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Transgenic Organisms

Risk Assessment of Deliberate Release

Edited by
K. Wöhrmann
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Preface

In our present society new technologies are being considered in a far more critical way than they were some decades ago. Despite the acknowledgement of the benefit of some techniques, we are also concerned about the risks that might occur with their application. Biological experiments and genetic manipulations, in particular, evoke old human fears and therefore provoke resistance. The aim of this book is to analyse the problems that might arise from gene technology from the points of view of different biological disciplines. The chapters of this book review our present knowledge in molecular biology, ecology and evolutionary biology and assess our present ability to estimate and minimize ecological and evolutionary risks caused by released organisms.

We are indebted to many colleagues, students and friends for their help and for reviewing the contributions to this book. Especially, we want to thank Lutz Bachmann, Reinhold Brückner, Jutta Gutknecht, Eduard Kellenberger, Michael Leipoldt, Volker Loeschcke, Caroline Pollex, Thomas Schmülling and Andreas Sentker.

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Tübingen, December 1992

Klaus Wöhrmann
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Prologue

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The genetic structure of organisms can nowadays be altered for human purposes to an increasing extent by molecular genetic techniques. At the beginning of this development mostly microorganisms were used, and experimental work was only carried out in laboratories and industrial plants. Very soon, however, organisms were generated to be released into nature, and in the meantime more than 500 transgenic organisms have been tested or utilized in the field. Considering the increasing number of international releases of transgenic organisms, it seems at first sight worthless to continue the discussion about the risks related to this procedure. In the Federal Republic of Germany, however, the progress in genetic engineering has always been and still is accompanied by intense and controversial discussions. The supporters of the new technique emphasize the opportunities and the benefits for mankind. They are convinced that molecular genetics is the biggest challenge for mankind after nuclear physics. Opponents of gene technology, on the other hand, point to possible hazards for the environment and mankind. They are furthermore very sceptical about it and doubt the advantage of such projects.

Without any doubt, genetic engineering will be a common technique in the future. The sensibility to problems arising from this technique is quite diverse among and within different countries and even depends on the degree of individual interest in this field. In most countries laws have been passed which regulate the handling of transgenic organisms. This legislation, however, cannot be totally effective because the basic knowledge of consequences in terms of ecology and of population genetics after the release of genetically modified organisms is still insufficient. Thus the best advice we can give at present is to insist on being careful and cautious. Against this background it is therefore of great importance to gain more insight into natural processes and to continue the discussion on the aims and the necessity of, and the risks related to, releasing genetically modified organisms.

In Asilomar, California, in 1975, at the first conference dealing with problems concerning transgenic organisms, scientists decided to practise self-control over their experiments. At that time rules were set up with respect to microorganisms cultured in laboratories. In 1979 the

safeguard was abolished to a great extent, on the basis of the argument that manipulated organisms were cripples and would not be able to survive in nature, should they escape from controlled conditions in laboratories. The arguments, however, have to be adjusted in the case of the release of manipulated higher organisms, something which has been tested only recently. Of course, the success of such a procedure requires some basic viability and reproductive ability of the organisms in natural conditions. These intended releases again provoked a debate resulting in the 1984 meeting where molecular geneticists, ecologists and population geneticists discussed the risks and the possibilities of risk assessment. Since that time, a number of other meetings have been organized and papers by some commissions have been published, providing that risk assessment is receiving increasing attention. Since the meetings on Kiawah Islands (1990) and in Goslar (1992), the symposium on "The biosafety results of field tests of genetically modified plants and microorganisms" has become a biennial institution. Despite the obviously increasing willingness to take into consideration the risk of experiments with transgenic organisms (a preparedness perhaps only the result of legislation?), scientific results are interpreted in quite different ways depending on the researcher's point of view and research area. A neutral observer might have the impression that on the one hand objections raised by ecologists and population geneticists are increasingly, though not yet uniformly, being taken into consideration by molecular biologists, and that on the other hand molecular biologists moderate the ecologists' extreme fear of hazards. Here, we state that genetic engineering is not a matter of approval or disapproval but rather a question of defining a risk and determining the extent to which we are willing to accept a risk in relation to the benefit. Therefore, we first have to study the consequences of the release of manipulated organisms, and we have further to consider the importance of the resulting changes and the frequency at which they may occur.

One of the unsolved issues is whether organisms bred by so-called conventional methods and those engineered by techniques used in molecular genetics are comparable. In transgenic organisms, certain gene combinations may have been created, either intentionally or unintentionally, which have not been observed in nature. Therefore, an answer can only be found, if we are able to interpret interactions between host DNA/RNA and the DNA/RNA introduced by the plasmid. This topic is discussed by P. Meyer for plants and W. Pinsker *et al.* for Drosophila.

Transgenic organisms are exposed to evolutionary forces in the same manner as are natural ones. We can therefore apply the knowledge we have about the adaptation of species to different environmental conditions, and about the evolution of species, to analyse the fate of transgenic organisms in nature. In this context, already published results on gene transfer and

introgression of genes into other species are assessed and discussed with respect to transgenic organisms by M.G. Lorenz and W. Wackernagel for bacteria and H.-R. Gregorius and W. Steiner for plants. In addition, W. Pinsker *et al.* review the evolution and spread of P-elements within and between species of Drosophila.

After the invasion of (alien) organisms into (new) habitats, the fate of this group of organisms and the spread of introduced genes into populations of the same or related species must be considered. One approach to risk assessment might be to estimate the conditions and the period of time necessary for the establishment or the loss of alien organisms in natural habitats, or of modified genes in natural populations. Some models for the establishment of populations are discussed by J. Tomiuk and V. Loeschcke, and the spread of genes within a population is analysed by W. Gabriel. New genes, and therewith new characters, introduced into populations might change the fitness of a population which in turn might change its competitive ability. Therefore, the spread of new genes might have consequences for the whole ecosystem. During the history of our living world, especially since the advent of human migration, numerous invasions of alien species into new habitats have taken place. Many of them were intentional introductions and some of them caused serious damage. W. Adam *et al.* discuss whether changes caused by the introduced animals could have been predicted on the basis of our present knowledge. In discussions on the release of transgenic organisms it has frequently been stated that modified cultivars cannot survive in nature without human care. This view is analysed by D. Bartsch *et al.*

One aim of genetic engineering is to control the size of pest populations or even to obliterate them through released manipulated parasites. The effectiveness of this measure, however, requires stable host-parasite interactions. Our knowledge of the stability of such interactions and the effectiveness of the release is discussed for the baculovirus by J.A. Jehle *et al.*.One risk related to the biological control is the accidental and uncontrolled growth of intentionally or unintentionally released bacteria. It is proposed to minimize the probability of such an event by the insertion of "suicide genes" in the genome, a topic which is reviewed by K.H. Hofmann and T. Schweder.

Risk assessment requires knowledge of the probability of the occurrence of events causing the risk. Thus, methods must be developed for estimating, e.g., the rate of horizontal gene transfer and other events. These problems are considered and methods of risk assessment and the experience at present are summarized by A. Dietz for plants.

Perhaps one of the most controversial ideas is the use of molecular methods for screening the human genome. The human genome project might pave the way for medical treatment of congenital diseases but might also result in social problems. Hj. Müller gives a review on the presently available methods and the possible consequences for the genetic structure of the human population.

With some exceptions, techniques used in molecular genetics are of course not harmful *per se*. Nevertheless, besides considering the risks related to the release of genetically modified organisms, other points need careful scrutiny, namely, whether every single aim being striven for in molecular genetics is in fact really desirable. Of course, this applies not only to molecular biology but also to all other techniques developed in our present time. Scientists are asked to take the consequences of their actions into consideration. Some thoughts on the ethics of these issues are given by D. Mieth.

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Expression and stability of foreign genes in animals and plants

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Summary

Transgenic organisms represent an important contribution to the analysis of individual genes which can be modified *in vitro* and subsequently tested after they have been inserted into the genome. One major prerequisite for this approach is the structural and transcriptional stability of the transgene. The aim of this article is to discuss certain phenomena, both from the animal and the plant field, which are associated with instability of transgenes or endogenous genes. Particular emphasis is put on the stability of gene expression, its regulation by DNA-methylation and on the influence of the host genome on transgenic DNA. Transvection and genomic imprinting phenomena are presented as examples of transcriptional instabilities in animals position-effect variegation. Paramutation, allelic interactions and co-suppression are discussed as plant-specific phenomena of instability.

Introduction

While homologous recombination is the predominant integration mechanism in yeast (Orr-Weaver *et al.*, 1981) foreign DNA in animals (Roth and Wilson, 1988) and plants (Mayerhofer *et al.*, 1991) preferentially integrates *via* illegitimate recombination. The insertion of transferred DNA into random positions of the genome leads to an alteration of the target region, which makes the transgene susceptible to target site specific effects that can influence transgene stability and expression. The aim of this article is to document some of the phenomena which reflect such destabilizing effects on foreign DNA integrated into the chromosome.

Apart from transgenic systems cellular rearrangements and transposon- or virus-specific integration events are included in the analysis, as they also represent the integration of particular DNA-fragments into a new chromosomal environment thus sharing similar effects of inactivation with transgenic systems. In addition to the description of mechanisms like position-effect variegation, which demonstrate the influence of the integration region, several phenomena will be discussed which are associated with the inactivation of the expression of cellular or foreign genes, such as transvection, paramutation and co-suppression. Although the molecular mechanisms responsible for these phenomena remain to be elucidated, there is reason to assume that both the organisation of chromatin and DNA-methylation processes are involved in the regulation of gene expression.

Stability of foreign DNA in transgenic organisms

Stability of integrated transgene DNA can be influenced by recombination as well as mutagenic effects which can create deletions, rearrangements or sequence modifications resulting in the inactivity of the introduced DNA. Only a limited number of examples for transgene modifications are reported, but so far there are no indications for a preferential loss or mutation of transgenic copies.

In a recent publication (Spencer *et al.*, 1992) a segregation analysis of a herbicide resistance marker (bar) in maize is described which has been transformed by particle bombardment. Most of the transgenic plants showed the expected Mendelian segregation ratios; one exceptional plant, however, was observed. Only one out of 12 progeny plants derived from this line contained the bar gene which suggested an abberant segregation. The authors argue that the chromosome carrying the inserted gene might be counterselected because it contains abnormalities such as small deletions or duplications created during the transformation process. This example indicates that counterselection can occur for individual transgenes, but it still represents an exceptional event of minor importance.

Alternatively the stability of the integrated transgene can be influenced by recombination as well as mutagenic effects creating deletions, rearrangements or sequence modifications in the introduced transgene. When duplicated substrates for intrachromosomal recombination were inserted into the plant genome deletion events could be detected at frequencies of 10^{-6}-10^{-4} (Peterhans *et al.*, 1990). Inactivation of transgene DNA due to mutation events also seems to occur at a frequency around 10^{-4}. Among 31,000 transgenic plants four individuals were isolated which contained a small deletion within the transgenic construct (Meyer *et al.*, 1992a).

It can be concluded that physical instability of foreign DNA is not a frequent event, apparently occuring at the same probability as endogenous genes are affected by recombination, rearrangement or mutational events.

Methylation patterns and gene activity

In contrast to the low degree of physical instability of transgenic DNA, variation in transgene expression is a frequently observed phenomenon.

DNA methylation has been significantly associated with the regulation of gene expression in a number of species (Doerfler, 1983; Razin and Cedar, 1991). While prokaryotes contain

N6-methyladenine and 5-methylcytosine the predominant modified base in eukaryotes is 5-methylcytosine. The methylation of certain C-residues and its conservation during subsequent cell divisions is regulated by *de novo* and maintenance DNA methyltransferases (Adams *et al.*, 1984). The recognition sites for methyltransferases differ among animals and plants. While CG-dinucleotides are targets for methylation in animal cells, CNG methylation in addition to CG-methylation is present in plants (Gruenbaum *et al.*, 1981). In higher plants up to 30% of C-residues can be methylated, in contrast to only 2-8% of total cytosins in animal cells, due to the lack of CG-methylation and the under representation of CG-dinucleotides in animals (Doerfler, 1983).

Restriction endonucleases which are sensitive to site-specific methylation within its recognition sequence can be employed in the analysis of the methylation status, if the restriction pattern is compared between methylation sensitive enzymes and isoschizomeric enzymes which are not sensitive to methylation. An identical pattern generated by both enzymes indicates a lack of methylation within their recognition sites, while larger fragments created after restriction with the methylation sensitive isoschizomer argues for 5-methyl cytosine residues within the particular recognition sites (Kessler and Manta, 1990). A more detailed analysis of every C-residue within a region of interest became feasible with the development of genomic sequencing techniques (Nick *et al.*, 1986).

The correlation between C-methylation with the inactivation of gene expression has been documented in numerous cases. Especially plant transposable elements are frequently found to be transcriptionally inactive when methylated (Chandler and Walbot, 1986; Schwarz and Dennis, 1986). A similar inactivation, associated with DNA-methylation, was observed when foreign genes were inserted into the plant genome *via* T-DNA mediated transfer (van Slogteren *et al.*, 1984). Both transposable elements and foreign DNA, however, are not generally affected by methylation, as this phenomenon is restricted to certain copies while other copies of the gene remain hypomethylated and transcriptionally active. This differential methylation of certain copies integrated at different positions of the genome could be an indication for a position-dependent determination of methylation patterns due to the particular influence of individual integration regions.

This assumption is supported by an analysis of several integration sites from transgenic petunia plants each carrying one copy of a pigmentation marker gene inserted into a different chromosomal location (Meyer *et al.*, 1987). It turned out that chromosomal regions contained a characteristic methylation pattern which was highly conserved among different petunia plants and which was also imposed on the border region of a foreign DNA fragment inserted into

such a hypo- or hypermethylated region (Pröls and Meyer, 1992). Hence a transgene integrated into a hypermethylated region became also methylated and transcriptionally inactive, while integration into a hypomethylated region also left the transgene unmethylated. Although a primary unmethylated transgene can become methylated at a later stage of development (Meyer *et al.*, 1992a) integration into a hypomethylated genomic environment apparently is an essential, though not sufficient prerequisite for transcriptional activity.

Chromatin organisation and nucleosome positioning

The accessibility of active genes and their promoter regions depends on the local topological organisation of the chromatin. It is widely believed that chromatin is organized into defined domains associated with chromatin loops (Gasser and Laemmli, 1987) and that these loops are important units of function. Specific sequences, referred to as Scaffold Attachment Regions (SARs) have been mapped to 5' and 3' flanking sequences of many housekeeping genes. SARs are thought to mediate a specific interaction between the genome and a structural matrix or scaffold (Mirkovitch *et al.*, 1984). When interphase nuclei are extracted with the detergent lithium di-iodosalicylate (LIS) histones can be stripped of the chromatin rendering the genome accessible to restriction enzymes (Gasser and Laemmli, 1986a). Most of the genome is released from LIS extracted nuclei after digestion with restriction enzymes; only the SAR containing fraction remains bound to the nuclei. Because of the presence of sequence elements related to the *Drosophila* topoisomerase II consensus (Gasser and Laemmli, 1986b) within SAR-regions and because of the association of Topoisomerase II with scaffold preparations from LIS extracted nuclei it has been suggested that SAR sites may define the ends of topologically closed chromatin domains which form independent regions of gene activity (Mirkovitch *et al.*, 1986).

It remains unclear, however, whether SARs which have been isolated under unphysiological conditions, such as LIS extraction of nuclei, actually represent DNA segments which are bound to the nuclear scaffold and organize chromatin structure. Recent reports strongly suggest that the extraction procedure favours the isolation of putative SARs which have no biological function. Jackson *et al.* (1990) demonstrated that the size of chromatin loops is critically dependent on the isolation procedure and that many loops represent artefacts as chromatin aggregates easily during the isolation procedure. Another critical estimation of the biological function of SARs isolated from LIS extracted nuclei comes from the work of Eggert and Jack (1991) demonstrating that an ectopic SAR site in transgenic *Drosophila* is not attached to a nuclear scaffold or matrix *in vivo*, although it is bound to the scaffold in

detergent extracted nuclei. Apparently a functional test *in vivo* is required before one can attribute a scaffold binding function to a particular SAR site which regulates gene activity.

In contrast to the negative results for SAR activity mentioned above, the regulatory function of matrix attachment regions has been demonstrated in at least two cases. Grosveld *et al.* (1987) constructed a 'minilocus' containing the human plobin gene embedded between a 21 kb region, which is located immediately upstream of the epsilon-globin gene, and a 12 kb region downstream of the plobin gene. In transgenic mice this 'minilocus' is expressed tissue-specifically at a level directly related to its copy number and yet independently of its position in the genome. These data strongly suggest that the human plobin gene is flanked by dominant regulatory sequences that specify its position-independent expression and which can be employed to stabilize expression of a transgene.

A similar result came from work with the matrix attachment regions of the chicken lysozyme gene which co-map with the boundaries of the chromatin domain of this locus as they are located at the base of a chromosomal loop in histone-depleted nuclei (Phi-Van and Straetling, 1988). The regulatory function of the matrix attachment regions was convincingly demonstrated by transformation experiments using a reporter gene which was flanked on both sides by a 3 kb attachment-element from the 5' region of the chicken lysozyme gene (Stief *et al.*, 1989). In contrast to the variable activity of a reporter gene commonly observed between individual transgenic lines (Palmiter and Brinster, 1986), this gene was expressed at significantly elevated levels, independently of its chromosomal positions when it was associated with the attachment elements. Recent data (Breyne *et al.*, 1992) suggest that SAR sequences isolated from plants can also stabilize transcriptional stability of transgene DNA.

Similar to the function of matrix associated sequences in a positive control of gene expression, certain DNA-elements have been identified in the vicinity of particular genes which regulate stable silencing of genes. The first example of a silencer element responsible for a position dependent regulation of genes was the repression of the HML and HMR genes of *Saccharomyces cerevisiae* (Brand *et al.*, 1985). The mating type of yeast is determined by the allele, either *a* or *alpha*, present at the MAT locus. Haploid cells with the homothallism gene (HO) are able to switch between these two alleles at almost every cell division. During this mating-type interconversion the DNA at the MAT locus is exchanged for one of the two silent copies HMRa and HML*alpha* which are located about 150 kb upstream and 180 kb downstream of the MAT locus, respectively. Transcriptional activation of these silent storage copies depends on its translocation to the MAT locus. At the HML and HMR-locus the genes are tightly repressed by products of four unlinked genes, SIR 1-4 which bind to *cis* acting sequences

(HMRE) located on either side of HML and HMR, about 1 kb from the mating type promoters. The SIR regulatory system is also able to switch off other genes which are transcribed by RNA polymerase II (Brand *et al.*, 1985) or RNA polymerase III (Schnell and Rine, 1986), independently of its orientation, if it is located within 2.6 kb on either site of the promoter.

Nucleosome formation is another example of an inhibitory effect on transcription due to the prevention of transcription factor binding to regulatory sequences that are packaged into chromatin (Lorch *et al.*, 1987). Precise nucleosome positioning is probably determined by DNA sequences (Travers and Klug, 1987) and modulates the accessibility of regulatory proteins to promoter regions (Pina *et al.*, 1990).

It is reasonable to assume that upon integration of foreign DNA neighbouring regulatory elements such as silencers, matrix associated sequences or sequences involved in nucleosome phasing can drastically interfere with stability of transgene expression.

Position-effect variegation and transvection

Variegation of gene expression due to its position in the genome was first described for *Drosophila melanogaster* (Muller, 1930), and has since been observed in several species (Spofford, 1976). The term 'position-effect variegation' refers to the mosaic phenotype which results from an inactivation of gene expression in some cells due to an inhibitory *cis* effect of an adjacent heterochromatic block. This effect includes a modification in chromosome structure and seems to be dependent on the amount of heterochromatin present (Dimitri and Pisano, 1989).

Position-effect variegation, which was discovered after x-ray induced lesions (Muller, 1932), has been most extensively studied for the white gene (Panshin, 1938) and the brown gene in *D. melanogaster* (Slatis, 1954). The white gene is necessary for deposition of pigment in the eye, the ocelli, the Malpighian tubules and the adult testes. After an inversion which placed the white gene next to centromeric heterochromatin the gene was repressed in some cells giving rise to a variegated mutation. Since this mutation could be reverted to wild-type by relocating the white gene from heterochromatin to another euchromatic site in the genome, it became obvious that its location next to heterochromatin, rather than a mutation, was responsible for the variegation. In contrast to the mostly recessive character of position effect variegation at the white locus, the variegated position effect at the brown gene, which is required for pteridine pigment in the eye, is dominant, as it also affects the expression of the

unrearranged homolog. Such *trans*-inactivating effects have also been discovered for particular white mutants, especially for an enhancer mutant of white repression which resulted from the deletion in the 5' end of the insertion region of the white gene that also *trans*-inactivates the white gene on the homologous chromosome (Hazelrigg and Petersen, 1992).

Apparently position-effect variegation reflects an alteration of chromatin structure mediated by an interaction of heterochromatin specific proteins and its target sequences located in the vicinity of the repressed genes. Somatic pairing of homologous chromosomes in Drosophila mediates a transmission of an altered chromatin structure to the homologous region (Henikoff and Dreesen, 1989). A model was proposed which predicted binding of repressor molecules to negative regulatory elements located within the DNA flanking an insertion. Cooperative interaction among repressors bound to several negative regulatory elements would explain the enhanced repression of transcription in certain deletion derivatives, if one assumes that the deletion favoured the accumulation of repressor binding sites (Hazelrigg and Petersen, 1992). This model of 'heterochromatinization' is supported by the identification of dosage-dependent modifiers which enhance or suppress position-effect variegation (Locke *et al.*, 1988). About 20 to 30 loci are thought to exist in *D. melanogaster*, most of which represent class I modifiers which enhance variegation when duplicated and suppress variegation when deficient. Few class II modifiers have been identified which suppress variegation when duplicated and enhance variegation when deficient. It was proposed that class I modifiers code for structural protein components of heterochromatin which have a dosage dependent influence on the extent of the assembly of heterochromatin at the chromosomal site of the position effect and that class II modifiers may inhibit class I products directly, bind to hypothetical termination sites that define heterochromatin boundaries or promote euchromatin formation (Locke *et al.*, 1988).

The molecular analysis of the suvar(3)7 gene which encodes a dose-limiting factor for position-effect variegation (Reuter *et al.*, 1990) confirms the suggestion that modifiers interact with the formation of heterochromatin. Suvar(3)7 encodes a protein with five widely spaced zinc-fingers which indicates that this unusual arrangement of DNA-binding domains is involved in packaging the chromatin fibre into heterochromatin and that an increase in its concentration might induce spreading of the heterochromatic conformation into euchromatic regions.

Another demonstration for the linkage of chromosome structure and positioning to the modulation of gene expression arose from the analysis of the zeste gene of *D. melanogaster*. The zeste locus encodes a DNA-binding protein that influences transcription of a number of genes which are associated with the phenomenon of transvection. This term describes the