Chapter 32

Post-Commercialization Testing and Monitoring (or Post-Release Monitoring) for the Effects of Transgenic Plants

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Background

It is recognized that the organisms created by recombinant DNA technology are basically different from those naturally present in nature, and may present special risks. Therefore, all GMOs/LMOs should be monitored for their health and environmental effects. Monitoring is essential to reassure that the original risk assessment was correct and the released GMO/LMOs are safe. Monitoring also identifies unanticipated effects.

Observing and recording the health and environmental effects of a GMO/LMO after its release is called 'post-release', 'post-commercialization', or 'post-market' monitoring. This activity is a must, independent of the costs and the resources required, and we should insist that it is done in the interests of present and future generations. The records of the monitoring activity should be kept for generations to come. However, *before* releasing any GMO/LMO, we should consider and decide how the post-release monitoring is to be carried out, what should be monitored and where, what are the best methods to use, for how long this activity should continue, and who will pay for it. It also has to be decided *in advance* where, and for how long, the records should be stored, and who is responsible for keeping and releasing the information. We have to bear in mind that monitoring should be carried out *independently, transparently and inclusively, and that the records should be made available for everyone*.

How should we start monitoring?

It is essential to start monitoring *before* the release of any of the GMOs/LMOs, otherwise it would be impossible to establish a baseline. Therefore, monitoring should start with an inventory of *all our natural resources*, cataloguing the local fauna, flora, and the health status of humans and their animals. It is important to pay due attention to all sites and locations where GMOs/LMOs are being produced, stored or transported. Without this information no data can be interpreted later.

Why should we monitor for the effects of a GMO/LMO?

There are compelling theoretical and practical reasons to carry out this expensive task (Box 32.1). Generally, monitoring of past and present status, or trend of a resource is essential for decision making. For example, storekeepers' record sales, stocks, consumer behaviour, etc. The records are used for forecasting business, and for making decisions about the stocks. Similar reasons apply for monitoring a GMO/LMO.

Box 32.1. Reasons for monitoring for the effects of a GMO/LMO.

Theoretical:

Pre-commercialization risk analysis has several weaknesses
Small-scale experiments only detect large effects
Low probability, low magnitude effects are unnoticed in test-experiments
Small, less frequent risks become evident only in the long term
Evidence collected over a long time confirms the accuracy of pre-release protocols

The public wants it
Learning process
Practical:
Essential for decision making
Part of quality control
Validation of risk assessment
Needed to forecast future trends

Theoretical justifications (BANR 2002) are firstly, that pre-commercialization risk analysis has several weaknesses (small-scale experiments are only capable of detecting large effects, order of magnitude differences). Secondly, all low probability and magnitude effects would likely escape detection in test experiments or field trials. To observe smaller and less frequent health or ecological risks, a longer time-scale is needed. Evidence collected over time can confirm the accuracy of pre-release protocols and risk assessments. Social factors provide additional rationale for monitoring: the public wants it, rigorous monitoring reassures them, and in a democracy to ignore public concerns is irresponsible.

From a practical point of view, monitoring is needed, since general characterization of a GMO/LMO may not pick up all the environmental effects. With post-release monitoring, there is an opportunity for multi-year testing of a GMO/LMO, and to see if the pre-commercialization testing protocols assessed the risks adequately. This is called validation. As Kareive and co-workers (UK GM Science Review Panel; July 2003) wrote 'we have so little faith in models and short-term experiments regarding prediction about invasion, that we advocate extensive monitoring of any introduced (GM-plant) with any ecologically relevant traits (such as disease resistance, herbivore tolerance, and so forth)'. Since GMOs/LMOs are different by nature and in their characteristics, no single rule can be applied for monitoring them. However, it should be kept in mind that our priority must always be monitoring for environmental and health effects, as well as socio-economic impacts. Post-release monitoring and testing of a GMO/LMO is a new endeavour, and at present it is not being done.

Who should carry out the monitoring of a GMO/LMO, and who should pay for this?
According to the EU directive 2001/18/EC, monitoring is the notifier's responsibility. However, if the producers of GMOs/LMOs are in charge of monitoring, it cannot be assured that this is carried out independently and transparently. Since the responsibility for the health of the citizens and their animals, and for the environment, lies with the national governments, monitoring should also be their responsibility, in spite of the high costs involved.

Long-term grants are needed for the monitoring projects, since any effect of a GMO/LMO might take a long time to develop and be noticed. As for who should bear these costs, it has been recommended (BANR 2002) that the cost should be covered by individuals (as tax payers), the private sector (the companies selling and distributing them), and by the local and state governments (as the regulators). However, it would be more just if the companies cover these costs (see the EU directive 2001/18/EC). Our recommendation is also, that the biotechnology companies, who profit from the sale and distribution of GMOs/LMOs, should cover the full costs of monitoring. One idea is to force companies to pay a levy of 0.1% of all the profits from the sales of their GMOs/LMOs, which would go towards covering the monitoring costs.

It is the duty of national governments and the local authorities to assure that the post-release monitoring of a GMO/LMO is properly carried out, preferably by independent scientists.

The authorities provide the costs and resources needed to monitor all the essential resources, such as water, soil, air, or public and animal health. It should thus also be their duty to provide the cost of monitoring for the effects of GMOs/LMOs, despite the manpower and large sums of money needed. It should be their task to devise means for recovering the expenses.

Environmental effects – what needs to be monitored?
GMOs are produced by novel techniques, and as a result, they represent unique risks (Box 32.2). Therefore, GMOs/LMOs require greater scrutiny than organisms produced by traditional techniques of breeding (Snow et al. 2005).

Box 32.2. Unique environmental risks of GMOs/LMOs.

* Little or no prior experience with the trait and host combination
* GMOs may proliferate and persist without human intervention
* Genetic exchange possible between a transformed organism and non-domesticated organisms
* Trait confers an advantage to the GMO over native species in a given environment (Snow et al. 2005)

The most important aims of environmental monitoring are either to prevent the development and spread of any undesirable effects, or, if such a risk has already occurred, to implement preventive strategies to impose immediate restrictions on commercialization. This can be done by instructing the producers to modify the conditions of production and release, or by any other means.

Based on our present understanding, some of the major risks associated with transgenic plants persist because of fundamental flaws in the risk assessment legislation. According to this, the pre-release risk assessment only considers the effects of a GMO/LMO, but ignores the risks associated with the gene-construct and the transgenic technology itself, which is declared to be neutral. However, these risks should be taken into consideration, and should form part of monitoring the impact of a GMO/LMO on the environment (Box 32.3). Monitoring should observe the result of gene escape and of the GMOs, the impact on pests, on agricultural practices, and on the evolution of resistance to their traits (Wolfenbarger & Phifer 2000; Lovei et al., see chapter 10). Transgenes are inherited and have the potential to disperse between individuals of the same species, or to wild relatives. Therefore, monitoring of the transgene movement is essential. In the case of some transgenic plants, fitness of the transgenes conferring resistance has an effect on plant population dynamics.

Box 32.3. Possible risks of GMOs/LMOs.

Persistence/invasiveness
- In the fields (GMO)
- Outside fields (GMOs)
- Transgenes

Gene transfer
- Vertical
- Horizontal

Target effects
- Resistance developing in insects
- Resistance developing in weeds

Non-target effects

Appearance/dominance of secondary pests
Creating new, and more vigorous pests and pathogens, or exacerbating the effects of existing pests
Harm to non-target species
Disruption of biotic communities, including agro-ecosystems
Irreparable loss or changes in species diversity or genetic diversity

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Horizontal gene transfer
Movement of a transgene via horizontal gene transfer (Box 32.4) must be monitored (see Chapter 13). Unfortunately, in the pre-release risk assessments submitted to the regulators, the probability of horizontal gene transfer is calculated to be near zero. Nonetheless, the risks associated with horizontal gene transfer can be significant, thus monitoring is essential.

All testing should be conducted at spatial scales appropriate to evaluate the environmental changes in both the agricultural and natural ecosystems. Ecosystems are complex and sensitive. Therefore, GM plants with some environmentally sensitive traits require closer scrutiny.

Box 32.4. Horizontal gene transfer.
1–20% of the DNA of an organism derives from foreign DNA (Ochman et al.
2000, Koonin et al. 2001)
Major source of microbial evolution
Depends on population density
Less frequent between distantly related taxa
Most likely to occur, and has been detected, in microbial communities
Gene flow

Special risks relating to herbicide-tolerant crops
Contamination of the soil, surface water and groundwater, and the herbicide residue in the GM crops should be monitored. The Roundup Ready gene, conferring glyphosate resistance, is the most often used transgene worldwide. It is recognized that its use may not be sustainable if weed shifts occur to favour glyphosate-tolerant weeds, or if weeds develop tolerance to glyphosate. The basis of the present popularity of glyphosate is based on the assumption that it breaks down quickly in the soil, and is more 'environmentally friendly' than many other herbicides. Unfortunately, this is not true. There is evidence suggesting that it persists in the environment and accumulates in the groundwater. Moreover, it harms mammals, including humans (see Chapter 14).

Special risks associated with Bt-transgenic plants
Special risks associated with Bt crops are the accumulation of the active toxin in the seeds and the green parts of GM plants, as well as in the soil. We also should monitor for the development of pest resistance in the target organisms.

A variety of Bt crops are grown worldwide. They are popular, since they are considered to be environmentally friendly by reducing the use of pesticides. However, growing them may not be sustainable if secondary pests become more of a problem and/or if target pests evolve resistance to Bt.

Problems with disease-resistant transgenic crops

Only a few crops with transgenic disease resistance have been released to date (such as virus-resistant squash, papaya and potatoes). With the virus-resistant crops, the main hazard is the occurrence of a new virus – transgene recombination, resulting in formation of new viruses, increased virulence of the virus, alterations in host-specificity, or the change of its transmission characteristics with transcapsidation (encapsidation of viral RNA of one virus by the coat protein of another). Synergistic interaction between viruses might also occur in mixed infections.

Human and animal health effects – what needs to be monitored?

When monitoring for the health effect of a GMO/LMO, we have to know when, what, and how much of a GMO/LMO was eaten, and for how long. In the case of foodstuffs, this means exact labelling of all GMO/LMO components. However, labelling of GM food or feed is not compulsory in many countries.

When monitoring for the effects of GM crops, we have to take into consideration that the pre-release risk assessment is mostly based on assumptions. One of these assumptions is that all DNA is degraded by the saliva and in the gut. However, in the case of edible DNA vaccines, sufficient amounts of the DNA must survive to be able to evoke an immune response. Therefore, it is important to determine the extent of DNA breakdown by using an in vivo system, and measure whether any foreign proteins and DNA survive passage through the stomach and small intestine.

Animal health monitoring

Short- and long-term monitoring of a GMO/LMO effect should be based on observing all changes in animal behaviour, physiology and metabolism, as well as observing alterations in the immune- and hormone-responses (Pusztai & Bardocz 2005, Pusztai & Bardocz Chapter 14 in this book). It is essential to monitor for any change observed in growth rate, organ development, life span, and reproductive function. Changes in disease susceptibility, of immune status, pathogeneicity, or infectiousness of an organism can also be important indicators. The aforementioned parameters should be monitored and recorded over at least four generations.

Monitoring of human health

In the case of humans, several non-invasive techniques can help to monitor the effects of a GMO/LMO. The easiest is to follow changes in immune responsiveness by taking consecutive blood samples. Hormone assays can be carried out with the same samples. It is easy to assess the changes in bacterial status from regularly collected faecal samples. With the help of invasive techniques, such as collecting gastric- and colon biopsies, one can monitor the primary effects of GMOs/LMOs in the alimentary tract, and in its bacterial flora.

Tissue samples from tumours collected for histological/pathological evaluation can be assessed for cancer effects, and also to establish the presence of foreign DNA, or of the vector/construct.

In the longer term, the science of epidemiology can help post-release monitoring. In particular, case-controlled epidemiological studies can give vital clues as to the effects of a GMO/LMO. However, in order to establish human health effects conclusively, one would need to carry out human volunteer studies. When these are performed, one should look out for new microbes (viruses, bacteria) containing GM vector elements, and bacteria with antibiotic-resistance, and other transgene- or vector elements. We should also monitor for immunological differences as well as changes in susceptibility to diseases.

A few years ago in the UK, plans were made to monitor for the effects of GMO-containing foods on humans. The idea was to use consumer loyalty cards of supermarkets, in combination with individual health records. Nothing came of these ideas, since several problems are connected with

the scheme. Firstly, cardholders do not shop for one person, and not all GMO/LMO containing-food is labelled. With the use of the cards there is no way to keep records on everybody's food consumption (consumers shop around, consume food outside their home, and eat out during trips and on holiday, etc.). There is also the problem of matching consumption with the individual's health records, which are confidential.

For the authorities, data collection is possible through regular health checks, medical reports, and using epidemiological studies.

Where should we monitor for the effects of a GMO/LMO?
Obviously, monitoring should be carried out on and around the sites where the GMO/LMO has been released, and also in the wild. The area should be dependent on the type of organisms released. It should include monitoring of all the natural resources, in particular, water, air and soil.

When monitoring for a local effect, we also have to consider: pollen transfer, local contamination by excreta, microbial spread, migratory populations, the food web, etc.

One of our target-sites should be the *soil*. However, there is a problem with this: only a small proportion of soil organisms are known. Their effects and the interactions between them and with other organisms are not understood at all, since we do not know 99% of the soil microorganisms. At present, soil is monitored for its nutrient content, structure, contamination by heavy metals, chemicals, etc. Monitoring for the effects of a GMO/LMO is still possible, based on differences between soil DNA extracts taken before and after the release of a GMO/LMO, and, with repeated measurements the differences can be interpreted.

Another target site should be the *air*. Pollen, for some, can be a major allergen, and air is continuously monitored for its pollen content in developed countries. Using the same samples, one could also monitor for GM pollen, and when it is detected outside the GM crop field, one should take immediate action. When pollen escape is a serious risk, the government could ask the growers of GM plants to prevent this, for example by building tall plastic/glass walls around GM production sites, or around the GM field trial sites. This would not stop all birds and insects from carrying the pollen around, but would somewhat decrease the chances of cross- pollination.

Water quality, and contamination by pesticides/herbicides and their residues are monitored regularly. Sea- and fresh-water organisms are monitored for stocks and contaminants (such as heavy metals, etc). When collecting the samples for monitoring these aspects, the same samples can be used for testing for foreign DNA, their effects or products. Changes in an organism's physiology/pathology should be monitored for at least four generations.

When monitoring for changes in the environment, we should look out for new microbes (viruses, bacteria) containing GM vector elements, and for bacteria with antibiotic-resistance genes. We should observe if invasion by a GMO/LMO of a neighbouring ecosystem has occurred, or if crops, weeds and other plants with resistance traits have appeared. Shifts in insect and predator populations and their feeding habits should also be monitored for any change.

Who should monitor for the effects of GMOs/LMOs, and for how long?

Monitoring should be carried out using every possible means. Everybody should be involved, from government employees and officials to farmers, civil societies, NGOs, interested individuals, and even schoolchildren through specific projects.

The time span of post-release monitoring should last for at least four generation-times, as a minimum. Generation-times for microorganisms vary between a few minutes to a few hours, and for humans it takes about one hundred years. This length of time is needed to detect long-term effects, and to observe the influence of a GMO/LMO on the reproductive function. Environmental influences, lifestyle, and even the amounts of food consumed by grandparents may have an influence on their offspring for generations. Therefore, as a minimum, a four generation-timescale may be required to observe the true effects of a GMO/LMO. This means that if we want to match up a late effect of any GMO/LMO, we must keep the records for 120–150 years, at least. Storing the data and making them available to anyone for consultation is a major task for the local and national authorities. However, it should be done and, if at all possible, it would be useful to keep the records for even longer.

A two-part approach should be used for monitoring: first, trained observers should monitor immediate post-release changes in the environment, since they are the ones who are able to differentiate between temporary and spatial effects of a GMO/LMO. Secondly, everyone should report any changes observed in connection with a GMO/LMO to the local and national authorities. These observations should also then be validated by trained personnel.

The present status of monitoring health and environmental effects in the EU and worldwide
In the EU, a Directive (Directive 2001/18/EC) was passed to regulate the post market-, or post-release monitoring of all GMOs/LMOs, but it leaves the question of how it should be carried out open for the individual countries. Nations should create their own laws on post-release monitoring systems, and provide the finances and trained personnel to carry out these tasks. The EU Directive sets out guidelines also for the design of a monitoring plan (Box 32.5), which should form part of the dossier presented by the notifiers (e.g. the company) to the regulatory authorities. According to the Directive, the request for releasing a GMO/LMO should contain plans for monitoring. The Directive also makes the notifiers directly responsible for paying and carrying out the monitoring. Therefore, it is *essential* that the notification contains a plan for monitoring, including a proposal for the period (Directive 2001/18/EC 2001; Bardocz & Pusztai 2004). The Directive also introduces an obligation for notifiers to implement monitoring plans in order to trace, and identify any direct or indirect, immediate, delayed, or unforeseen effects on human health or the environment of GMOs after they have been placed on the market, including obligations to report to the Commission and competent authorities. In addition, to ensure transparency ‘the results of monitoring should also be made publicly available’. According to the Directive, monitoring should be developed on a case-by-case basis. It also gives guidelines for working out a monitoring strategy (Box 32.6).

Box 32.5. The monitoring strategy.
Risk assessment, before release and background information
- Approach: case-specific monitoring, general surveillance
- Baselines
  - Status of the environment and changes therein
  - Causes of such changes
  - Expected development of the environment
- Time period
- Assigning responsibilities
  - Notifiers
  - Third parties
- Existing systems of monitoring

The regulators may use the monitoring plan set out in the Dossiers, or can work on other plans.

Box 32.6. Design of monitoring plan.

–Should contain guidelines for:
–The monitoring methodology
–Monitoring parameters/elements
  –Areas/samples
  –Inspection
  –Sampling and analysis
  –Collection and collation of data
–Analysis, reporting, review
  –Evaluation
  –Review and adaptation

In the USA, no official monitoring programme exists. We know very little about monitoring systems in other parts of the world.

In reality, only a few countries have an inventory of the various biological resources, and the health status of the population, which can be used as a baseline. In many countries, GMOs/LMOs have already been released into the environment, and most of their populations have already been exposed to foods prepared from GM crops. Based on data in the scientific literature, very little is being done at present to monitor the effects of any released GMO/LMO. It is crucial that public programmes of biological risk assessment and management be expanded substantially.
We must conclude that at present not a single country has developed an efficient post-release monitoring system, although several countries are producing GMOs/LMOs on a large scale.

Cost versus benefits analysis of post-market/post-release monitoring for the effects of GMOs/LMOs

At present, the cost of monitoring, health care and cleaning up the environment is the responsibility of the national governments, through the taxes the citizens pay for the expenses of monitoring, data collection and storage. At the same time, the citizens are the ones who are exposed to most of the risks of GMOs/LMOs.

The most surprising fact in connection with a GMO/LMO is that, in the absence of international rules on liability and redress, which are only now being negotiated under the Cartagena Protocol on Biosafety, it is extremely difficult to hold a GMO/LMO producer, especially if a foreign entity, legally responsible for its product. This means that if anything goes wrong with a GMO/LMO, the company may be free to walk away and leave the national authorities to deal with the problem and force the citizens to pay for the clean up.

In summary, monitoring should be carried out *independently, transparently and inclusively*. It should start with an inventory of *all* GMOs/LMOs, and the sites/locations where they are being produced, stored and released. Without this knowledge, no data can be interpreted later. The inventory should be *kept for a minimum of four generations*. When considering deliberate release of any GMOs/LMOs into the environment, we should think first, and not forget that governments have the power to legislate, but the citizens – who are also the consumers – have a vote, and can vote also with their money. The national governments and the regulators have the right to ask the

producers to carry the costs of all extra tests relevant to the special conditions of a country before a GMO/LMO is released there, and also the costs of monitoring, after the GMOs/LMOs are released.

Emergency planning

Even during the very short time-period since the first GMO was released into our environment and food chain, we have already seen escapes of genes and contamination of our food supplies. For instance, there has been the StarLink disaster, or the controversy and the problems with Prodigene, growing pharmaceuticals in GM plants, not to mention the presence of additional, unapproved cry-proteins in some Bt crop varieties. Therefore, before we release any GMO/LMO, we must have emergency plans in place. We have to keep in mind that we have no techniques to 'take back' or recall any of the escaped genes or organisms. Furthermore, it is very difficult to contain or control the spread of an already escaped GMO/LMO. If contamination has already happened, we are more or less sure that it will happen again. We also have to have some ideas in advance, of how we are going to clean up any contamination in case something goes wrong.

We must have different emergency plans and be prepared for emergencies and have an action plan to be able to act to control the situation. In addition to having emergency procedures in place for all kinds of scenarios (Box 32.7), we must have the capacity and personnel to deal with the problems.

Box 32.7. Steps in emergency planning to deal with a GMO/LMO-related accident.

SCENARIO:

A. Plans for accidents that occur in containment
B. During transit
C. Food/feed production, food chain contamination
D. Deliberate release into the environment of
   –organisms unable to self-replicate
   –self-replicating organisms

STEPS:

1 establish facts – verify source, collect the material to prevent its spreading
2 assess damage
3 clean up – beware of 'dumping'
4 follow-up (health/environmental checks)

Coexistence

The EU and several other countries have chosen to regulate GMOs/LMOs on a case-by-case basis, and thus they do not exclude the growing of GMOs/LMOs, however unfair it is to those who want to remain GM-free. Therefore, the national authorities have to regulate the conditions in law to allow the coexistence of agricultural practices for growing organic- (bio), traditional-, and GM-crops. However, the national governments also have the right to regulate GMO/LMO production by restrictions, setting special requirements or conditions of production (walls around sites, separate irrigation systems, etc.). National governments can also, by legislation, force labelling and monitoring, and make the producer liable for damage caused by their product(s).

When it comes to cost-benefit analysis, one must consider all alternatives (sustainable, low chemical input/organic, local produce using local seeds), and weigh up the costs. We also have to see if there is a real chance for the coexistence of the different production systems. It is clear that

GMOs/LMOs make organic production systems impossible in the neighbourhood. In contrast, organic production endangers neither traditional agricultural methods, nor the growing of GM crops, even if organic crops cross-pollinate them.

According to German law, the production system that was in place first, has the priority over the newer methods and technologies of crop production. Accordingly, in Germany, the farmer or producer who contaminates the lands or products of another pays compensation. It is worth noting, that the responsibility is not assigned to the GMO/LMO producer, such as the biotechnology companies, although liability can be eventually channelled to them by the GMO/LMO farmer. This, however, means that they may not be held legally responsible for their products and the damage they inflict.

Identity preservation systems

In March 2006, the Third Meeting of the Parties to the Cartagena Protocol on Biosafety agreed new documentation requirements for shipments of GMOs/LMOs that are intended for direct use as food, or feed, or for processing. At issue is the need to know exactly which GMOs/LMOs are entering a country. This international minimum standard will help encourage a global system of identity preservation, segregation and traceability for GMOs/LMOs, The idea of bio-tagging has also been considered separately. Bio-tagging means that every biotechnology company should have a 'company sequence' inserted to the genome of all of their GMO/LMO products, although the risks associated with such insertions should also be assessed.

The reason for the efforts to ensure identity preservation is intimately linked with monitoring. It is important to be able to track and trace the GMOs/LMOs that are entering a country for monitoring requirements, risk management and reviews of decisions in the light of new scientific information. In case something goes wrong, such a system is also critical to be able to ensure product recall and to take emergency measures. It is also important to have a clear system of traceability, to be able to identify what caused the damage and to identify the producer, so that liability can be assigned and redress obtained. This would be important in light of the future development of an international liability and redress regime for GMOs/LMOs under the Cartagena Protocol. Although all manufacturers are prosecuted for selling dangerous articles, or shops and restaurants closed down and taken to court for selling dangerous products or bad/infected foods, at the present there are no international liability and redress laws for GMOs/LMOs.

All previously developed and established technologies are fully controllable. Electricity, and even nuclear power, can be turned off. Production and distribution of GMOs/LMOs is a new endeavour. This is a technology with a difference. GMOs/LMOs are self-replicating, they cannot be recalled, their genes cannot be turned off, and we have no method to take a released GMO/LMO or their genes out of the environment once it is released. *This is the first irreversible technology in human history*, therefore it requires more scientific scrutiny, legal control and monitoring, not less.

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