed in each program. In order to clearly distinguish the differences between the two programs, we analyzed the general principles of existing environmental monitoring programs (Hellawell, 1991; Vos et al., 2000). The terminology used in Directive 2001/18/EC is not very precise, since the term monitoring is used as an umbrella term in PMM, and subsequently two specific programs are distinguished, of which one is called CSM. The term monitoring is often used in a very broad sense, although based on conceptual differences it can be clearly distinguished from the term surveillance. The purpose of monitoring is defined as the detection of changes and effects related to specific causes (Hellawell, 1991), such as the cultivation of GMPs. The purpose of surveillance is defined as the detection of changes without focusing on a specific cause. Various environmental indicators are analyzed in order to detect shifts in environmental quality as a pure assessment of state (Hellawell, 1991). Based on these conceptual differences, CSM and general

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Table 1. Objectives of a monitoring program for genetically modified plants (GMPs) according to EU Directive 2001/18/EC, plus a judgment on the possibilities and limits of case-specific monitoring and general surveillance.

	Case-specific monitoring	General surveillance
Objectives according to 2001/18/EC	– To assess, if anticipated adverse environmental effects related to a specific GMP do occur (confirm assumptions of environmental risk assessment - ERA)	– To detect unanticipated adverse environmental effects which were not identified in the ERA
Approach	– Detection of changes related to GMP cultivation during a defined time period	– Assessment of state of the environment independent from any preconception and time period
What the program can provide	– Case-specific confirmation or rejection of a previously formulated hypothesis in comparison to a reference system – Draw conclusions on the cause of detected changes	– Provide information on the state of the environment and of possible environmental changes – Provide fundamentals to forecast the likely development of the environment (early warning system)
What the program can not provide	– Draw conclusions on the long term development of the environment	– Determine the cause of an environmental change – Draw conclusion on the effects of GMP cultivation

surveillance can more clearly be defined, and their respective limits can be identified (Tab. 1):

1. CSM has the objective to assess whether GMP-related adverse effects on the environment do occur. It is based on specific risks that a certain GMP could present. CSM can be regarded as the continuation of the investigations performed during PMRA, since defined hypotheses on possible anticipated effects are tested. The hypotheses can be confirmed or rejected after a defined period of time, and CSM can be terminated (Fig. 1). As CSM is performed in close relation to the cultivation of a certain GMP, it should be possible to draw conclusions on the causes of detected changes. The gain of knowledge from PMM may lead to new questions, which have to be answered in specific risk assessment studies. CSM helps to reduce remaining uncertainties, and its results may influence the PMRA of new GMPs with comparable properties.
2. General surveillance has the objective to detect unanticipated adverse environmental effects that were not identified and considered in ERA II. Results obtained from general surveillance cannot be linked to any specific attributes of GMP cultivation, since the program provides a general assessment of the state of the environment, independent of any preconception. It can provide information on exceptional environmental events and changes, and possibly provide basic information to forecast the likely development of the environment. General surveillance is not designed to determine the cause of possible environmental changes, as a multitude of factors could be involved. If environmental changes are observed, and it is likely that the cultivation of a specific GMP has caused them, the causality will have to be determined through specific risk assessment studies (Fig. 1).

CONCEPTUAL STRUCTURE FOR CASE-SPECIFIC MONITORING

Many existing monitoring programs face the problem of providing only limited information on quality and changes of the environment, because their purposes have not been exactly defined (Vos et al., 2000). We propose to develop CSM programs according to a strict framework, following four distinct phases, each consisting of three defined steps (Tab. 2). The responsibility for CSM lies with the consent holder (European Community, 2001). In most cases this will be a company, which has obtained approval for marketing a specific GMP. Each application for placing a GMP on the market must contain a plan for CSM. The plan must describe how the applicant plans to carry out the monitoring program, and has to be approved by the competent authority (European Community, 2001).

Phase I: Defining the CSM strategy

The first step involves the identification of possible risks that could be caused by the cultivation of the specific GMP. One can assume that they are mostly known from PMRA, and that they depend on the plant, its genetic modification and on the cultivation area. Sometimes influencing factors, such as the presence of wild relatives of a plant can be excluded, while other risks can be more important due to specific geographic conditions. ERAs and CSM are closely linked, since the risk assessments

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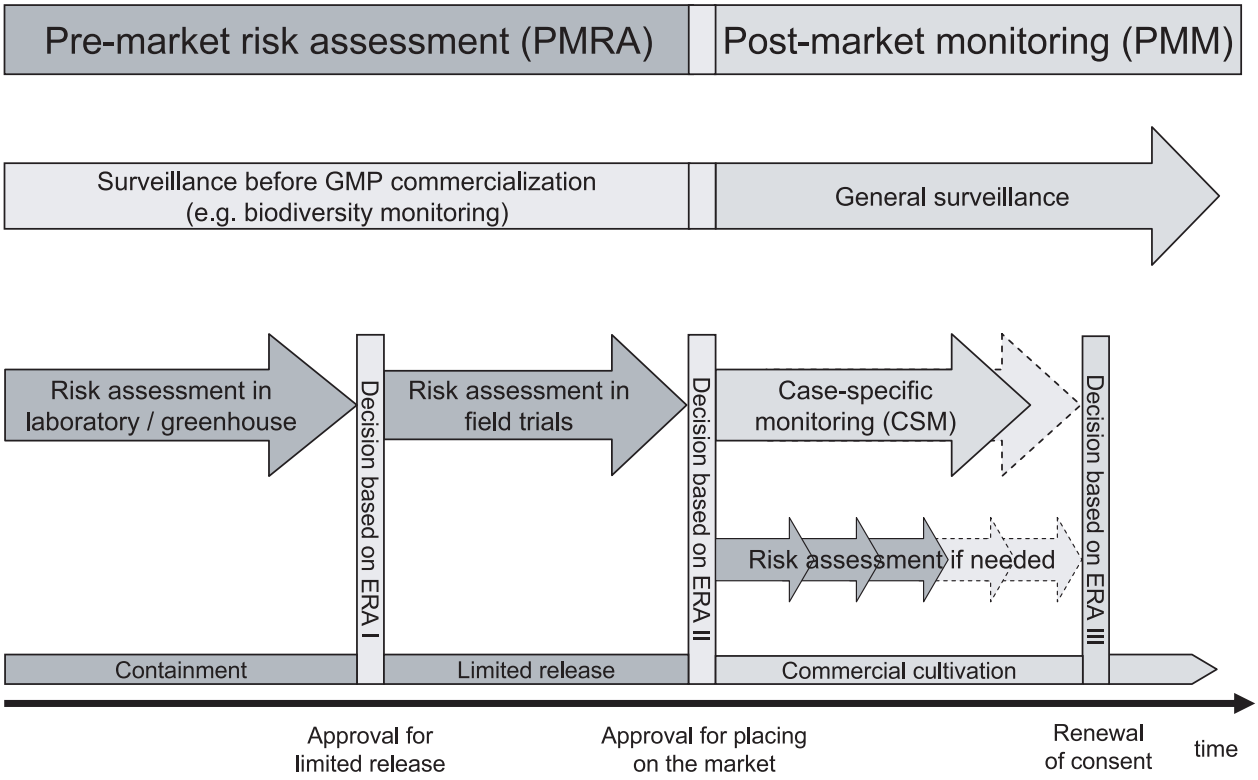

Figure 1. Stepwise procedure of ecological risk assessment during the life cycle of a specific genetically modified plant (GMP). Pre-market risk assessment and post-market monitoring are two distinct phases during the evaluation of possible risks of GMPs. The two phases are separated by the approval for commercial cultivation, which represents a significant step in this process (ERA = environmental risk assessment).

provide the basis for the subsequent CSM. A CSM strategy should identify how data obtained from PMRA can be validated. In addition, detection of possible effects that may only arise in large-scale and long-term releases may also be part of CSM (European Council, 2002). The second step concentrates on determining potentially affected environmental safeguard subjects, such as biodiversity and the natural resources: air, soil and water. The term safeguard subject is used here to denote an environmental subject that is commonly accepted as valuable for the society and thus needs to be protected. Step three consists in defining effects that could occur in these safeguard subjects. Current proposals for ERA limit analysis of environmental effects of GMPs mainly to two safeguard subjects, biodiversity and soil (for review see Conner et al., 2003; Dale et al., 2002; Pretty, 2001; Wolfenbarger and Phifer, 2000). This restriction of safeguard subjects, however, is based on results of PMRAs performed on the currently commercially available GMPs.

For CSM we propose six different environmental risk categories that could be of relevance for monitoring (Fig. 2): (1) introgression into wild relatives, (2) invasiveness of GMPs, (3) environmental behavior of transgenic products, (4) effects on non-target organisms, (5) resistance development in the target organisms and (6) effects due to changes in agricultural practice and cropping systems. In each risk category possible effects can be separated into consecutive steps. Depending on the characteristics of the GMP, the applicant has to identify on a case-by-case basis, whether a CSM of certain risk categories is necessary and at which step the effects shall be monitored. This involves an initial evaluation of possible effects that are regarded as relevant and worthwhile monitoring. For each effect that will be monitored, a hypothesis has to be formulated that can be tested using scientific methods. If the ERA II has not identified a risk, or if possible adverse effects are negligible, CSM may not be required (European Council, 2002). According to Directive 2001/18/EC, confirmation

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Table 2. Procedure to be followed for developing a case-specific monitoring (CSM) program for genetically modified plants (GMPs).

Phase	Step		Description	Examples
		CSM strategy		
I	1	Risk identification	What risks could occur due to the GMP in a geographic area?	Non-target effects due to *Bt* Maize (Cry1Ab) in the Swiss plateau
	2	Safeguard subjects	Which relevant safeguard subjects could be at risk?	Biodiversity (non-target arthropods *e.g.* butterflies)
	3	Effect definition	What are potential effects? Formulate hypothesis	Increased larval mortality of *Bt*-sensitive non-target butterflies
		Determination of scales		
II	4	Effect size	What effect size should be detected?	0.5-fold change in population size compared to an equivalent non-transgenic crop
	5	Spatial scale	Where should the safeguard subjects be assessed?	In habitats adjacent to *Bt* maize fields (< 10 m from field edge)
	6	Temporal scale	How long should the safeguard subjects be assessed?	No exceeding of the defined threshold within the next five years
		Planning		
III	7	Indicator selection	Select suitable indicators according to defined criteria and define trigger values for each indicator	*Bt*-sensitive butterfly species living as larvae in habitats adjacent to *Bt* maize. A trigger value might for example be a 50% reduction in population size.
	8	Feasibility study	Select method, define organization structure and data management, determine synergies with existing programs	Counts of adults of butterfly species
	9	Sampling plan	Design sampling plan	Parameters, frequency of sampling, sample size, resources and costs
		Operational program		
IV	10	Data collection and analysis	Assessment of potential effects by measuring specific indicators	
	11	Data evaluation	Evaluation of analysed data – confirm or reject hypothesis	Compare population changes to previously defined trigger values
	12	Decision	Decision by competent authority on immediate action	No action required Risk management is required Cultivation has to be suspended

of the assumptions made in the ERA prior to commercial approval is thus not *per se* mandatory.

Phase II: Determining the scale of CSM

Step four aims at defining the effect sizes that have to be considered in CSM (Tab. 2). CSM is usually hypothesis-driven, *i.e.* one tests if expected effects do occur during cultivation of a specific GMP. The detection of environmental effects is closely related to the sensitivity or the discriminatory power of the test used (for review see Fairweather, 1991; Marvier, 2002). The required sample size thereby is inversely proportional to the expected effect size, *i.e.* increased sample sizes are required to detect smaller effects (Lang, 2004). In order to reduce costs, one aims to keep sample sizes as low as possible. It is consequently crucial to pre-define the effect size that needs to be detectable for each indicator. For the Farm-Scale Evaluation project in the UK, detection of a 1.5-fold difference was chosen as effect size and a power analysis

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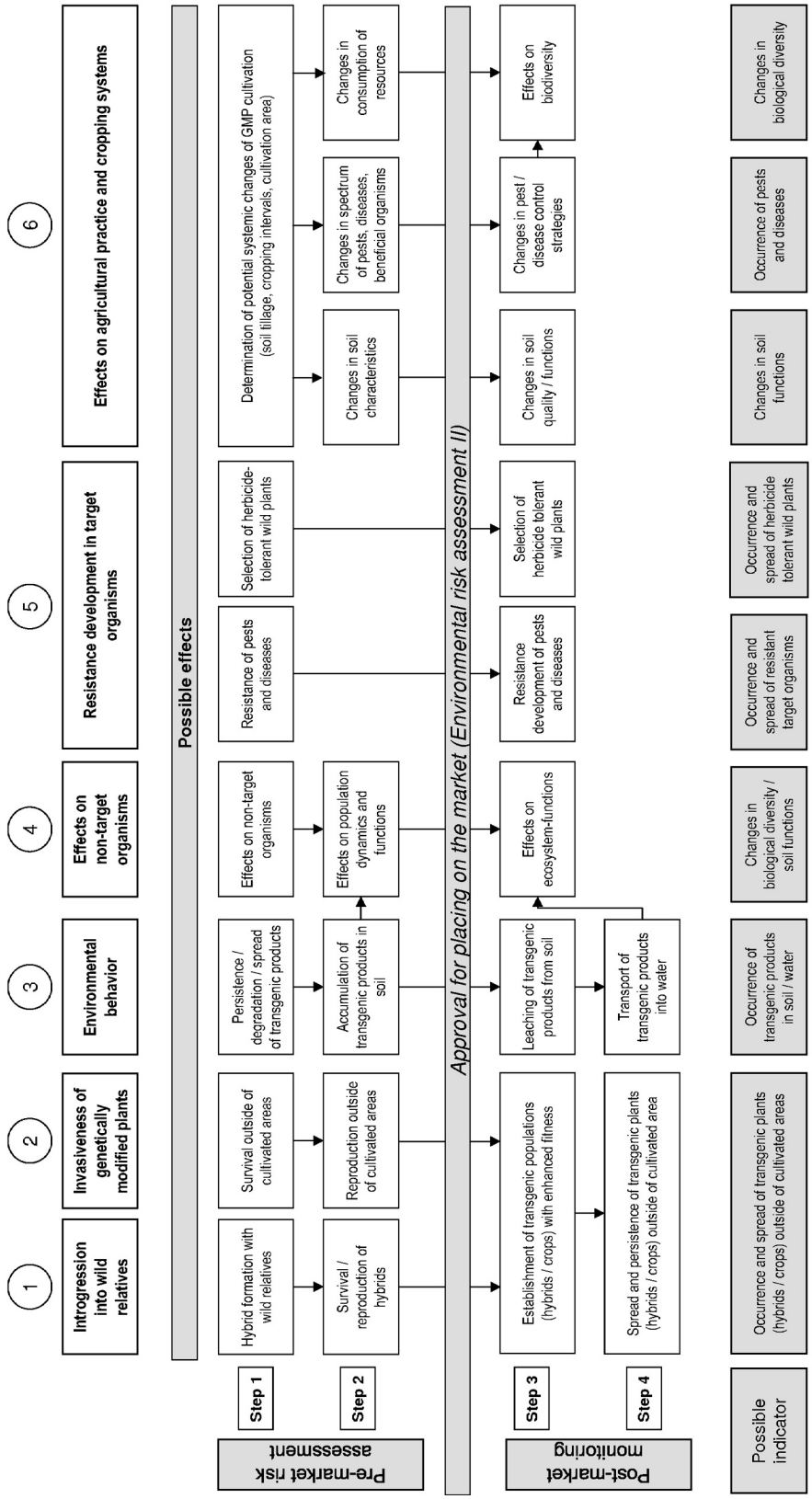

Figure 2. Differences in the questions investigated during pre-market risk assessment and the effects monitored during post-market monitoring. Possible effects of genetically modified plants (GMPs) can be subdivided into consecutive steps (no. 1 to no. 4). Possible indicators for post-market monitoring are proposed. The authors do not consider horizontal gene transfer as a possible risk that should be part of a post-market monitoring program.

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suggested that a replication of about sixty fields per crop over three years was needed to provide sufficient information for valid statistical inferences (Perry et al., 2003). Although sixty fields represent a rather large number of samples, a 1.5-fold difference in population sizes appears quite drastic. Consequently, the aim to detect a 5% or a 50% difference in the population sizes of a species can have a considerable impact on the sampling effort needed (Lang, 2004). In the last two steps of this second phase, where and for how long CSM needs to be performed should also be defined. According to EU Directive 2001/18/EC, the time period may not necessarily correspond to the ten year period given for the consent (European Community, 2001), but it could be extended beyond the consent period for detection of delayed effects (ACRE, 2004). However, it is important to consider that the life-span of modern crop varieties may be shorter than the ten year period. While during the 1980s the average life-span of an oilseed rape cultivar, for example, was about ten years, it dropped to three years by 1997 (Lindner, 2004). Therefore, it might become difficult to perform CSM over a long period of time for a specific GMP variety.

Phase III: Planning the operational CSM program

Step seven consists in selecting specific indicators to test the specified hypothesis (Tab. 2). The term indicator is used according to Duelli and Obrist (2003a), who defined that "an indicator should be a measurable portion of an entity that correlates with this larger entity". The safeguard subject "biodiversity in agricultural landscapes" could be such an entity, while the biodiversity of butterflies could represent one indicator among others, used to represent the biodiversity of agricultural landscapes. For biodiversity assessments, several indicators such as flowering plants, birds, and butterflies are often combined to assure the quality of the data obtained (Hintermann et al., 2002; Jeanneret et al., 2003). The term parameter is used as contributory to the term indicator, since an indicator is often assessed by the measurement of several parameters. Indicators for CSM have to be selected according to the effect that has to be monitored, or more generally, according to the hypothesis that has to be tested. Since every risk category can be subdivided into several steps, it is important to determine at what step the effects are best monitored (Fig. 2). Taking the possible risk of introgression from genetically modified plants into wild relatives as an example, PMRA will mainly have allowed to determine how far pollen can disperse, how frequently gene flow occurs, whether resulting hybrids are viable and fertile, and whether the transgene confers increased fitness. Since pollen dispersal and gene flow do not *per se* represent ecologically adverse effects, monitoring transgenic pollen dispersal would be an inappropriate indicator to assess introgression. PMM should rather concentrate on assessing the establishment and spread of hybrid plants and determine whether they replace other species, due to increased fitness acquired by the uptake of genetically engineered DNA sequences.

Based on experience with a monitoring program on biodiversity in agricultural landscapes (Jeanneret et al., 2003), we underline the importance of the indicator selection process. The selection of species or groups of species should be based on objective criteria (Tab. 3) to assure quality and acceptability of the indicators (Hunsaker, 1993; Noss, 1990; Pearson, 1995; Stork and Samways, 1995). Beside pure scientific criteria, the selection could also be driven by social, ethical and economic factors. Indicators may to a certain degree be selected based on their perceived value for the society, such as flagship species, which serve as symbols for conservation awareness (*e.g.* butterflies and bees). In addition, specific trigger values should be defined for each indicator selected, in order to allow for later data evaluation and decision making in the operational CSM program. The function of these trigger values is to initiate subsequent action by competent authorities. Since selection criteria for a robust indicator include knowledge on natural variability of the species selected, a definition of an approximate trigger value should be based on existing scientific knowledge. However, if definition of trigger values is not possible due to incomplete ecological knowledge, the selected indicator may not be suited for the assessment of possible adverse effects on biological diversity. The indicator selection process should be followed by the selection of an appropriate method for indicator assessment, *i.e.* a feasibility study, in which experts have to determine in detail how selected indicators can be assessed. Feasibility studies include the definition of the organization structure needed to perform data collection and management, as well as the determination of synergies with existing monitoring programs.

In some cases it may be difficult to relate environmental effects that could be detected during CSM unambiguously to the GMP or its cultivation. All crops and all farming systems do cause environmental impacts, and the effects detected could have been caused by other factors than the GMP. Furthermore, a range of environmental stresses, like weather conditions, might have an important additional impact on ecological parameters. An unbiased evaluation therefore has to consider a reference

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Table 3. Criteria for the selection of species or groups of species for the assessment of biological diversity (according to Hunsaker, 1993; Noss, 1990; Pearson, 1995; Stork and Samways, 1995). Specific criteria relevant for indicators for case-specific monitoring of genetically modified plants (GMPs) are added.

	General criteria
1	The taxonomy of the group is well known and its identification is easy
2	The functional importance of the group within the ecosystem is known
3	The higher taxa occur over a broad geographical range
4	The populations of a single species are closely associated to a specific habitat
5	The populations are readily monitored, *i.e.* the species are always present and easy to locate
6	The taxonomic and ecological diversity is high, *i.e.* there are many species in each habitat
7	The indicator taxon should be sufficiently sensitive and responsive to changes in order to provide an early warning
8	Monitoring is easy and inexpensive
	Specific criteria relevant for GMPs
9	The higher taxa occupy a spectrum of habitats in the agricultural landscape
10	The indicator taxon shows patterns of sensitivity to a specific GMP or to changes in agricultural management practices related to GMPs

system, which displays the environmental effects occurring without the cultivation of GMPs. For CSM, a comparable cropping system without GMP could serve as a parallel control. The evaluation of CSM requires the comparison of both crop systems in parallel over the same period of time and in a comparable ecosystem. Nevertheless, a paired comparison might become difficult in practice, if for example the non-transgenic control is not cultivated in the same region or in a comparable agricultural landscape. An additional difficulty could arise from differences in crop management techniques for GM and non-GM plants. For example, GM herbicide-tolerant crops should be managed best by using a no-till strategy, while this technique may not be advisable for cropping systems based on conventionally bred plants. The last step in the planning phase involves the design of sampling plans based on the feasibility study. For each indicator the set of parameters has to be defined and the extent of sampling has to be specified. This allows determination of resources and funding needed to perform the CSM program.

Phase IV: Running the operational CSM program

The first two steps of the operational monitoring program will involve data collection, analysis, and evaluation (steps ten and eleven, Tab. 2), where the consent holder or a contractor will in most cases perform all three operations. The competent authority, however, will also have to perform a separate data evaluation. Data evaluation clearly needs to consider effects of all currently applied agricultural practices. Intensification of agriculture, for example had a range of impacts on biodiversity, with widespread declines in the diversity of many groups of organisms associated with farmland in Europe (Hails, 2002; Robinson and Sutherland, 2002). If a parallel control with a comparable cropping system without GMP is not possible, environmental impacts of GMP cultivation need to be compared to the effects caused by current agricultural practice. While the cultivation of *Bt* maize for example may have weak effects on non-target arthropods, the use of a synthetic insecticide can significantly affect a large number of plant dwelling non-target arthropods (Candolfi et al., 2004). Step 11 leads to a conclusion whether the formulated hypothesis can be confirmed or rejected.

In the last step, the competent authority has to consider two questions (1) have any relevant adverse effects been detected during CSM, and (2) if relevant adverse effects have been detected, do they exceed the defined trigger value. If a relevant adverse effect or damage can be excluded based on the pre-determined trigger value, CSM can be terminated. If the trigger value has been exceeded, the competent authority will have to decide if immediate corrective action relating to GMP cultivation is needed in order to avoid environmental damage. Possible measures include termination of the cultivation of that GMP variety, suspension of the consent for cultivation

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Table 4. Procedure to be followed while developing a monitoring plan for general surveillance of genetically modified plants (GMPs).

	Step	Description
1	Definition of safeguard subjects	Which safeguard subjects should not be affected by the cultivation of GMPs?
2	Collection of reports on adverse incidents	Collect reports on adverse incidents via existing surveillance programs and reporting system on adverse environmental effects
3	Analysis of reports on adverse incidents	Detect changes that lie outside of expected variation
4	Valuation of reports on adverse incidents	Decide if relevant changes represent an environmental damage
5	Determination of likelihood to GMP cultivation	Determine if causality to the cultivation of a specific GMP is likely Decide if cultivation of a specific GMP must be suspended
6	Determination of causality to GMP cultivation	Determine causality through risk assessment study
7	Final decision	Decide if causality is unambiguous and the consent for cultivation of a specific GMP has to be withdrawn

followed by further risk assessment studies, or specific risk mitigation measures. The final decision on renewal of consent (ERA III), on the other hand, will consider all results of the various CSMs for a specific GMP that have been performed in different regions and possibly with different designs.

CONCEPTUAL STRUCTURE FOR GENERAL SURVEILLANCE

General surveillance follows a different approach than CSM (Tab. 4), since it is not based on anticipated risks of a specific GMP, but has the scope to detect unexpected changes in the environment (see above *Principles of environmental monitoring programs*). There is an inherent challenge in trying to detect the unexpected. Due to its scope, general surveillance must therefore concentrate on the environmental subjects that need to be preserved, rather than focusing on a specific hypothesis, as is done for CSM. However, since the term environment is much too unspecific for practical use, there is a need for defining specific safeguard subjects, which will be the focus of general surveillance.

Defining safeguard subjects for general surveillance

The protection of natural resources is primarily dominated by factors necessary for humans and the society, such as the quality of air and water as fundamentals for life, or the fertility of the soil as prerequisite for a sustainable agriculture. Natural resources that should not be affected by the cultivation of GMPs are identical to those that should not be affected by agriculture in general. Among other fields, the OECD has identified key agri-environmental issues for soil, water, air and biodiversity, which may reflect changes in the environment caused by agricultural practice (OECD, 1997). When taking into account possible effects that could arise from the cultivation of various GMPs, these key issues could be adapted to define safeguard subjects for general surveillance (Tab. 5).

Collecting reports on adverse incidents in general surveillance

Reporting systems as part of risk management after commercial approval already exist in other fields, such as pharmaceuticals and medical devices (FDA, 2005; MHRA, 2005). These reporting systems are maintained by regulatory authorities, and aim to collect reports on adverse incidents or serious problems detected and reported by healthcare professionals, manufacturers and consumers. The programs allow to report incidents either by sending in specific forms or by using an online reporting system (FDA, 2005; MHRA, 2005). Collected data is used as a basis to decide whether corrective action is needed to prevent possible harm. Taking these existing reporting systems for healthcare products as an example, it may be possible to build up similar reporting systems for general surveillance of GMPs, using *e.g.* specific questionnaires, forms and online reporting systems.

There exist various organizations that will be able to report adverse effects occurring in the environment. It is

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Table 5. Safeguard subjects to be covered by general surveillance, plus possible unanticipated effects that could occur in agricultural landscapes due to the cultivation of genetically modified plants (GMPs).

Safeguard subject	Possible unanticipated effects of GMPs or their use
Biodiversity	Adverse effects on biodiversity (species, habitats and landscapes) due to the cultivation of GMPs, especially: – the spread of transgenic plants in habitats, where an occurrence would be unusual – the spread of certain plant species due to selection advantages of transgenic hybrids – an increased mortality of prominent non-target organisms – an increase of pests, diseases and weeds due to changes in cropping systems, *e.g.* soil tillage, cropping intervals, pesticide use *etc*. – an increase of resistant target organisms due to insufficient resistance management – the spread of herbicide tolerant weeds
Soil	Effects on soil functions caused by environmentally and/or ecotoxicologically relevant transgenic products Adverse effects on soil fertility and soil functions due to increased erosion or compaction which is caused by the cultivation of GMPs
Water	Pollution of water caused by environmental and/or ecotoxicologically relevant transgenic products Pollution of water due to an increased application of fertilizer or pesticides caused by the cultivation of GMPs
Air / climate	Increase of climate relevant gases and volatile organic compounds due to the cultivation of GMPs

likely that most of the unanticipated effects will be related to agricultural practices and will occur in the agricultural landscape (Tab. 5). Effects such as the increase of pests and diseases, or the occurrence of new weeds, would be observed first by farmers working in the field, or by personnel working in close relation to the topic, such as plant protection services. Effects on biodiversity, like unusual spread of certain plant species, or increased mortality of prominent non-target organisms, may be more difficult to observe. Nature protection organizations, bird watching societies and bee-keepers have an ecological knowledge of their respective field, and they are likely to detect unanticipated ecological changes that lie outside of the expected variations they have experienced over years. Specific national biodiversity monitoring programs such as the Swiss Biodiversity Monitoring (BDM) (Hintermann et al., 2002) can also be used for general surveillance. The Swiss BDM combines existing data series on the presence and distribution of species, with an additional data collection of new biodiversity indicators using standardized sampling methods and a regular sampling grid. In contrast to many existing programs, which often focus on rare species, the BDM concentrates on common and widespread species. By surveying species that are typical of the prevailing landscapes, the BDM program aims at providing evidence for significant changes in large areas. To detect environmental effects other than those occurring on biodiversity, national or regional water quality surveys, soil quality or air monitoring programs could also be used for general surveillance. Unanticipated effects will only be detectable by relying on these existing programs.

According to Directive 2001/18/EC, the main responsibility for general surveillance lies within the consent holder. The consent holder has to provide organizational structures, and show how it intends to retrieve relevant information collected through established routine programs (European Council, 2002). We believe that governmental structures have to be established at an early stage, in order to centralize collection and analysis of reports on adverse incidents, or at least evaluation of these reports. An organizational structure involving three different bodies is proposed (Fig. 3). Collection and analysis of reports on adverse incidents could be performed by a central reporting office, while the evaluation and subsequent decision processes could be performed by a decision-making authority. Both offices could be part of the competent authorities of their respective countries and possibly linked within the EU. For guidance on scientific questions, the two offices could consult an expert panel, which could be composed of scientists from various fields, *e.g.* environmental sciences, agriculture, biology, and statistics.

Analyzing reports on adverse incidents from general surveillance

The linkage of reports on adverse incidents originating from various sources will represent a challenge for the central reporting office. In contrast to CSM, the data is

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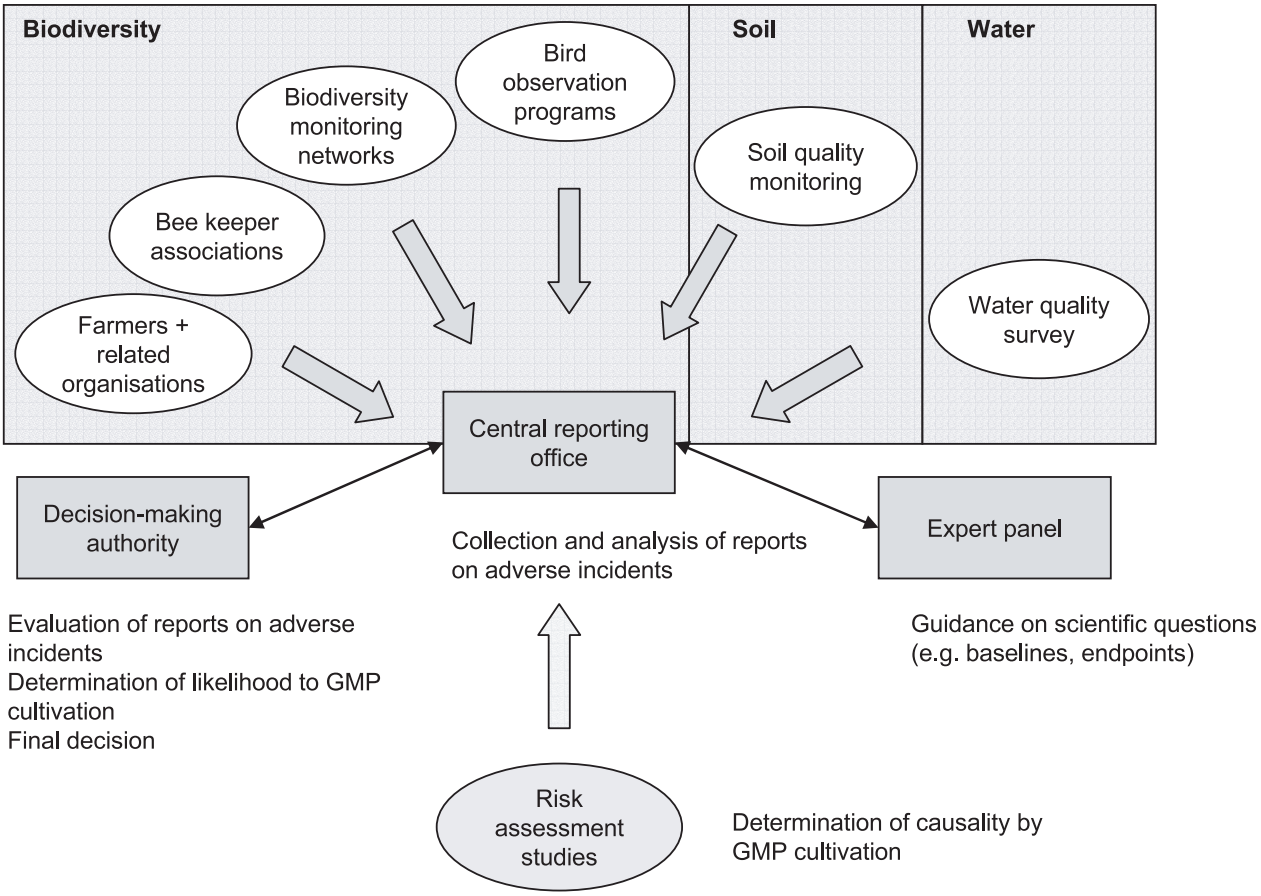

Figure 3. Possible organization structure for general surveillance of genetically modified plants (GMPs) involving several existing monitoring programs related to agricultural landscapes. A central reporting office would collect and analyze reports on adverse environmental effects while valuation of reports and the subsequent decision process could be performed by a decision-making authority. For guidance on scientific questions both offices could consult an expert panel.

not deriving from scientifically designed studies but rather from observations, which may be biased by subjective perception of the observer. Analysis consists in identifying similarities and correlations among the reports, such as the accumulation of events in certain areas or for certain safeguard subjects. A multitude of reports has to be compared to the baseline of existing knowledge in order to identify exceptional changes. In addition, there exists knowledge on species distribution and on ecological interactions occurring in agricultural landscapes (Swiss Web Flora, 2004). Although these studies are often restricted to a specific country or region, they may provide important information, and be of assistance in decision-making. In Switzerland for example, studies on biodiversity and ecological changes occurring in agricultural habitats have been performed for vegetation (Dietl, 1995; Studer-Ehrensberger, 1995), birds (Schifferli, 1999, 2001) and invertebrates (Duelli, 1997; Duelli and Obrist, 1998, 2003b).

Inherent to the concept of general surveillance is the fact that a practicable program will only be able to detect major environmental changes. We believe that minor environmental changes, *i.e.* small effect sizes, will not be detectable by general surveillance, simply because these effects will not be noticed. One might criticize this as a weak point of the proposed model, but the model would guarantee that the reported effects have been weighed, based on the knowledge of the reporting person and the judgment of its significance in the respective ecological context. In addition, we believe that the model is a cost-effective possibility to fulfill the requirements of general surveillance.

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Evaluating reports on adverse incidents from general surveillance and determining the likelihood with GMPs

After consultation with the scientific expert panel, the central reporting office would report relevant environmental changes to the decision-making authority. Evaluation of reports on adverse incidents by the decision-making authority will have to answer two questions: (1) do the relevant changes represent an environmental damage and (2) if they represent an environmental damage, is it likely that these changes have been caused by GMP cultivation. In most cases, it may be impossible to establish causality to the cultivation of GMPs, since many other factors may be the cause of environmental changes. If it is regarded likely that the cultivation of a specific GMP has caused that damage, the causality will have to be determined through specific risk assessment studies. First, reasonable risk assessment studies will need a plausible hypothesis, which links the detected damage to a specific GMP cultivation. Determination of causalities should also consider data from PMRA and the corresponding CSM of this specific GMP, and aim to link these results with the hypotheses derived from general surveillance. The decision-making authority will also have to decide whether approval for cultivation of a specific GMP must be suspended or other precautionary measures taken.

Determining possible causalities with GMPs and taking a final decision

The risk assessment studies to determine the causality between a GMP and the detected change will have to be performed on a similar basis as the studies performed during PMRA. Causalities can be confirmed or rejected by testing specific hypotheses. The results of the studies will have to be presented to the central reporting office, which will summarize them and present a report to the decision making authority (Fig. 3). They will finally decide if the causality is unambiguous, and risk mitigation measures have to be undertaken, or consent for the cultivation of a specific GMP has to be withdrawn.

CONCLUSIONS

Environmental PMM of GMPs represents a new challenge for farmers, the agricultural industry, scientists and regulators, since comparable monitoring programs have not to be performed for conventional crops. However, the challenge to obtain information on the state of the environment is not new, and the underlying principles have been established previously. Although these monitoring programs were originally designed for general environmental protection, the inherent principles remain also valid for environmental PMM of GMPs. The existing experience documented in the literature shows that monitoring programs require defined aims and a rigid structure in order to provide the desired information. PMRA and PMM are two different phases during the development and commercialization of a GMP. While the character of the activities during PMRA still remains related to research, PMM activities are strongly related to the implementation and enforcement of legal requirements. Competent authorities will make decisions on maintaining consents for GMP cultivation based on the results of PMM. PMM is composed of two conceptually different programs. CSM focuses on potential risks and effects of a specific GMP that need to be monitored. This requires definition of effect sizes and detection limits. Therefore, standardized methods and protocols have to be developed for CSM. The focus for general surveillance lies on unanticipated effects in the environment, which will only be detectable by using existing monitoring networks. Both programs have to be designed and implemented according to a pragmatic and realistic approach to be feasible. Competent authorities can support this approach by applying comparable valuation criteria for the effects of GMP cultivation as for effects caused by current agricultural practice.

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