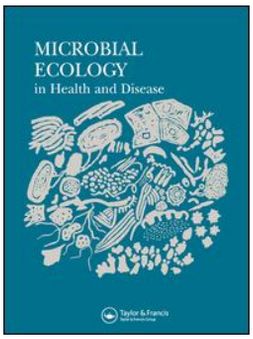

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The Precautionary Principle Applied to Deliberate Release of Genetically Modified Organisms (GMOs)

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Deliberate release of genetically modified organisms (GMOs) may contribute to sustainable development, world food supplies and economic prosperity. On the other hand, environmental release may initiate serious, irreversible ecological damage. In this article we discuss the scientific basis for regulation of GMO use, and to which extent present risk assessment procedures provide means to predict and reduce potential ecological hazards. Potential hazards related to gene transfer from GMOs to indigenous organisms and prospects of secondary ecological effects are given special attention. It is important to recognize that possible adverse ecological effects may have impact on other processes affecting human and animal welfare. A major conclusion is that the present state of scientific knowledge is inadequate for reliable ecological risk assessment. The basic information with regard to mechanisms governing the environmental interactions of GMOs is insufficient. The ecosystems are too complex, and our understanding of them too fragmentary. Furthermore, currently available methods to monitor short and long-term ecological consequences of GMO release are non-existent or unreliable. Finally, the socio–economic and biodiversity aspects of GMO usage are ambiguous, and often unpredictable, based on the present state of knowledge. Hence, applying the precautionary principle should be an important basis for initiation of risk-associated research as well as for elaboration of more satisfactory risk assessment methods and procedures. *Key words*: deliberate GMO release, horizontal gene transfer, naked DNA, the precautionary principle.

INTRODUCTION

The advantages of new technology are often easily conceived, while the costs are difficult to appreciate considering uncertainty and risks coupled to imperfect knowledge. The benefits may be harvested and enjoyed in short-term time scales, whereas forecasts of detrimental effects are based on worst-case scenarios, and actual harmful consequences may only become apparent after extended periods of time. Presently, genetically modified organisms (GMOs) are utilized and commercialized by agricultural, biomedical and biotechnological industries. GMOs as transgenic animals, agricultural crops and genetically modified microorganisms/viruses are being made from a wide range of related and unrelated organisms by recombinant DNA/RNA and transfer techniques.

The purpose of risk analysis is to perform a risk identification of ecological effects and a risk assessment (1). Risk assessment describes and quantifies effects by analysis based on scientific data from the risk identification. Finally, if ecological effects are identified and their risk assessed, risk management follows by recognition of methods for reducing the identified risks. The purpose of such regulatory procedures is to generate scientific advice about potential ecological effects towards the policy process. Ecological effects caused by GMO release depend on characteristics of the organism to be introduced, the genetic novelty and conditions in the receiving ecosystems (2). However, at present the scientific information available is not sufficient to conduct reliable risk assessment for a proposed GMO release. Knowledge about probability and ecological effects of horizontal gene transfer from GMO to other organisms is lacking (3), and the inherent complexities and limitations in predictions of interactions and impacts on ecological systems may prohibit identification of important risks (4). In addition, present methods for the monitoring and detection of ecological effects are insufficient and this may result in inadequate control (5). Potential environmental impacts related to introduction of GMO are now being reported. Herbicide tolerance genes have been transferred from rape to weedy relatives (6, 7), while in cotton such genes have been inactivated (8). Beneficial predator insects have been harmed by eating aphids on plants modified to resist pests (9). Such observations may lead to increased credence of hypotheses about other possible processes that might have adverse effect on health and environment.

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Deliberate release of GMO invalidates the traditional reliance on awaiting scientific proof. In situations where potential ecological impacts constitute a serious and irreversible threat, and scientific evidence for harmful effects is lacking or uncertain, the precautionary principle should have a role in the risk assessment process (10).

In this paper, we intend to describe and discuss whether regulation of deliberate GMO release needs involvement of the precautionary principle. Inevitably, this implies recognition of scientific uncertainty, and the complex tasks that assessments of biological and ecological effects represent. Another important feature is that the precautionary principle should be involved as a scientific norm among scientists working with the use and production of GMO. It is obvious that scientific uncertainty opens up for interpretations of risks besides value judgments. Therefore we also want to discuss how scientific uncertainty influences the quality of ecological risk assessment and thereby biotechnology policy. Also a recommendation considering socio–economic impacts and public involvement for evaluating the quality of the scientific basis of risk assessments for regulation purposes is included.

THE PRECAUTIONARY PRINCIPLE

The precautionary principle has been accepted by many national governments as a basis for policy making, and it has also become important in international environmental law and international treaties (10, 11). The origin of the principle is the 'Vorsorge prinzip' of German law (12). The precautionary principle was first developed to restrict marine pollution discharges in the absence of proof to environmental damage and entered international policy with The Conferences on the Protection of the North Sea (in Bremen 1994, London 1987, The Hague 1990, Esbjerg 1995). Principle 15 of the Rio Declaration on environment and development (13) reflects the traditional formulation of the precautionary principle. According to the Rio Declaration principle 15: 'In order to protect the environment the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of scientific certainty shall not be used as a reason for postponing cost effective measures to prevent environmental degradation.' Although the precautionary principle provides a general approach to environmental issues, the actual content and practical implications are discussed (11, 12, 14).

To learn from the experience and the predictions of the past and to perform environmental forecasting, the precautionary principle should be involved in risk regulation when scientific uncertainty is obvious. It has been argued that the precautionary principle shifts the direction of scientific research towards perspectives of scientific uncertainty (15–17). In such situations, application of the principle should not require full scientific evidence before initiative of preventive and remedial action. As an ethical principle it challenges scientific work by questioning the traditional reliance on methods, hypotheses and the content in the scientific discipline (17). The precautionary principle thereby emphasizes a need for caution when changes to the environment might result from scientific practice or use of technology, and confer a responsibility to scientist of initiating research to gather scientific information towards perspectives of uncertainty.

LIMITS FOR RISK ASSESSMENT RELATED TO DELIBERATE GMO RELEASE

For decision making processes risk assessments are required by anyone proposing use or production of GMO (18). The aim of risk assessment is to quantify ecological risks and evaluate the probability of possible effects on health and environment by use of scientific data (19). In situations where undesired effects may result from scientific practice or use of technology, risk must be defined as probability $\times$ consequence(s). The magnitude and scope of consequences must be considered even if the probability is low, since ecological effects may cause irreversible changes in ecosystems. At present, there is not enough information to conduct proper risk assessment with deliberate GMO release. For deliberate GMO release, both the probabilities of undesired effects and the magnitudes of the assumed effects are unknown. As long as scientific data concerning ecological effects are absent, risk assessment related to deliberate GMO release regulation, are better described as an uncertainty-based regulation (20). Scientific uncertainty concerning deliberate GMO release into the environment may be defined at three different levels:

(i) Uncertainty linked to insufficient information concerning the behavior of the specific GMO that is proposed to be released. The genetic modification process and/or the genetic novelty introduces new environmental properties to the GMO. Genetic alteration may also cause unpredictable secondary changes in the organism. Besides the specific properties of the individual GMO being introduced, transfer of genes to related or unrelated organisms has to be considered (3, 21).

(ii) Uncertainty due to ecological complexity or scale of an ecosystem making predictions about the outcome or forecasts about cause–effect relationships by introduction of GMO into the environment difficult (4, 22). Even if the GMO has been extensively studied before introduction, there might be a change in interactions with and responses to the environment, or new interactions between GMO and the ecological systems including microbial systems may occur.

(iii) Uncertainty due to limited methods for detection and monitoring of effects. After GMO has been released into the environment, it is important to compare the

actual and predicted outcomes (5). However, even if monitoring strategies at present is required, is the need to monitor ecological impacts continuously often ignored and developments of methods for detection are lacking, which might cause an inadequate control of risk. Ecological consequences important to monitor includes; the organism becoming a problem, gene transfer from the GMO to other organisms, and if the organism represent a hazard to humans, animals or natural organisms.

Organisms made with the purpose of release to the environment, are designed to survive. This enables reproduction, persistence and introduction of mutations, besides a potential for dispersal and invasion of other ecosystems. The process of intentional GMO release into the environment must therefore be considered an irreversible decision, since after release the GMO is 'nonrecoverable.'

ECOLOGICAL EFFECTS OF GENE TRANSFER

In the environment GMO may cause unintended harm by gaining a competitive advantage and causing an ecological imbalance. Organisms that contain new combinations of genetic information are more likely than others to find new niches (23). Genetic alteration modifies ecological or environmental relevant properties of the organism. If the novel gene confers an ecological advantage to a modified organism, the organism will have an opportunity to reproduce and spread their modified genes to nonmodified organisms and affect the genetic diversity and natural interactions of ecosystems.

CROSS-POLLINATION

Novel genes in plants, encoding for instance herbicide tolerance or insecticide resistance, might escape and be transferred to weedy relatives or other crops by cross-pollination. A number of studies demonstrating transfer of genes by cross-pollination have been published. Field trials in Denmark (6) and Scotland have shown that genetically modified oilseed rape, expressing herbicide tolerance, easily cross-pollinated relatives such as wild *Brassica* varieties. French researchers (7) have demonstrated that pollen from transgenic rape was able to cross with wild radish, and occasionally the genetic novelty was transmitted to the next generation. Bergelson and colleagues (24) have shown that *Arabidopsis thaliana*, modified to tolerate the herbicide chlorsulphuron, developed greater ability than nonmodified *A. thaliana* to cross-pollinate relatives. In addition, wild type *A. thaliana* was more frequently fertilized by pollen from the transgenic plant than from nonmodified plants. The enhanced ability of the transgenic plants to pollinate wild plants, also increased the probability of herbicide tolerance gene transfer. These findings have relevance for considerations of gene transfer since the herbicide tolerance gene (*csr*-1) are now introduced into several plants as a selection marker for transformation. Widespread transfer of herbicide tolerance and insecticide resistance to weeds or crops would have negative impacts on ecosystems, decrease biodiversity and create resistant weeds and pests.

HORIZONTAL GENE TRANSFER

Horizontal gene transfer is defined as nonsexual transfer of genetic information between genomes (25). It is most commonly used in the context of transfer between nuclear genomes in different species, but include transfer between different organelles in same or different species. There is growing evidence that such a transfer may occur even between distantly related species (25, 26) General mechanisms of horizontal gene transfer is based on: i) mobile genetic elements, such as transposable elements moved by site-specific recombination; ii) conjugation, gene transfer during direct contact between cells; iii) transduction, gene transfer when a cell is infected by virus; iv) transformation, when DNA is taken up by recipient cell, called transfection when the recipient is a mammalian cell (3, 21, 27, 28). Genomic sequences might be transferred among eukaryotes, from eukaryotes to prokaryotes, from prokaryotes to eukaryotes and vice versa or among prokaryotes (25, 26).

An important question is whether one may expect the novel or modified genes to be transferred horizontally into other organisms (see Fig. 1). Antibiotic resistance markers, genes that produce proteins neutralizing specific antibiotics, are used for selection of recombinants (29). The use of such markers represents a potential for transfer of antibiotic resistance from genetically modified plants to bacteria, or from modified bacteria to naturally occurring bacteria (21). Among bacteria, there are three main mechanisms for gene transfer: i) transformation; ii) transduction; iii) conjugation (28). Such horizontal gene transfer would cause an increase in the already high load of antibiotic resistance genes in bacterial populations. Horizontal gene transfer from plants to bacteria might take place in the guts of livestock fed on genetically modified plants, and then transmitted to bacteria infecting other animals or humans (30). Furthermore, antibiotic resistance genes might be transmitted from GMO to naturally occurring pathogenic bacteria and might then represent a risk to animal and human health. Introduction of genetic novelty as herbicide tolerance, insect resistance and other genes conferring specific properties do represent an environmental and health hazard, since the potential of horizontal gene transfer to relatives and nonrelatives confers a risk of harm.

Shorter DNA sequences, such as promotor–enhancer motifs might be transferred or translocated between organelles or to other organisms (see Fig. 1). Transfer or translocation followed by integration of new promotor–

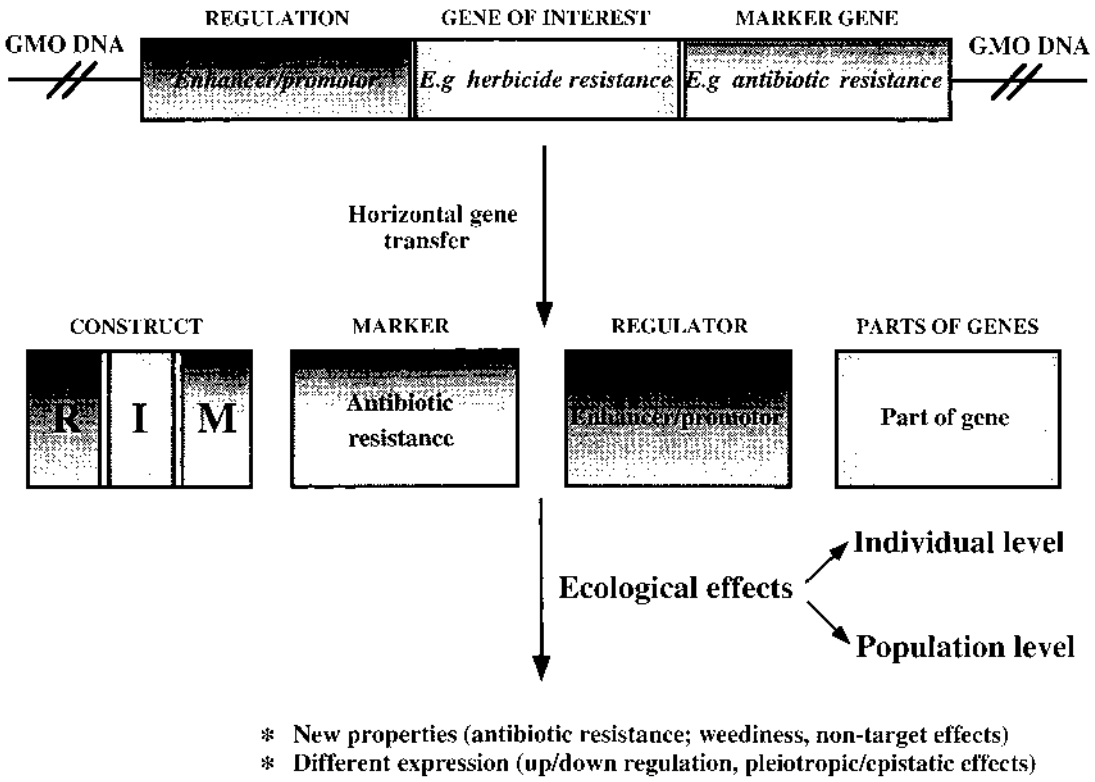

Fig. 1. Ecological effects of horizontal gene transfer.

enhancer elements into cell chromosomes might effect the gene expression and replication of the recipient. A transfer of, for instance, a strong promotor might result in enhanced or reduced expression of indigenous gene products in the recipient organism (31). Different regulation patterns of active genes may cause serious changes in the functional properties of recipients (32). Such secondary effects may result in altered protein levels, increased toxicity or other adverse effects on health and environment. Parts of genes or noncoding DNA sequences that are translocated or transferred, may have pleiotropic or epistatic effects on other distantly located genes that regulate expression, and reactivate silent genes. Consequently, even when horizontal transfer between nuclear genomes or organelles in the same organisms or between organisms do not confer any new phenotypic traits, unpredictable detrimental effects may arise due to the numerous complexities involved in biological processes.

Mechanisms that distinguish easily transferable DNA are not well known, neither the mechanisms that function as preventive barriers for horizontal transfer (27, 33). Such mechanisms might, however, be affected by ecological variations as stress (caused by drought, heavy metals, saline soils, temperature variations and nutritional status) and chemical pollution as xenobiotika (3, 34, 35). After integration into host genomes, transmitted DNA may also be transferred vertically to the next generation.

NAKED DNA

Naked, recombinant genetic material remaining undegraded in the environment is capable to transform cells (3, 35). Hence transformation may be an important route of horizontal gene transfer, enabling transfer of naked recombinant DNA from GMO to cells. DNA is released naturally when a GMO dies, for instance from plants in the winter, after drought, or from degraded genetically modified microorganisms (28). DNA may also be actively secreted from living cells or escape from contained use (35, 36). Earlier studies left the impression that naked DNA is easily degraded in the environment. More recently, this picture seems unpredictable due to observations indicating that naked DNA released from live or dead cells persists intact in laboratories, waste water, aquatic systems, soils and digestive systems of mammals for considerable time periods (37, 38). Increased frequency of transformation can be measured when naked DNA is adsorbed in ground water and to surfaces of minerals and clays (36, 39). Recent observations indicate that fragments of viral DNA, can survive intestinal digestion, thus reaching circulation and other organs/tissues. In mice fragments of naked DNA, M13mp18DNA, have reached the bloodstream and the spleen, and were linked to chromosomal DNA (38). If naked DNA can resist digestion in the gut, transformation of gut and intestinal microorganisms might occur. The long-time persistence of DNA in the environment and gut

suggests that transformation of DNA from GMO might affect bacteria, fungi, plants and animals. Even if the frequency of transformation is small, a cell with increased fitness might have the ability to compete with neighbors during selection. After integration into host genome, the novel DNA may be transferred vertically to offspring or horizontally to other prokaryotic or eukaryotic cells/organisms.

RECOMBINATION

It is impossible to assess all effects following insertion of foreign DNA into the genome of an organism, especially since the insertion might accidentally introduce unintended functional changes as well as destabilization of the recipient genome (40, 41). Recombinational events in the genome during integration might result in rearrangements of genes and changed gene expression patterns not present in either parent (42). Greene and Allison (43) reported that a viral gene inserted into a plant could recombine with infecting viruses to create hybrids with new properties. Horizontal gene transfer combined with recombinational events may pose long term environmental and health hazards that have not been observed in nonmodified organisms. The long-term consequences of such events are impossible to predict.

ECOLOGICAL EFFECTS DUE TO INTRODUCTION OF A NEW SPECIES OR GENOTYPE

Some animals, plants and microorganisms that have been introduced into natural environments have intentionally or unintentionally gained competitive advantages. For example, among all newly introduced plants, 10% have established themselves as wild populations and 10% of the wild population have become a problem (44). After introduction of organisms into the environment it is difficult to determine whether an organism will have harmful impacts (22). By analogy to the behavior of nonindigenous organisms, GMOs might also have selective advantages and the capacity to reduce the biodiversity of natural populations upon release. The genetic novelty might alter biosynthetic pathways and thereby change levels of bioactive compounds in the organism. Inose and Murata experienced such an event, when their genetically engineered yeast (enhanced glycolytic activity), increased the cellular level of the metabolite methylglyoxal to toxic concentrations during fermentation (40). In addition, the genetic alteration itself may result in ecologically relevant properties not found in nonindigenous organisms. Furthermore, the composition of the environment is never stable, it is constantly changing by human activity as well as its own continuous evolution, making it difficult to figure out cause–effect relationships of GMO introductions. Unexpected conditions, for instance an unusual rise in summer temperature, might influence the gene expression in cells or result in phenotypic changes (8, 45, 46).

The ecological risks imposed by deliberate GMO release depend on the specific gene that is introduced, the phenotypic alteration of the organism and the properties of the receiving ecosystem (2). Transgenic fish, modified for instance to increase the growth rate, might escape raring facilitates and disrupt aquatic ecosystems, besides interfering with indigenous fish populations (47). Transgenic plants with herbicide tolerance genes pose a risk of tolerance transfer to weeds by pollen or seeds (46). This may have adverse consequences for weed-control options such as increased herbicide use (48). Pleiotropic effects on other genes might arise, which may alter ecological relationships and have adverse health effects, e.g. caused by change of secondary metabolites. Various pest-management systems have been developed by genetic engineering, for instance plants modified to produce Bt toxins (from *Bacillus thuringiensis*) as their own insecticide to prevent damage by pest insects (49). Bt strains are used as natural biopesticides by organic growers and in some procedures of conventional agriculture. However, Bt transgenic crops cause an extensive exposure of toxins and might intensify the selection pressure in pest populations to develop resistance properties (50, 51). Further on, Bt plants might harm nontarget organisms like beneficial insects. ''In addition, might organisms further up in the foodchain be harmed. Lacewings were affected by eating aphids fed on Bt transgenic maize (9). British researchers have reported that another pest-management system, transgenic potato with snow-drop lectin, disturbed the reproduction and lifetime span of ladybirds (52).'' Genetically modified baculoviruses for control of insect pests have been developed in order to reduce the use of classical pesticides (53). Recently it has been shown that baculoviruses may also infect mammalian cells, and are now vector candidates for gene therapy of liver cancer (54, 55). Genetically modified viruses used in pest-management might escape into the environment and infect new hosts, and thereby reduce populations of non target species or decimate key species in the ecosystem (56). Plants engineered with viral coat protein genes in order to resist pests, may result in recombinants between inserted virus and incoming naturally infectious virus to create new virus strains with altered host range (43). However, by targeted deletion of the 3′UTR in the transgene, Greene and Allison (57) demonstrated that potential recombination between the transgene and viral RNA could be reduced significantly. Genetically modified viruses used as vaccines may have the potential to form hybrids with naturally occurring viruses in the area of release, resulting in enhanced pathogenicity as well as altered host tropism of the progenies (58, 59).

A NEED FOR GOOD RESEARCH

Although experience and existing knowledge may be employed to roughly predict the potential risks of a GMO release, there will always be considerable uncertainty concerning the character and extent of health and environmental impacts.

Extrapolation from one context to another, i.e. from laboratory research to small scale field trials and finally to commercial scale, raises many unanswered questions concerning the fate of the GMO in the environment, and is far beyond current capabilities for detection and regulation (4, 60). Small scale use may provide valuable information related to, for instance, survival and persistence, competitive fitness and some ecological implications of release. However, small scale trials are limited by size and management, and commercial releases involve a higher number of GMO to be released as well as different and more complex ecosystems. Small scale trials concern limited variables of environmental conditions, biological and ecological processes. To base predictions of long-term impacts on such data will obviously give inadequate knowledge and control.

The scientific understanding of biological and ecological mechanisms and processes are imperfect. Present methods for introducing genetic novelty in an organism, do not give precise knowledge about location and number of inserts. The genetic alteration and the resulting changes in the organism's phenotype, for instance altered gene expression pattern, is impossible to predict with available information, and thus indirect effects have implications for the safety of the technology (61, 62). In addition, knowledge about potential of horizontal gene transfer within and across barriers is absent (3, 25). Characteristics of nucleic acids and constructs that are easily transferred are needed, besides research about mechanisms for and barriers against horizontal gene transfer. To evaluate potential ecological effects of gene transfer it would be necessary to develop mathematical models to estimate probability of gene transfer (63). Such models can be used when frequency of gene transfer depends on environmental selection pressure of the new construct and fitness characteristics. However, in small scale trials gene transfer may not be statistically detectable, due to short duration and low selection pressure. Eventually more knowledge about processes and mechanisms of gene transfer is needed to suggest effects by introduction of GMO, and for making reliable mathematical models to assess probability of effects.

The issue of scientific uncertainty raises questions concerning detection and evaluation of ecological effects. The key issue may be the behavior of the GMO in the area of release and surrounding areas, especially the abilities for reproduction, dispersal and survival over time and space (22, 59, 60). Environmental risk assessment must imply information about the capability of GMOs to reproduce or propagate and persist in the target area. If the GMO has the potential to establish in the area of release, characteristics that may affect invasion or dispersal within and between ecosystems must be investigated. The scale of release may also influence the establishment ability of GMOs (64), which need to be taken into consideration since commercial release involves huge numbers of GMO compared to small scale trials. Potential ecological effects must be targeted in small scale to focus on changes in critical steps of the GMO's life cycle (65). GMO might have properties that affect its ecological range and competitive ability. Consequently, small scale releases must include thorough characterizations of release areas as well as surrounding habitats. In addition, information about how different climatic and environmental conditions may affect persistence and dispersal properties are needed, with the purpose to reduce the GMOs ability to invade or interact with other ecosystems (42, 62).

The capability of introduced GMOs to cause nontarget effects should be addressed. Nontarget effects include influence on and interactions with all organisms in the environment, and may be direct or indirect. Direct effects concern ecotoxic effects on other organisms, for instance adverse effects on insects feeding on insect resistant plants. Indirect effects concern health effects on consumers or alteration of ecological relationship (62). Disturbance of food chains, for instance decrease in insectivorous birds due to reduced insect populations, would be considered as an alteration of ecological relationships.

In order to gather relevant scientific knowledge, secondary effects of GMO release should be unveiled. Methods for detection and monitoring in the environment are necessary to follow up the performed risk assessment, to map the actual environmental effects and to identify unforeseen adverse ecological effects (5). Encouragement of new monitoring and detection methods and tools are therefore vital for assessment and control of environmental impacts as well as collection of ecological knowledge of relevance to future releases (66). Deliberate release experiments should also be repeated to span a variety of sites and run over years, since unpredictable effects may depend on rare coincidences.

DISAGREEMENT CONCERNING RISK ASSESSMENT

The regulatory scope of the international recommendations concerning deliberate GMO release covers an agreement towards the need for risk assessment (18). The European Community directive 90 (220) and the Norwegian Gene Technology Act facilitates a precautionary approach to environmental risk. In order to minimize health and environmental risk, pre-assessment of the planned release is demanded on a case by case basis of each GMO. The purpose of the case-by-case practice is to treat every release as unique, since every GMO represents different genetic characteristics. Each applicant or notifier must obtain a prior consent from the authorities and has to perform deliberate release and field trial before the GMO is being commercialized, according to a step by step procedure. Such practice is important since GMO release raises

questions about unknown effects on ecological interactions and balances. Risk regulation based on these principles is considered to be precautionary, since the use and production of GMO are regulated in advance to documented harm, and is required for any experimental or commercial release. A precautionary approach that demands risk assessment before permission, shifts the burden of proof from those who seek to protect the environment to the proponents of development.

Obvious lack of data and insufficient information calls for application of the precautionary principle in the regulatory process. The precautionary principle emphasizes an awareness of scientific uncertainty (16). However, there may be divergent opinions among scientists about the relevance of a problem, criteria for significant evidence of harm, and whether to take action to prevent harm. At the moment, scientific uncertainty concerning environmental impacts of GMO release makes it difficult to achieve consensus among scientists concerning the relevance of hypothetical, but possible impacts. Different perceptions of risk by scientists causes disagreement concerning risk assessment.

Divergent interpretation of environmental effect

Although horizontal transfer of genes between organisms have been demonstrated, its relevance to risk assessment is debated among scientists. This was illustrated by an application from Plant Genetics System to market oilseed rape, genetically modified to tolerate the herbicide glufosinate (67). Different European authorities took up conflicting positions and expressed different opinions with regard to the significance of risk resulting from horizontal gene transfer (68). The Norwegian authorities denied marketing of the herbicide tolerant plant, fearing that transfer of tolerance genes to weed might cause excessive use of herbicides. The denial was based on the results of Mikkelsen et al., providing strong evidence that modified oilseed rape could transmit its transgene to a weedy natural relative, *Brassica campestria* (6). The transfer was accomplished during only two generations. Eventually, if these novel genes confer an ecological advantage, they may become retained in weed and thereby create a potential of horizontal and possibly vertical transfer of genes. On the other hand, the Plant Genetic Systems did not recognize gene transfer to other organisms as a risk. The competent authorities in the European Directive decided that the reported uncertainties of gene flow was not significant, thus the transgenic plant was approved for marketing (69). Many scientists consider that horizontal gene transfer might take place. The existence of ecological uncertainty was acknowledged, but the different authorities disagreed about the significance of the environmental effect. Thus different interpretations of scientific evidence may limit risk assessment and the quality of scientific advice for regulative purposes.

Present implementation of the precautionary principle

The regulatory scope of the international recommendations for deliberate GMO release accommodates a precautionary approach (18). Before release at a commercial level is granted, marketing applicants have to provide evidence obtained by a stepwise procedure (reduced confinement from laboratory to microcosms then to small scale and further on to large scale), that the GMO do not represent a risk of harm. Involvement of a precautionary approach in regulation implies that the approach must be understood in the context of deliberate release. The precautionary principle makes scientists responsible for pointing out scientific uncertainty. This must include awareness of uncertainties and critical attitudes towards reliability of experiments and hypotheses (17). At the present, however, scientific uncertainty concerning use of GMO seems underestimated or overlooked in most scientific communities.

Laboratory and small scale trials have limited predictive values, since the parameters and consequences being observed depend on the experimental condition of the studies, and information being available in advance (70). Recommendations for deliberate GMO release do not specify the stepwise procedure in detail. It is up to the applicant (or notifier) to define the steps, the time scale and sites (20). The definition of evidence for harm and parameters for safety consideration is left open to those who perform the deliberate release and field trials (62). Lack of established definitions of terms makes it difficult to prohibit release when evidence of adverse effects is unavailable. The reliability of extrapolations from small to large scales depends on the validation of hypothesis, models and assumptions. The outcome of risk judgments hence depend on the validity of the initial assumption. Evaluation of ecological effects has made evident the choice between considering biological effects of the GMO, or whether the GMO might engage in interactions with other ecosystems. Eventually a more comprehensive study of ecological effects would include potential secondary effects of GMO release on environmental processes and adverse effects on human and animal welfare (40).

Lack of unequivocal definitions of terms such as 'undesired effects' makes it difficult to postpone release when evidence of significant adverse effects on the environment or health are unavailable. When the precautionary principle is applied to policy discussions, more emphasis should be put on scientific uncertainty with regard to detrimental effects. However, current regulatory systems in most countries overestimate scientific knowledge and therefore may not be in accordance with the precautionary principle.

Bias or split interests

Scientific knowledge may be conditioned by economic or political factors. Interpretations of risk may hence rely on commitment to specific objects or ambitions (71). Scien-

tists working as counselors in the regulatory process are in danger of being hijacked by those mainly interested in ensuring a specific regulatory outcome (72). Funding organizations might have different motivations for supporting research. Biotechnology companies, mostly interested in economic growth, may form close connections with both scientists and policy regulators to favor a decision that promotes more favorable economical prospects.

Scientists may be reluctant to conclude that application of their own research results may cause unforeseen harm, particularly when no conclusive evidence about adverse effects is available. The exclusion of important scientific questions or underestimation of uncertainty by scientists, might also result from lack of experience or willingness. Most scientists have problems regard to critical and objective evaluation of own work, particularly in the context of risk and harmful effects (73).

Deliberate GMO release demands increased responsibility from the scientist, since the introduction may represent a hazard to ecosystems and human and animal welfare. This implies the obligation to make scientific uncertainty explicit and to present 'early-warnings' (15). Regulatory policy needs basic scientific information. More openness about lack of knowledge and potential risk would make science more useful for policy making.

SCIENTIFIC UNCERTAINTY AND REGULATION POLICY

Experience with risk assessments of chemical discharges, air pollution and, more recently, the mad cow disease, has illustrated the limitations of expert predictions and advice. Science-based advice to regulatory decision makers is at the moment met with growing skepticism, and with appeal for public participation in the decision-making process (9). Approval of technology application based only on expert advice, may not be in accordance with important democratic principles, especially when scientific uncertainty exists and adverse impacts may affect the public. The predictive ability of science with regard to risk assessments of GMO release is limited at the present. Von Schomberg (20) considers that current regulation must be characterized as uncertainty-based regulation, and questions the functional authority of science in the policy process. He further argues that involvement of normative standards are needed in a response to the lack of scientific standards for evaluation of environmental impacts. The Norwegian legislation requires that both sustainability and benefits dictate limitations on GMO release. The purpose of the Norwegian Gene Technology Act is to enforce containment and control release of GMO while ensuring that 'production and use of GMO should take place in an ethically and socially justifiable way, in accordance with the principle of sustainable development and without detrimental effects on health and the environment'(74).

PUBLIC INVOLVEMENT

How much, or what kind of, knowledge is sufficient to pre-assess consequences of a given GMO release or escape? The answers to such questions should be based on both scientific and value-based judgments (75). Ecological risks posed by a deliberate GMO release may outweigh the intended economic and productional benefits. Ecological risks involves potential hazards to human and animal welfare. Thus, regulation requires value judgments of they who might become affected. This implies that the public should have the right to participate in decisions concerning acceptable degrees of precaution, and be made aware of research-related uncertainties and all potential consequences (14, 75). Extended peer groups to value accept of risk to environmental and human welfare, should be considered (71). Extended peer groups might catalyze debates between experts and public concerning the preconditions for technology use and production. Many different parties might be affected by GMO use and production, i.e. biotechnology companies, farmers, NGOs, the public and the environment. The different parties hold different opinions, depending on primary interests, concerning the urgency of GMO use and production. A consensus conference, giving 14–16 lay persons the opportunity to confront experts and elaborate consensus policy recommendations, might achieve such goals (76).

CONCLUDING REMARKS

The most discomforting aspects of GMO release are the unpredictability and lack of criteria to sort out the harmful ones. Hence, we maintain that GMO release ought to be regulated by the precautionary principle. The precautionary principle emphasizes risk of harm, and when unintended environmental or health effects are possible, a decision ought to be delayed until more information is available.

Potential gene transfer between GMOs, or to other organisms, represents a risk that should not be underestimated. Other important ecological effects that should be unveiled are secondary effects and nontarget effects. The divergence of the new characteristics displayed by the introduced GMOs may not allow any generalized risk assessment of ecological effects. Consequently, methods for risk assessment and identification of secondary effects should be tailored according to the actual case, dependent on the origin and genetic novelty of the GMO. However, to avoid unwanted effects on ecosystems or environmental quality more research is needed. The current lack of predictive capability with regard to ecological effects, confers to scientists a responsibility to initiate research aimed at collection of scientific information that might minimize uncertainty.

More general knowledge with regard to biological and ecological mechanisms is badly needed. Model systems to

gather relevant scientific understanding to support reliable risk assessment must be developed. Experimental testing of carefully elaborated risk hypotheses may result in a solid basis for avoidance of potentially harmful GMOs. Such research may, however, also demonstrate ways to eliminate risks. This concept is illustrated by Greene and Allison's work on genetically modified viruses. In 1994, they reported that recombination between a viral plant transgene and naturally occurring viruses might pose a problem (43). This observation initiated further research, and in 1996 they reported that the probability of recombination could be considerably reduced by deletion of the 3'UTR in the transgene (57).

The GMOs that are commercially available at the moment must be considered as a first generation. Future development of GMOs must include improvements of these first generation organisms and introduction of second generation GMOs. We propose the precautionary principle applied to risk assessment for such releases. This will reduce environmental and health hazards, promote sustainable development, and initiate creative risk-associated research.

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