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Green genetic engineering

Summary

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SUMMARY

»Novelty« and »societal benefit« are two central criteria for the possible significance of technological developments, and the two are also the basis for much of the interest of politicians in solidly-based and early TA. The present report on transgenic plants of the 2nd and 3rd generation (with the emphasis on molecular farming) is devoted to a balanced consideration of these two perspectives: In terms of novelty, the aim is to focus on new questions of evaluation, while the aspect of societal benefits will focus on the societal context as a whole, rather than one-sided consideration of the risk dimension or specific economic interests.

BACKGROUND AND OBJECTIVES

The term »transgenic plants of the 2nd and 3rd generation« is not clearly defined. Frequently (as in the present report) »2nd generation« is used to describe genetically modified plants (GMP) which are in the pipeline (i.e. in industrial development and shortly before licensing), while »3rd generation« is applied to those in research or a very early stage of development.

The TAB project to study the potential and risks of future transgenic plants commissioned by the Committee for Education, Research and Technology Assessment in summer 2003 was limited to the subset of GMP with modified use properties (so-called »output traits«). In other words, it did not look at GMP with only improved agronomic characteristics, i.e. characteristics optimising agricultural cultivation, such as increased yield, improved resistance or tolerance to diseases and pests, or against dryness, salt and heavy metal concentrations.

The TA project aimed to answer the following questions:

> how the targeted additional benefits of these GMP are defined,
> how they are supposed to be achieved,
> what economic potential can be expected,
> what new (types of) risks should be assumed,
> what new questions of safety assessment result from these,
> whether existing safety measures appear adequate, or whether they need to be modified, expanded or supplemented,
> what regulatory challenges result, and also
> what effects on consumer acceptance are to be expected.

AN OVERVIEW OF RESEARCH AND DEVELOPMENT – LICENSING AND RELEASE

The GMP with currently foreseeable output traits can be divided into six groups:

- improved contents in plants which are a source of food (»*functional foods*«, e.g. healthier fatty acid composition, reduced allergenic potential);
- improved contents in plants which are a source of animal feed (e.g. easier digestion, increase in the share of essential amino acids);
- optimised or modified plants for production of industrial materials (changing oil/fatty acid composition for industrial uses, reducing the lignin share in wood for paper production, winning »plastics«/polymers from plants, production of industrial enzymes, all summarised under the term »PMI« – »plant made industrials«);
- plants as a source of pharmaceutical substances for human and animal medicine (recombinant antibodies, vaccines, blood proteins – »PMP«, or »plant made pharmaceuticals«);
- improving the properties of plants for phytoremediation (treatment of contaminated soils using plants);
- modifying the properties of decorative flowers (flower colour, shelf life) and plants (e.g. lawn quality).

Transgenic plants have yet to play any role in global cultivation, which is currently dominated by genetically modified resistance to herbicide and insects.

To date, eleven GMP with modified output traits have been licensed in various countries, although nine of these are irrelevant for the purposes of the present report (five tomatoes with longer shelf life, a carnation with longer shelf life and two with blue flowers, a tobacco with reduced nicotine content). The two remaining varieties, a rapeseed with high lauric acid content (Laurical), which was licensed in the USA as long ago as 1994, and a soy bean with increased oleic acid content (licensed in the USA since 1997), are approaches with a dual use in the food and other industries. Both have, however, been unsuccessful on the US market, and are accordingly not grown to any effective extent. In the EU (and so in Germany), only the three carnations have been licensed to date (since 1997/98). The licensing pipeline currently contains (since 1997) 21 applications, including one PMI GMP, a potato *with* modified starch composition.

Among the releases (the most accessible indicator of advanced R&D work), GMP with modified output traits account for c. 20% of the c. 10,000 applications in the USA (1988–2003), equivalent to 150–230 a year since 1994. A

breakdown by the above groups shows a strong and growing commitment to animal feed uses (particularly important in the USA), while there are signs of a slowdown in releases towards the end of the documented period for GMP for (functional) foods and PMP GMP. In the case of foods, this may be due to hesitation on the part of the processing industry, retailing and large-scale catering, while the decrease in PMP GMP was probably due to the more rigorous regulatory requirements. In the particularly heterogeneous group of PMI GMP, there has been an increase in release activities in the past few years involving the fibre properties of cotton, lignin reduction in wood, and enzyme production.

In the EU, GMP with modified output traits account for c. 15% of all releases in 1988–2003 (over 270 of 1,850 applications). In line with the trend for GMP generally, there has been a very definite decrease in release applications since 1996/97. A breakdown by individual groups shows a much smaller significance of the feedstuff sector than in the USA. Because in the EU (unlike in the USA), release applications can take up to 10 years and no statistics are kept on whether the releases applied for have actually taken place, caution must be taken when interpreting the trend in release activities over time. A further complication is that important European firms are increasingly carrying out releases in the USA, so that their activities have probably increased overall.

Under EU Research Framework Programmes 3–5 (application phases 1990-2002), 40 projects dealt explicitly with the development of output traits. Industrial materials dominated the field with 20 projects. In the current Framework Programme 6, only isolated relevant projects for PMP and functional foods were identified. It is only possible to derive trends from this to a very limited extent, as both the promotional instruments (integrated projects, excellence networks) and the promotional philosophy (greater orientation towards problems and markets) have been changed.

The TAB report looks at the three most important groups of GMP with modified output traits in section III »Characteristics and prospects for use«, namely for the production of functional food (»FF GMP«), for the production of proteins for pharmaceutical use (»PMP GMP«) and for the production of substances useful in other industries (»PMI GMP«). GMP for animal feedstuff, which have been particularly important numerically in the USA, are not dealt with in depth, as their uses are more comparable with agronomically modified GMP, and hence do not open up new prospects for use in the same way as the other three groups, and because they play only a minor role in Europe, quantitatively speaking.

GMP FOR THE PRODUCTION OF FUNCTIONAL FOODS OR THEIR INGREDIENTS

The range of functional ingredients produced or (to be) modified in plants by genetic engineering is still very manageable. It covers fructanes, polyunsaturated long-chained fatty acids or GMP with a custom-tailored fatty acid pattern which is nutritionally desirable, secondary plant substances, and particularly several antioxidant carotinoids and flavonoids, vitamin E and GMP with an increased iron content or lower content of substances causing food allergies. The GMP developed so far are predominantly prototypes to demonstrate fundamental feasibility, which need further development for commercial use and must be tested not only in the field but also on humans in nutrition studies.

Even within the general field of »functional foods«, GMP approaches will remain relatively insignificant in the next few years. This is clear from (among other things) the small share of GMP-related EU projects on functional foods (ten projects with GMP parts of a total of 69 projects on functional foods in the period 1989–2006), and is also suggested by the reticence of the companies active in the field of functional foods.

For most functional ingredients, the current genetic engineering approaches – overexpressing or reducing the activity of individual genes directly involved in the relevant metabolic pathways – are not sufficient to achieve commercially attractive content of the functional ingredients in the GMP. Hopes involve conceptual and methodological further developments in metabolic engineering, which seeks to affect entire metabolic pathways and regulatory networks in a coordinated way. Whether FF GMP can be established in the medium term as a source of functional food raw materials and ingredients depends crucially on whether the assumed cheaper production of functional ingredients in GMP can be actually achieved. This is not easy, as there are established production platforms already in existence (e.g. chemical synthesis, microbial production, isolation from natural sources) for most of the ingredients currently being researched in GMP, which FF GMP will have to compete with. The resource-intensive and comparatively long development period for new GMP varieties and the functional foods or ingredients produced from them represent a comparative disadvantage, as the regulatory requirements mean tying up resources in the long term in a dynamic market which actually requires a rapid and flexible response. In addition, GMP approaches generally have to be supplemented by other food technology options, as functional GMP for direct consumption can only meet a small segment of the possible entire supply of and demand for functional foods, for reasons of shelf life, seasonal availability, convenience and bioavailability.

Questions of the benefit from and safety assessment of the entire concept of functional food remain to be resolved, so that there is no point in limiting them to the genetic engineering part of the concept. It remains to be seen how far the rejection by consumers of genetically modified foods would also extend to functional foods from GMP, where consumer benefits result from genetic modification. However, we can assume that such additional health benefits would not be sufficient by themselves to create acceptance for GMP. Even with conventionally produced functional foods, the additional health benefits represent a necessary but not adequate product characteristic for surviving in the market.

PLANT MADE PHARMACEUTICALS

GMP have been discussed for many years as a highly promising new production platform for drug production. The hope is particularly for low-cost production in large quantities.

Products produced using genetic engineering methods account for the overwhelming part of pharmaceutically effective proteins and peptides, which are also called »biopharmaceuticals«. Significantly less important (and also in very early stages of development) are genetic approaches to influencing pharmaceutically effective so-called secondary metabolites, which are not discussed in the present report.

To date, no PMP GMP has been licensed for placing on the market anywhere in the world. There are intensive research and release activities in the USA and Canada, while the activities in the EU come predominantly from two French firms (Meristem Therapeutics and Biocem). The plant species used are predominantly maize and tobacco, followed by rapeseed and soy bean.

No PMP has yet been given »real« approval as a drug. Several proteins which also have pharmaceutical uses are already on the market, although so far they can only be sold as research or diagnostic reagents. They come from experimental releases (in the USA).

Of those PMP in development, so far only two have been recognised as having so-called orphan drug status (for treating rare diseases). In the EU orphan drug status (for use with mucoviscidosis sufferers) was granted in 2003 to a so-called gastric lipase (from maize). To date the protein comes from experimental releases in France, and could be the first PMP for application for approval as a drug

in the EU. In the USA a so-called galacosidase was granted orphan drug status in the same year. 15 PMP were identified in various phases of clinical testing. In addition to gastric lipase, an antibody for caries prophylaxis and patient-specific antibodies for treating non-Hodgkin lymphomas are in an advanced stage of testing. Several PMP are currently being developed for veterinary use, with the option of extending these to human indications later if successful. Besides these concrete examples, there is a vast number of PMP in preclinical R&D stages. A key area is developing antibodies, presumably because possible specific advantages of production in GMP seem most within reach.

To assess the future potential of PMP GMP, comparison with competing production platforms is needed. To date, biopharmaceuticals have almost entirely been produced microbially or in animal cell cultures, and transgenic animals are rather more advanced than PMP approaches (although here again no drug has yet been approved). The various production platforms are briefly presented and described in the report (section III.2.2).

Possible specific advantages of PMP GMP were considered in terms of freedom from human-pathogenic agents, correct glycosylation and of investment and production costs including scalability (section III.2.3). These were found to be predominantly dependent on the product. For example, it is clear that glycosylation closer to mammalian cells (modification of the protein in the cell) from PMP has an advantage over microbial systems for many drugs, although this may also prove a pharmacological disadvantage for others. It is fairly certain that general cost advantages cannot be assumed for production from PMP – these are only plausible on the unrealistic assumption of only slightly regulated open cultivation (plus ideal yields).

An in-depth investigation of the foreseeable potential of possible oral vaccines (section III.2.4) shows that oral vaccines do not seem very important for vaccine development, and particularly that the idea of ingestion in the form of unprocessed fruits (still frequently cited) is entirely unrealistic.

The overall assessment of the currently foreseeable economic potential (section III.2.5) concludes that in view of the major and growing importance of biopharmaceuticals generally, there is probably also growing potential for production in PMP, without the general cost advantages generally assumed. Their competitiveness is decisively determined by advances in competing production systems and development of specific regulations for cultivation and corresponding risk management measures (sections IV, V).

PLANT MADE INDUSTRIALS

Use of PMI GMP seems comparatively further away. This is a little surprising, given the intensive work on relevant GMP concepts over many years, and the fact that the first two such GMP (the lauric acid rapeseed and soy bean with enhanced oleic acid content referred to above) were approved and commercialised years ago. The only currently foreseeable example here in the EU is the starch potato, which has been in the approval pipeline for years.

For all other approaches (whether in »designer oils« or »designer starches«, production of industrial enzymes, biopolymers or other special ingredients) it is virtually impossible to assess how far the work has come in concrete terms. In some cases, this is in-house work, in other cases the development work – e.g. on bioplastics from GMP – seems to be taking significantly longer than hoped. The reasons for this differ, depending on the development goal and plant species, but the examples presented suggest possible general assessments (which also apply e.g. to development of FF GMP).

> In several cases, expectations particularly of attainable product yields have been not been satisfied even after many years of development. In the course of maximising content, apparently undesired side effects have emerged (are emerging) in many cases which then result in lower yields. While this does not make the concept (economically) unusable, it does affect the range of substances which can be produced on a commercially competitive basis.
> In several cases, the transition from the highly promising model plants to specifically usable ones did not proceed as hoped, as the genes failed to »function« accordingly.
> In other products, the alternative production systems (cell-based systems, transgenic animals) developed faster or more efficiently.

An assessment of the prospects for PMI concepts is accordingly (even) more difficult than for PMP. Production of bulk products seems unlikely in the foreseeable future, the production of renewable raw materials is more likely to be optimised through breeding of non-genetically-modified plants. Industry sees realistic prospects for high-price special applications, if these can only be produced in GMP and not in conventional varieties or the cultured varieties otherwise used. Dual use (e.g. bioplastic and feedstuff) depends on relevant approval, which is only conceivable for selected approaches. Transgenic trees for plantation farming could become more significant worldwide, but cultivation in the EU is unlikely for a long time.

POSSIBLE ECOLOGICAL AND HEALTH RISKS

Given the early stage of GMP modified for output traits, no risk discussion has developed for most sub-aspects, so that no presentation is possible. This applies particularly to the possible ecological risks of FF GMP and the possible health risks of PMI GMP. At the same time, GMP modified for output traits fundamentally change the situation for risk regulation (i.e. risk assessment, risk evaluation and risk management), because at least PMP GMP and also many PMI GMP and possible several FF GMP have an inherent risk because of the medical and physiological impact of their ingredients. The current risk concept or goal of risk regulation is to approve only GMP which are risk free: this must be at least modified by developing comprehensive and rigorous safety requirements for cultivation and processing e.g. for PMP GMP with their potential environmental and health risks (as in Canada and the USA). It will be necessary here to impose group-specific measures (a start has been made in the form of variety-specific coexistence rules). This means moving away from the pure case-by-case principle, or at least supplementing it. At the same time, the discussion of benefits is taking on new priority compared with the 1st generation of GMP, including risk evaluation and regulation. So far, it has been possible to ignore doubts about the benefits of the genetically introduced properties e.g. from the regulatory point of view (because no concrete risks to health and the environment were established as a prerequisite for approval), and to leave evaluation to market forces. In future, however, the desired benefit (e.g. of drug production) is likely to play a greater role – at least in individual cases – in risk evaluation, including in the approval decision.

There is little reliable information on the individual aspects of possible ecological and health risks of the various groups (or even individual transgenic properties). The risk discussion for FF GMP is focusing on the basic question of safety evaluation of innovative and primarily functional foods, while for PMP GMP the emphasis is on possible release into the environment and food and preventing this (depending on the individual instance, PMI can be closer to FF or PMP GMP). Particularly with regard to PMP, the risk debate on molecular farming generally has so far concentrated almost entirely on the question of reliable sequestration and containment/confinement of GMP (section IV.4).

BIOLOGICAL AND PHYSICAL CONFINEMENT MEASURES

In considering possible risk management measures for GMP modified for output traits, it is necessary to distinguish between two groups of cases which pose very

different requirements for regulation, namely the GMP which can be regarded as just as safe as the current approved 1st generation GMP, and all others.

The first group could include several of the conceivable PMI applications, e.g. if these involve modified food plants which are currently being used for industrial purposes in their conventional form. At least if the relevant GMP have explicit approval for food or feedstuff, large scale cultivation is conceivable subject to the prevailing variety-specific coexistence regulations, and would not differ substantially in quality from the food sector. The second group presumably includes most PMP, together with a range of conceivable PMI plants for which special containment/confinement will be required. In the event of open cultivation, and possibly greenhouse cultivation, particularly strict biological and physical confinement measures must apply, as the current regulations in Canada and the USA require.

How reliable are the various methods in preventing undesired dissemination of GMP? Restricted dissemination of transgenic plants or their genetically modified properties is possible up to a certain relatively high degree using containment and confinement measures. However, (almost) complete prevention of the escape of a transgene is only possible in closed systems. A general problem of restriction of dissemination by confinement measures for transgenes in GMO is the open nature of systems. In addition, few biological confinement methods have reached a state of development where studies on integrity and leak tightness can be carried out. The present state of science and technology is unable to offer any system for confinement of transgenic nonfood plants which permits coexistence in open cultivation of GMO and non-GMO species completely free of any influence. The extent to which such influence can be tolerated and under what conditions are matters for society to decide.

REGULATION ISSUES IN MOLECULAR FARMING

Consideration of the state of regulation of genetic engineering shows that the present regulations and procedures for molecular farming are not entirely appropriate or adequate. For molecular farming of »high price« products or ingredients on comparatively small areas, approval for release under Part B of European Directive 2001/18/EC is inadequate in many cases (because the relevant products may not be placed on the market), although approval for placing on the market under Part C would actually not be required, because free trade and unlimited cultivation are not goals of GMP development. At least in the medium term, there will accordingly be a need for change, particularly in the regulation

of genetic engineering. By contrast, there is currently hardly any need for change apparent in drug and chemical regulation.

Current activities and discussions in the EU (section V.2) show that very little attention has been paid to the issue of molecular farming so far, particularly in comparison with Canada and the USA. This implies a need at EU and national level – the speed regard to research policy – for more intensive consideration of the opportunities and potential risk of GMP modified for output traits.

AREA FOR ACTION: OPERATIONALISATION OF VISIONS AND SCENARIOS

Although molecular farming has been described as a future option for many years in the debate on genetic engineering, it has mostly been presented in very vague terms, either as largely unsupported assumptions about possible benefits (and/or risks) or as visions of the future. The relevant documents typically focus on scenarios for the use of possible products from GMP modified for output traits, describing scenarios for production and cultivation which have little contact with reality, and completely ignore regulatory aspects and realistic coexistence scenarios. Such operationalisation accompanied by greater social opening seems very important for the coming debates on possible future use of transgenic plants. These tasks should be addressed with a view to the coming Framework Programme 7, together with more substantial links to the relevant policy areas, strategies and goals (including more extensive use of renewable raw materials, development of rural areas, sustainability of agriculture, healthier nutrition).

AREA FOR ACTION: RESEARCH POLICY

A possibility for national research policy is the development of interministerial promotional measures for research into the potential of GMP modified for output traits. Particularly with a view to possible large scale use of PMI GMP as renewable raw materials, coordinated promotion of major projects by the Federal Ministry of Science, Research and Technology (BMBF), Federal Ministry of Food, Agriculture and Consumer Protection (BMELV) and Federal Ministry for the Environment (BMU) would be useful, in later stages also involving the Federal Ministry of Economics (BMWi) and for PMP the Federal Ministry of Health (BMG). A viable and societally acceptable approach would require not only bringing together the ministries' technical points of view but also including various interest groups in developing such promotional programmes and projects.

No serious assessments are currently possible for R&D approaches deserving promotion or safety issues requiring particularly urgent investigation. However, a specific proposal is made for a »Progress report by the Federal Government on the status of publicly funded activities in connection with research, approval, cultivation and marketing of GMP«. This could possibly offer a basis or at least a point of reference for constructive and sustainable further development of research policy on green genetic engineering and alternative strategies.

AREA FOR ACTION: MODIFICATION OF REGULATION AT EU LEVEL

With regard to possible modification of the regulation of genetic engineering, there is a need for an amendment of EU law as a first stage, after which national regulations can be revised accordingly. The Federal Republic of Germany co

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