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Planned Releases of Genetically Modified Organisms into the Environment: the Evolution of Safety Considerations

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Abstract. Issues of safety and risk have taken the foreground in discussions on the deliberate release of genetically modified organisms. In most cases, the organisms being introduced into the environment are modified versions of familiar organisms with a long history of safe use and are expected to have no direct adverse effects for human health or for the environment. However, there is legitimate concern about the environmental fate of these organisms, in particular, about the genetic information which they carry. In the past, discussions of technological risk have often been based on the terminology and logic of the familiar risk-assessment strategy developed for characterizing risks from hazardous chemical processes. While the direct transfer of this assessment model to evaluating contained biotechnological processes has been successful, attempts at molding the model to the requirements of open systems have been unsatisfactory. To be meaningful, the safety evaluation for environmental releases must accomodate the distinguishing features of this open system: the lack of an intrinsic hazardous property, the lack of quantitative thresholds for adverse effects, and the lack of a common currency in which to express potential damages. A survey of risk-assessment strategies in the chemical and biotechnological sectors is presented here. This will provide the necessary background to understanding the current situation of assessing and communicating the risks associated with the reintroduction of familiar organisms into environments where they were already naturally present.

Introduction

Biotechnology is the term given to processes which make use of biology to improve human material welfare. Products of biotechnology range from foodstuffs, such as cheese and alcoholic beverages, to drugs for the protection of human health, such as antibiotics, interleukins, interferons, or vaccines. Breeding is one of the oldest forms of biotechnology practiced by farmers to select for desired traits in plants and animals. Although traditional biotechnology has a long history (10000 years) of safe application, this track record is apparently not enough to validate the applications of 'modern' biotechnology which proposes the modification of organisms through the alteration of gene signals or through the transfer of genetic information encoding specific characters.

The ambitions of genetic engineering appear to be far greater and much quicker to achieve than what was previously possible with traditional biotechnology. This is due to the accuracy and ease of application of well-honed, molecular-biological methods. The rapidity of pace, the fear of future harm, and the ethical issues on the nature of life itself, all contribute to the current unease regarding the widespread application of genetic engineering. With modified organisms targeted for release, there is also concern about their long-term impact on ecosystem processes. While all concerns are legitimate, they may be shaped by the culture of the individual or they may reflect a state of incomplete knowledge about a given situation. The positive and negative consequences of technology are inextricably bound together. It is thus a challenge to regulators to move beyond the paradox, such that mandatory rules are drafted to be commensurate with the actual technological risks.

Issues of risk and safety in biotechnology have taken the foreground in discussions on the deliberate release of genetically modified organisms (GMO). As a first step, the logic of the familiar risk-assessment model for chemical processes was adopted to describe the situation of deliberate releases; after all, the methodology had been successfully applied to evaluate contained biotechnological applications for safety [1]. This approach soon proved to be unsatisfactory for several reasons. Hazardous chemical processes and contained biotechnology applications satisfy the underlying condition for quantitative risk assessments: both have intrinsic hazards which can be identified, characterized, and described either quantitatively or qualitatively. The toxicity of chemical substances or the pathogenicity of production organisms are properties which can be directly correlated with specific hazards. On the other hand, organisms targeted for releases usually have no known direct adverse effects for human health and the environment. However, the materialization of hazard can be affected by the scale of release, the potential for organisms to proliferate beyond geographical boundaries, and the potential for the inserted genetic information (*e.g.*, antibiotic resistance) to cross taxonomic classes.

The types of damage potential often forecasted in the worst-case scenarios for deliberate releases are usually not new, but have already occurred as a result of more traditional activities of agriculture. There is legitimate fear, *e.g.*, that the antibiotic marker genes present in modified crop plants might be transferred to pathogenic organisms, thereby reducing the efficacy and usefulness for the clinical treatment of infections using this class of drugs. This concern should also extend to other environmental sources of antibiotics, such as the use of antibiotics in animal feed for prophylaxis, chemotherapy, and growth promotion. The damage potential for deliberate releases is difficult to express in terms of a common currency, especially

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when naturally occurring background processes such as pollen flow, gene transfer, and gene acquisition are the vehicles for damage in hazard scenarios.

It is the task of the environmental risk assessment to sift the facts about risks from the perceptions about risks. Ideally, this assessment should be as objective and scientifically based as possible, but maintaining the transparency and comprehensiveness necessary to encourage effective communication about risks. ***The purpose of this paper is to provide some background on the logic, pattern, and evolution of the chemical risk-assessment model: how it has been effectively applied to evaluating the safety of contained biotechnology applications; and how the situation of open systems might require another approach for evaluating potential hazards.*** With this background, it might become easier to understand the current predicament of assessing and communicating the risks associated with the reintroduction of modified, familiar organisms into environments where they were already naturally present.

Risk Assessment for Chemical Processes

The dissemination of known hazardous substances is legally regulated in order to avoid untoward exposure and adverse effects to people and to the environment. Good industry safety practices rely on the systematic use of risk-assessment schemes to identify, assess, and control the risks from hazards. Although risk is never zero, it can be made very small through specific control actions at each stage of hazard evolution over time by modifying wants, changing the technology, and preventing initiating events [2]. In its formal structure, the risk-assessment scheme for chemical processes focuses primarily on the management of risk through the identification and prevention of intiating events. What follows will be a brief introduction to the logic and arrangement of tools used to arrive at an unambiguous characterization of risk for chemical processes. The risk-assessment strategies that have been proposed for biotechnological applications – contained or open – owe a lot to the concepts expounded originally for debating the risks from hazardous substances.

Endorsed models for the quantitative risk assessment of chemical processes contain the stages shown in *Fig. 1* [3][4]. The first stage is the system description and provides details on the process: its background, objectives, and material requirements. Once this has been established, the identification of all hazards relevant to the process operation can be performed by answering the two questions: *1*) what dangerous situations exist within a plant or a process operation; and 2) how these situations may materialize [4]. All situations in which the potential for harm might exist must be considered, including the sequence of events that could transform this potential into an accident. A number of hazard identification techniques, including scenario analysis, checklists, Hazard and Operability Studies (HAZOP), can be used to ensure the comprehensiveness and level of detail required [4]. Categories of danger range from plant accidents involving serious injury and death such as explosions, fires, or the dispersal of chemicals to the less visible, but potentially harmful effects from long-term, low-dose exposure during normal operation.

In the next stages of the risk assessment, conditional probabilities of harm are calculated based on the maximum amplitude of damage and the probability of occurrence. Consequence estimation uses two types of models to assess the effects on man, animals, and the environment from exposure to identified hazards: *1*) physical models are used to evaluate the effects from the production of overpressure during an explosion, the dispersion of airborne flammable or toxic materials, the creation of high levels of thermal radiation from various types of fires; and 2) toxic effect models are used to assess the adverse health effects to man from exposure to toxic substances. These models have their weaknesses and strengths, but it is enough to mention here that the intrinsic properties of chemical substances, *i.e.*, flammability, toxicity, or thermodynamic properties, can evolve into hazards. The degree to which the processing system can prevent dangerous situations is given by the overall failure frequency rate, calculated from failure data for individual components or, when available, for similar processes.

The outcome from the probabilistic calculations of the preceding stages of the risk assessment is then compared to the official risk criteria which provide the

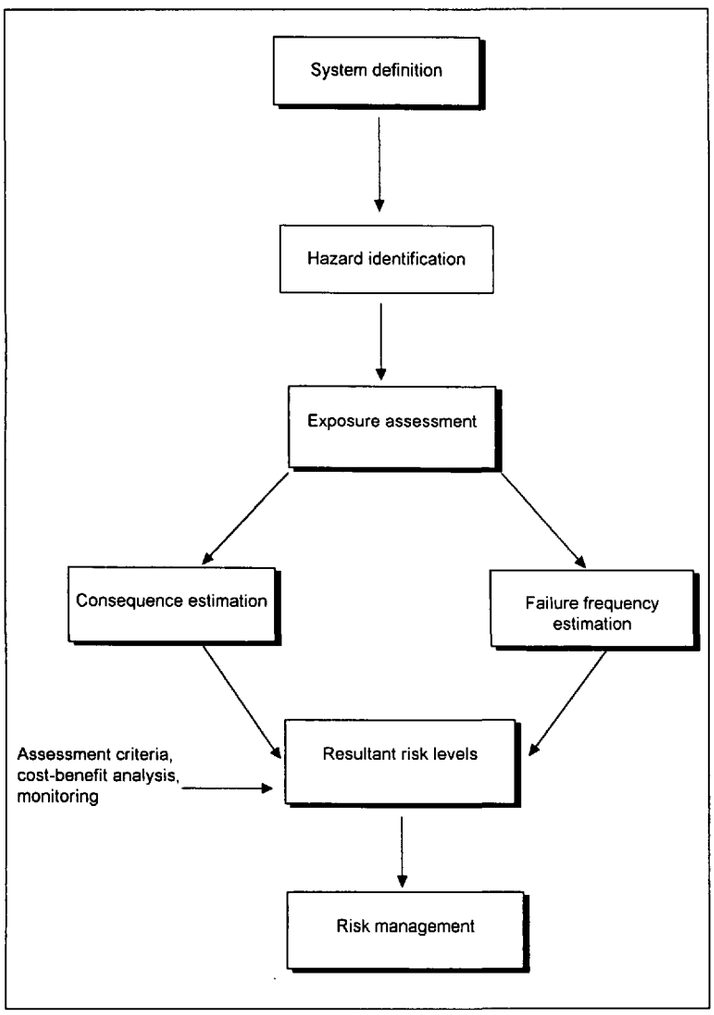

Fig. 1. *Risk-assessment model for chemical processes*

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limits of death or injury from known industrial hazards. Depending on the result of this comparison, the overall risk associated with operating a chemical process may be broadly acceptable, conditionally acceptable or intolerable. If the risk is judged unreasonable, specific actions taken during risk management may succeed in reducing the risk to 'acceptable' levels (*Table 1*).

Table 1. *Risk-Assessment Stages for Chemical Compounds, Contained and Open Biological Applications*

		Biological Systems	
	Chemical Compounds	Contained Applications	Deliberate Release
Hazard	Flammability Toxicity: Impacts on human health and the environment	Pathogenicity, environmental impacts	Not apparent: Potential environmental impacts and/or food toxicity
Exposure Assessment	Quantitative data and models available for the dispersion and behavior of the chemical substance in different organisms and environments	Based on considerations of infection dose, host range, transmission mode, dispersion mode and dynamics	No predictable genotype-phenotype relationship; the relevance of scale to potential hazard not known
Consequence Estimation	Adverse effects related to toxicity Quantitative indicators of loss (deaths per year)	Adverse effects related to the organism's pathogenic properties (*e.g.*, mortality, morbidity); potential spread and persistence in the environment	Endpoints for adverse health effects or 'environmental damage' given by risk acceptance and tolerability levels
Failure Frequency Estimation	Quantitative probabilistic calculations Incremental safety gain for increased cost	Given by the safety analysis of the technical system Incremental safety gain for increased cost	Not applicable: No containment (probability of occurrence given by natural processes)
Monitoring	Chemical concentration	Organism concentration, epidemiology	Effect on ecosystems, biodiversity
Risk Management	Technical measures, good maintenance practice, organizational measures	Technical measures, good maintenance practice, organizational measures	Not applicable: Expert and societal debate needed to decide on the risk-acceptance levels

Contained Biological Processes

Contained biotechnological applications operate under sterile conditions, which means that contact of the culture fluid at any stage of the process with the surrounding environment is restricted. At the industrial scale, process components consisting of carefully sealed pumps, vessels, and pipes resemble the equipment for chemical processes [1]. Analogous also to chemical conversions, intrinsic hazards can be identified for closed systems in biotechnology: technical hazards related to the process maintenance and operations, such as high-pressure steam used during sterilization or toxic solvents used during downstream processing; and biological hazards from the pathogenic properties of the production organism. The risk-assessment model for chemical processes is adaptable to the assessment of closed biotechnological applications, because the apparent hazards can be identified and characterized with probabilistic calculations (see *Table 1*). The remainder of this section will focus mainly on the risk assessment of hazards arising from the biological system. In contrast to the high temperatures and pressures characteristic of industrial chemical conversions, the technical hazards from biological processes are comparatively mild, because of the physiological conditions required for bioconversions.

According to internationally recognized guidelines, organisms are classified into four hazard classes, based on their pathogenic properties and their impacts on the environment [5] (*Table 2*). Class 1 organisms are harmless, while Class 4 organisms represent a high risk to human health. Organisms in Class 2 and 3 are of minor and moderate risk, respectively. An example of Class 2 organisms are bacteria of the genus *Salmonella*, some of which cause typhoid fever and food poisoning. These hazard classes also delineate the stringency of containment measures – expressed as the corresponding level of safety at which the production facility must operate (*Fig. 2*). Beginning at Safety Level 2, the facility must include in its design the means to inactivate the production organism at the interface of the containment with the environment.

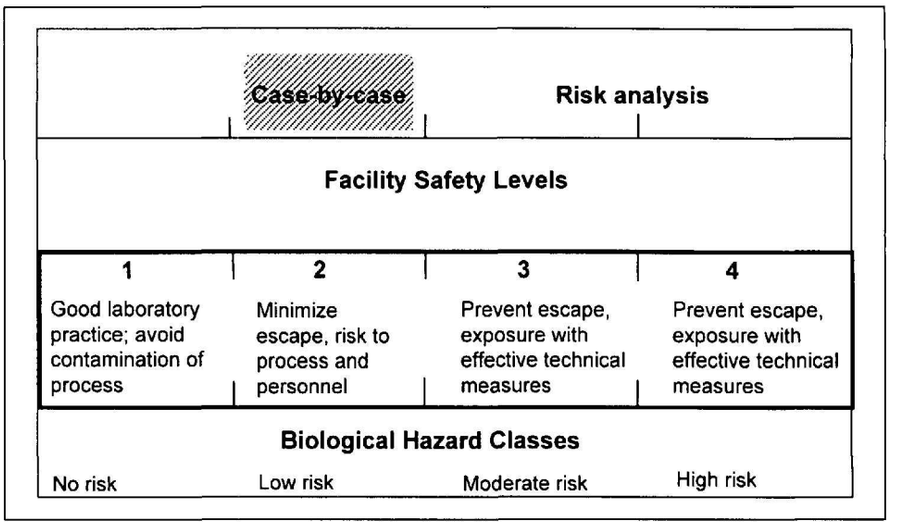

Fig. 2. *Hazard categories of the biological system and the corresponding facility safety measures*

Biological risk assessments for contained applications are not strictly required for Class 1 organisms, are formally carried out on a case-by-case basis for Class 2 organisms, and are consistently applied for Class 3 and 4 organisms [1]. After the hazard class of the organism has been determined, the first activity of the risk assessment is to identify the suite of causal events belonging to plausible scenarios describing the various routes of accidental release. These scenarios indicate the vulnerable points of the system that may become initiating events for major acci-

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dents affecting the integrity of containment, such as failure of exhaust air or wastewater inactivation. As are available for chemical processes, detailed methods exist for the characterization of possible incident scenarios in biotechnology, such as the Failure Mode Effect Analysis (FMEA) and the Event Tree Analysis [6–8].

Subsequent to the scenario elaboration is the determination of the probability that escape might occur (failure frequency rate), how the organisms might be dispersed, and what the damage potential might be (exposure and consequence assessments). Airborne dispersion models may be used to predict the concentrations of organisms as a function of time since release and their position with respect to the release site [9]. Further spread through different media such as water and soil could also be assessed based on models developed to predict the scope of contamination [10].

Unlike the numerical results expected of chemical process risk assessments, the risks associated with contained biological systems are given descriptively. Criteria categories exist for the qualitative characterization of risk-reduced or elevated from exposure to hazardous organisms. These risk criteria cover the range of pathogenic properties of an organism: lethality, morbidity, transmission, contagiousness, dose of infection, availability of medication.

For the risk assessment of contained processes which use genetically modified organisms, the hazard classes are generally considered applicable. However, the new genetic information must be given due consideration based on information about: the recipient or host organism, the donor organism(s), the vector used, the inserted trait, and any empirical data available on the physiology or phenotype of the modified organism. The hazard identification stage for GMOs also needs to examine the possible effects resulting from the gene insertion event, such as pleiotropic or mutational effects. If the modified strain is derived from an industrial strain with a history of long-term optimization, then knowledge and experience with the unmodified strain can be used to definitively classify the modified strain.

The Challenge of Safety Assessments for Open Systems

The recommendations by the National Academy of Sciences to focus the safety assessment of GMOs on the product itself – and not on the process which produced it – are an attempt at acknowledging the substantial equivalence of organisms modified by recombinant DNA techniques with those modified by older methods [11]. Scientific judgment supports the premise that modified organisms cannot be distinguished from their unmodified counterparts if properties were the sole basis of contention. It is highly unlikely, *e.g.*, that a proven nonpathogenic organism would acquire pathogenic properties after transformation, unless pathogenicity-related factors (*e.g.*, virulence, host range, or transmission) or toxic products were deliberately introduced. Most transfers are confined to one or two genes and result in organisms not fundamentally different from those created by other methods of genetic alterations commonly used in the past. Proper expression of the introduced genes normally results in specific target effects like the overproduction of valuable metabolites, resistance to herbicide or to pests in plants; or even resistance to low temperatures for fish species used in pisciculture.

The lack of a direct relationship between an intrinsic property of the modified organism and its potentially harmful consequences limits the usefulness of the key stages of the endorsed risk-assessment scheme for chemical processes (*Table 1*). The source of potential hazards is rarely the organism itself, but instead the environmental fate of the genetic *information* which is carried by the modified organism. During the operation of contained processes with Class 2 organisms, a low rate of escape is tolerated and taken into account during the exposure assessment. For a Class 1 GMO introduced into the environment, it is not so clear what a corresponding threshold for adverse effect would be. Potential hazards arising from the fate of the inserted genetic information in the environment may still need to be examined from the perspective of scale. As the scale of use of GMOs increase, low-probability events may still occur with an observable frequency. *This implies that new risk criteria based on levels of tolerable damage – and not on calculations of likelihood – would have to be discussed before the implementation of any risk management strategy.*

The preceding discussion would seem to suggest that while most releases will be benign, generic arguments for the safety of all introductions must be rejected due to a lack of irrefutable evidence that no harm will occur. At the present moment, this rhetorical paradox is resolved by requiring the case-by-case environmental safety assessment for all deliberate releases. General concepts from the risk-assessment model developed for chemical processes can be used in discussing the safety of deliberate releases, but inconsistencies are encountered if the various stages of

Table 2. *Hazards Considered for the Categorization of Industrial Production Organisms*

Type of Hazard	Impacts
Pathogenicity	Toxicity of metabolic products
	Pathogenicity of a genetically modified organism compared to the wild-type strain
	Characterization of pathogenicity:
	Type of disease caused, mechanisms, invasiveness, virulence, availability of therapies
	transmission, infection mode
	infection dose
	host range
	survival outside host
	vectors for transmission
	stability
	antibiotic resistance
Environmental Impacts	Survival, growth/decay, dispersion
	Impacts on animals, plants, cycling of bioelements
	Impact on ecosystems
	Invasion of managed or unmanaged habitats
	Gene transfer
	Possibility for monitoring

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chemical hazard analysis are directly applied. In an earlier paper, we described another approach for endorsing the safety of GMOs on a scientific basis [12]. This methodology consists of a two-stage environmental safety evaluation adapted to the features of open systems. The first stage is the scientific safety assessment which uses scientific methods, data, and models to describe the damage potential; the second stage is risk assessment where the consideration of essential benefit *vs.* risk are debated (*Fig. 3*).

The Safety Assessment

Most authorizations for release have been made on the basis of safety arguments alone. The working definition of safety states that a 'safe' condition or process is associated with tolerable damage or acceptable risk not significantly different from background levels. During the safety assessment, scientific methods, models, and data are used to obtain information and knowledge on potential hazards and on the damage consequences, if hazards were to materialize (a hypothetical probability = 1). This is achieved in the three separate steps of safety assessment: *1*) impact recognition; *2*) hazard and damage scenario elaboration; and *3*) conclusions about safety by comparison to tolerated background hazards arising from ubiquitous natural processes.

In contrast to the assessment model for chemical processes, the safety assessment for deliberate releases begins with impact recognition rather than hazard assessment. As mentioned earlier, there are no apparent hazards associated with the reintroduction of familiar organisms into their native environments or into agricultural systems. Thus, the potential impacts of deliberate releases are defined as the list of unwanted future outcomes related to the presence of modified organisms in the environment. Covering both the short- and long-term, impact aspects may include: increased allergenicity of crop plants hosting genes from other species; the loss of genetic diversity through large-scale planting of modified crops; and unwanted vertical or horizontal transfer of genetic information. The ultimate endpoints for the scope of impact recognition are the body of drafted regulatory guidelines which must be fulfilled prior to approval for release.

Once the most important impact aspects of an environmental release have been identified, plausible problem scenarios are constructed to describe all possible causally – or conditionally – related states, events, and actions which may lead to damage. A hypothetical scenario is given in *Fig. 4*, describing one possible environmental fate for the genetic information encoded in the antibiotic-resistance marker gene present in modified food crops. During plant transformation, only a small percentage of the recipient plant cells actually take up the introduced genes, and many desirable traits are not easy to detect before the plant has fully developed. Marker genes that are linked to the genes for desirable traits are therefore used to distinguish the successfully transformed plant cells from the non-transformed ones.

It is well known that bacteria can exchange genetic information amongst themselves, and there is valid concern that soil or intestinal bacteria in contact with the marker-gene-containing plant source might acquire antibiotic resistance and then transfer this genetic information further to pathogens in the environment. Widespread resistance in pathogen populations would have drastic implications for human medicine: the efficacy of prescribed antibiotic therapies for infectious diseases will likely be limited, morbidity will likely increase, and the periods during which individuals are infectious will also likely increase [13]. With respect to this scenario, it would be worthwhile to mention that, whenever possible, the marker genes conferring antibiotic resistance to plants are preferably chosen from the li-

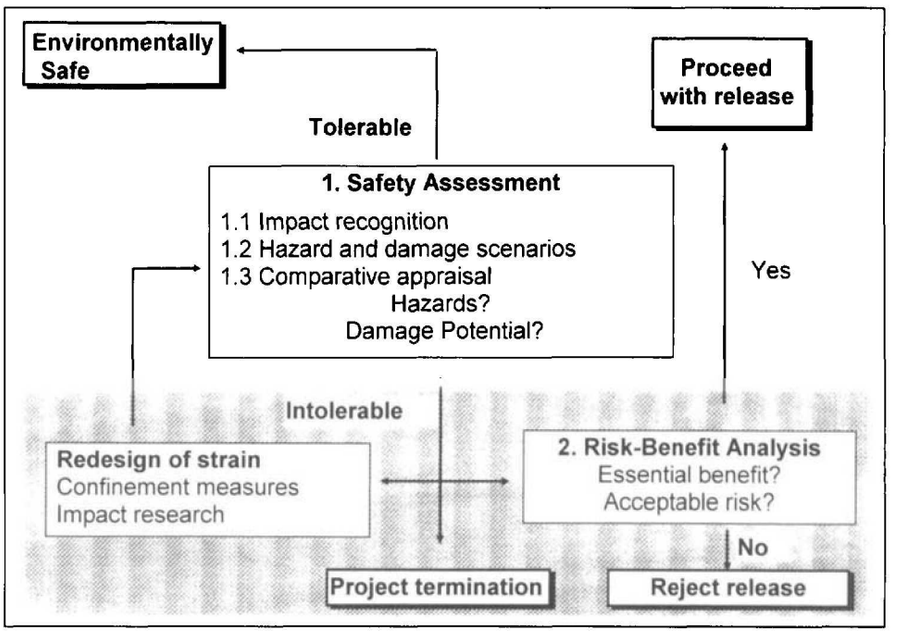

Fig. 3. *The environmental safety evaluation for deliberate releases with genetically modified organisms*

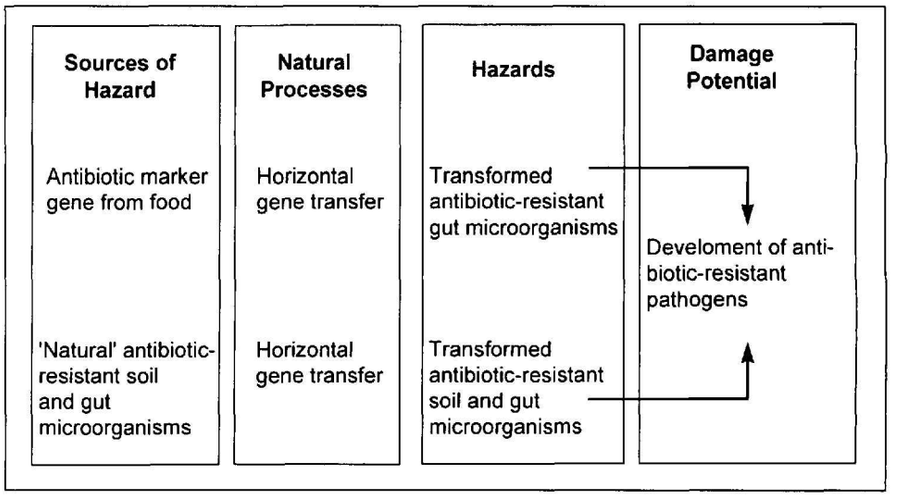

Fig. 4. *Hazard and damage scenario for the horizontal gene transfer of antibiotic resistance from plants to microorganisms*

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brary of antibiotics which are not commonly used in the clinical treatment of human diseases.

Unlike the risk characterization stage of chemical process assessments, where numerical figures exist as quantitative indicators of loss (*e.g.*, deaths per year), there is no common currency in open systems for quantifying the potential damage from deliberate releases. The plight of the damage appraisal might be rescued with additional information provided by retrospective scenarios which consider alternate pathways in the background that result in the same damage potential. In a recent article on the medical consequences of antibiotic use in agriculture, it was reported that the prophylactic use of antibiotics in animal husbandry has been a crucial driving force for the development of antibiotic resistance in certain pathogenic bacterial species [14]. A comparative analysis of both the animal feed pathway and the GMO pathway in *Fig. 4* demonstrates a similar damage potential. It can be concluded that the introduction of antibiotic-resistance genes into the environment through GMOs would not be new, for this has already occurred and has been tolerated. Such comparisons have great value not only in providing a basis for damage appraisal and for demonstrating likeness between 'new' and 'old' or the 'regulated' and 'tolerated', but also in attracting attention to urgent issues of hazards which exist in a dimension outside of genetic engineering. As long as no effective therapeutic alternatives to antibiotics exist, the policies on *all* forms of antibiotic usage in the environment need to reflect the importance of this class of drugs for human health care.

Risk Assessment

The analysis of risk is central to any technological debate. Numerical values for risk are expressed in common units of damage in the dimension of time, based on the likelihood that a hazard will occur and the extent of damage that this will produce. For technological activities under scrutiny, 'acceptable risk' is defined as the unavoidable or manageable risk level associated with the intended benefits of the particular option which has been chosen.

Performing reliable risk analysis for environmental releases is a challenging task and is necessary only if the safety assessment could not provide conclusive or acceptable proof that released organisms will be safe for human health and the environment (*Fig. 3*). Until now, most decisions about GMOs have been made on the basis of the safety assessment alone. In most cases, the identification of any realistic hazard associated with an open biotechnological application was sufficient for terminating a project in its early stages, thereby avoiding any risk.

More scientific knowledge and experience beyond the current expertise would be required to ensure the accuracy of risk assessments for deliberate releases. The question of threshold for effect or scale beyond which low-probability events in biology come to significance would need to be addressed by more research, which, ironically might only be possible through careful monitoring of deliberate releases. On another level, the difficulties in performing good risk assessments can be ascribed to the current predicament that common units do not exist for the potential types of damages forecasted for the environmental use of modified organisms. Risk then becomes a matter of individual convictions, held up against personal yardsticks for tolerability. Because decisions of the scope of environmental releases affect whole societies, teams of decision makers consisting of people with various opinions should ideally be assembled to come to some sort of consensual decision, but without straying too far from scientific rationale and evidence. Unlike the incommunicable lofty truths of human existence which vary from culture to culture and from one person to another, scientific truths can be communicated and understood by different people in the same way.

Conclusion

Promising biotechnological applications are being planned and carried out beyond the contained laboratory and production settings. It is now recognized that genetic engineering has the potential to become a valuable tool for environmental management. In most of the cases, modified strains of familiar species are being reintroduced into environments in which they were already present, but this time as optimized agents for bioremediation or for biological pest control. Other agricultural applications include the modification of crop plants to carry desirable agronomic characters difficult to achieve by traditional methods of plant breeding. Plants modified to metabolize nitrogen more efficiently could spare the environment from high fertilizer loads. The problem of excess nitrogen runoff from agriculture has been known since the 1960s and has resulted in the eutrophication of estuaries and coastal oceans as well as lakes and rivers [15].

Most of the organisms planned for release are expected to have no direct adverse effect for human health or the environment, and there is scientific support that genetically modified organisms are not fundamentally different from their unmodified counterparts. However, the environmental release of genetically modified organisms is strictly regulated, and their safety must be demonstrated prior to release. There is legitimate concern about the long-term effects of modified organisms in the environment, and the demand for a safety assessment that can show that these hazards are not new, but have been previously tolerated in the background, is justified.

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[1] O. Käppeli, *Int. J. Environ. Pollut.* **1996**, *6*, 557.
[2] B. Fischhoff, S. Lichtenstein, P. Slovic, S.L. Derby, R.L. Keeney, 'Acceptable Risk', Cambridge University Press, New York, 1981.
[3] National Academy of Sciences, 'Risk Assessment in the Federal Government; Managing the Process', National Academy Press, Washington, D.C., 1983.
[4] 'Guidelines for integrated risk assessment and management in large industrial areas', International Atomic Energy Agency, Vienna, 1998.
[5] J. Küenzi, F. Assi, A. Chmiel, C.H. Collins, M. Donikian, J.B. Dominguez, I. Financsek, L.M. Fogarty, W. Frommer, F. Hasko, J. Houland, E.H. Houwink, J.L. Mahler, A. Sandkuit, K. Sargeant, C. Sloover, G. Tuijenenburg Muijs, *Appl. Microbiol. Biotechnol.* **1985**, *21*, 1.
[6] E.J. Henley, H. Kumamoto, 'Reliability, Engineering and Risk Assessment', Prentice Hall, Inc., Englewood Cliffs, New Jersey, 1981.
[7] Deutsches Institut für Normung (DIN), 'Ausfalleffektanalyse (DIN 25424)', Beuth Verlag GmbH, Berlin, Köln, 1979.
[8] Deutsches Institut für Normung (DIN), 'Ereignisablaufanalyse (DIN 25419)', Beuth Verlag GmbH, Berlin, Köln, 1985.
[9] E.W. Peterson, B. Lighthart, *Microbial Ecology* **1977**, *4*, 67.
[10] F.J. Hurst, Ed., 'Modelling the Environmental Fate of Microorganisms', American Society for Microbiology, Washington, D.C, 1991.
[11] National Academy of Sciences, 'Field Testing Genetically Modified Organisms; Framework for Decisions', National Academy Press, Washington, D.C., 1989.
[12] O. Käppeli, L. Auberson, *Tibtech* **1997**, *15*, 342.
[13] R.J. Williams, D.L. Heymann, *Science* **1998**, *279*, 1153.
[14] W. Witte, *Science* **1998**, *279*, 996.
[15] A.S. Moffatt, *Science* **1998**, *279*, 988.