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Risks and Policy Challenges of Third Generation GM Crops

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Keywords

molecular farming, industrial crops, biotechnology policy, risk assessment, GMO regulation

Abstract

Commercial and academic activities in the production of pharmaceuticals or other substances of industrial interests from genetically modified plants, i.e. molecular farming, have so far centred in the USA and Canada. Recent increases in EU activities and the proximity to market stage of the first plant-made pharmaceuticals, some of which from EU based companies, represent a call to action for EU regulators. Drawing on the North American debate on molecular farming it will be argued that both the rationale of and the risk issues associated with molecular farming will differ significantly from those of first generation GM crops. Based on these differences, the suitability of the existing regulatory framework, which essentially was developed in response to the arrival of insecticide and herbicide tolerant crops for food and feed use, is discussed. Possible options for adapting the already complex EU regulatory system to cater for molecular farming are examined. It will be argued that the policy challenges posed will inevitably spark a broader public debate. As an issue for debate, molecular farming is located at two crossroads: of the risk debate on agricultural biotechnology and the sustainability debate on renewables and greening of industry and of red and green biotechnology. Complex scientific, technical and legal issues, new issues at stake and a new pattern of actors are likely to give EU regulators a difficult time.

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1 Introduction

Since the mid 1990s an increasing number of research papers have described the production of substances of industrial interest from genetically modified (GM) plants, also referred to as "molecular farming"[1]. As a fundamental difference to present-day industrial crops most of these substances are not naturally occurring in these plants. The majority of R & D activities has so far focussed on high-value proteins, especially on biopharmaceuticals (plant-made-pharmaceuticals or PMPs) (reviewed in Ma *et al*. 2005). Furthermore, plants are used for the production of enzymes and other substance such as fatty acids, bioplastics, spider silk, and gelatine (plant-made-industrials or PMIs) that can be used in various industrial sectors (e.g. Arcand and Arnison 2004, Hood *et al*. 2003, McKean 2003, Neumann *et al*. 2005, Scheller and Conrad 2005).

Until recently, most R & D as well as public debates have centred in the USA and Canada, with little activity in the EU. As this article shows the picture in the EU is now changing and challenges for regulators are looming.

This article is structured into the following sections: Firstly, the driving forces of the technology will be introduced. Secondly, the present status of commercialisation and the most important aspects of the North American public debate are reviewed. Thirdly, evidence will be presented that molecular farming is about to gain a foothold in Europe. In a forth section, it will be argued that specific hazards and risk dimensions are associated with molecular farming. A fifth part identifies specific challenges for EU regulation by drawing on the technical and risk-related characteristics of molecular farming. In a concluding section, it will be argued that the policy development for molecular farming have to be pursued in a complex environment where unresolved problems with first generation GM crops[2] are still prevalent.

The focus of the article will thereby be on PMPs but frequent reference is given to PMIs.

[1] Some authors are using the terms biopharming interchangeably while (molecular pharming) is less inclusive and refers to the production of pharmaceuticals only.

[2] First generation GM crops comprises so called output traits that are not aiming to directly benefit the final consumer. This group comprises various types of tolerance traits, mainly herbicide and insect tolerance.

2 Technology drivers

Plant molecular farming is being developed as an alternative production system competing with a range of systems some of which are well established while others are under development. Table 1 provides a comparison of plant molecular farming to other production systems. Bacterial production systems have been used since 1977, with the landmark of recombinant insulin in 1982. Yeasts can be used for the production of more complex proteins and are for example used for the production of Hepatitis B subunit vaccine. Mammalian cells have dominated the biopharmaceutical industry since the mid 1990ies because they can produce authentic complex proteins that are functionally and in many cases structurally equivalent to their native counterparts. This is especially true for the three-dimensional structure – the folding of the protein and for the coupling of sugar residues to the protein – the glycosylation. Indeed more than half of all biological products – therapeutics, diagnostics, and vaccines – approved by the US Federal Drug Administration (FDA) are produced from mammalian cells.

All three technologies of producing biopharmaceuticals – bacteria, yeast, and mammalian cells – require high-tech facilities and sterile production with mammalian cells being the most expensive one. They are well established production systems in contrast to animals and plants. Transgenic animals can produce biopharmaceuticals in their body fluids, providing a production system without the need to kill the animals, for instance in the milk of mammals or in chicken eggs (animal pharming). This technology is presently being developed as an alternative option for production and is in a very similar stage of development and proximity to the market as molecular farming. Commercial attention has so far focussed rabbits, cows, pigs, sheep, goats and chicken. Although productivity in animal pharming is high, the process is time consuming and expensive. Furthermore, pharmaceutical proteins might affect the health and physiology of the production host thereby creating problems of animal welfare (Twyman et al. 2005). Production in chicken eggs seems to be more competitive in terms of timescales and production costs but is still in earlier stages of development.

Regulatory frameworks are established for both production and products from microbes and mammalian cell lines. A framework for animal pharming is still under development and has triggered a fierce ethical debate about animal welfare. Very recently, in mid 2006, the first biopharmaceutical from transgenic animals, a goat-derived drug for people with a rare inherited disease that leads to blood clotting, won approval of the European Medical Agency EMEA (Heuser 2006).

Table 1: Comparison of production systems for recombinant human pharmaceutical proteins.

System	Overall cost	Production timescale	Scale-up capacity	Product quality	Glyco-sylation	Contamination risks	Storage cost
Bacteria	Low	Short	High	Low	None	Endotoxins	Moderate
Yeast	Medium	Medium	High	Medium	Incorrect	Low risk	Moderate
Mammalian cell culture	High	Long	Very low	Very high	Correct	Viruses, prions and oncogenic DNA	Expensive
Transgenic animals	High	Very long	Low	Very high	Correct	Viruses, prions and oncogenic DNA	Expensive
Plant cell cultures	Medium	Medium	Medium	High	Minor differences	Low risk	Moderate
Transgenic plants	Very low	Long	Very high	High	Minor differences	Low risk	Inexpensive

Source: Ma et al. (2003).

The main drivers of molecular farming seem to be of economic and technical nature (see Table 1): scaling-up of production by simply enlarging the cultivated area is considered an asset over presently used bioreactors that require expensive high-tech buildings, machinery and equipment and a time-consuming process for optimising production. This would enable producers to quickly adjust to changing market requirements (Raskin *et al*. 2002). Plant molecular farming would also provide sufficient capacity to manufacture biopharmaceuticals well beyond 10.000 kg/year – what constitutes the highest annual tonnage presently derived from microbes or mammalian cell lines (see Figure 1). This is considered by industry as especially important for novel high-dose antibodies[3] that would be required in annual tonnages of 10.000 to 50.000 kg. For this kind of antibodies a shortage of production capacities is anticipated if relying on production in bioreactors only (Ko and Koprowski 2005). Beyond these high-volume biopharmaceuticals, most of presently used therapeutic proteins are sold at tonnages of less or even much less than 1.000 kg/year. Even in these cases it seems tempting to produce this amount on a total area of 2 to 40 hectares (see Table 2).

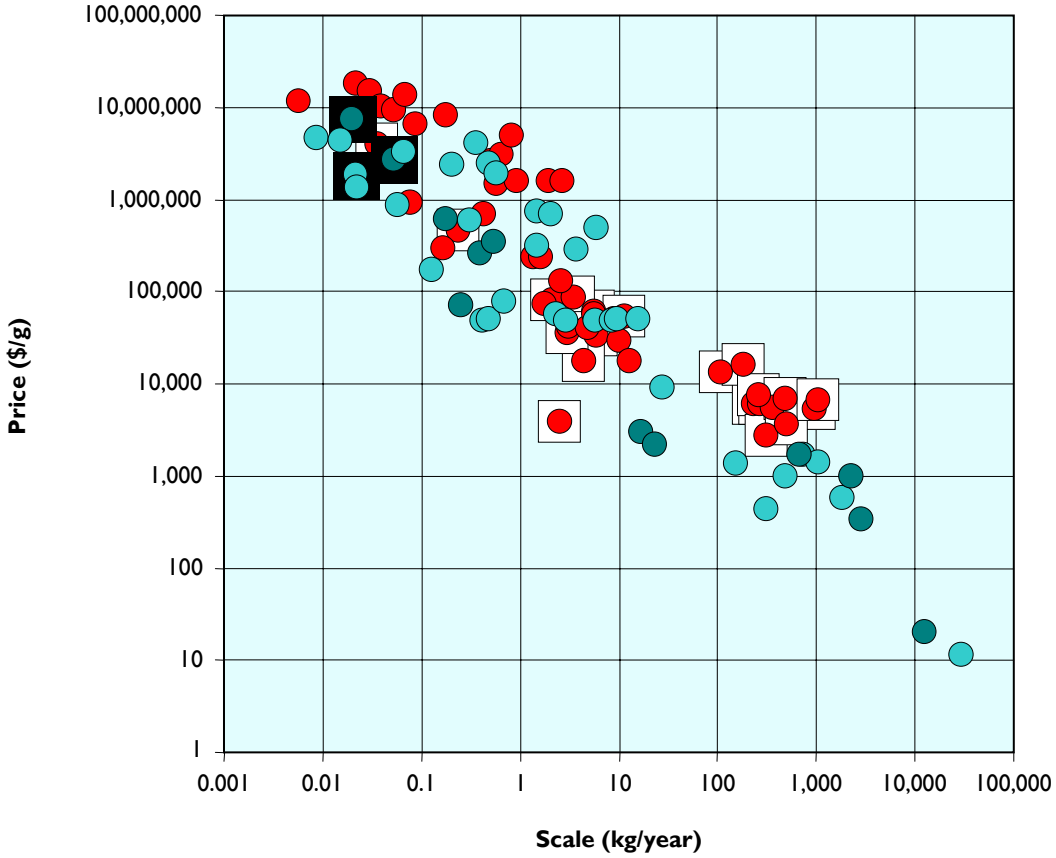

Figure 1: Price and Sales of 89 therapeutic proteins presently marketed.
Abbreviations: $/g…US$/amount of biopharmaceutical [g]
Source: Steiner (2005).

[3] Monoclonal antibodies are widely used as diagnostic and research reagents. Their introduction into human therapy has been much slower. Still, more than 150 antibodies are presently in preclinical and clinical development, many of them aiming at the treatment of cancer.

Plants are also an interesting alternative for proteins that are difficult or impossible to be produced in microbial systems. The protein resulting from the same gene might be slightly different in structure and function depending whether it is expressed in microbes, mammals or plants. Bacteria for instance, do not add certain sugar residues (glycosylation) and might not be able to correctly process complex human proteins (Twyman *et al*. 2003).

Product safety is another reason, frequently reiterated by industry as PMPs would be free of contaminating human or animal viruses, which is a concern in case of production from mammalian cell lines (Commandeur *et al.* 2003). While a presence of such viruses in mammalian cell lines might pose risks to human health, plant viruses are not known to infect humans.

Potential savings in production costs were strongly emphasised until very recently (Seon et al. 2002) with industry in the meantime becoming less optimistic. In fact the production of biomass that includes the target protein is likely to be much cheaper compared to microbes and mammalian cells. According to earlier and optimistic estimates recombinant proteins could be produced in plants at 2 to 10% of the cost of microbial fermentation systems and at 0,1% of the cost of mammalian cell cultures, although this depends on the product yield (Giddings 2001). Cut down in costs would, however, only affect the production of the crude protein, whereas the purification of the protein and formulation of the biopharmaceutical in the subsequent downstream processing amounts 50 to 80% of the total production costs. Furthermore, higher compliance costs have to be anticipated for approval under respective GMO legislation and medicinal product legislation. The pre-clinical and clinical trials of new biopharmaceuticals are already a year-long and very expensive procedures required by pharmaceutical legislation. With PMPs companies are facing uncertainties and additional challenges how regulators, who are used to deal with contained production facilities and strictly controlled and validated production processes will deal with open-field production environments that will be influenced by weather, climate, soil and pests.

Table 2: Estimate of productivity of different production platforms for pharmaceutical proteins.

Production platform	Productivity [kg/hectare/year]	Area needed for 1.000 kg [hectare]
Maize (kernel)	0,2-4	800-40
Rice/barley (seed)	2-12	80-12
Alfalfa (foliage)	4-6	40-8
Potato (foliage)	20-80	8-2
Chicken egg	12 g/chicken	80.000 chickens
Mammalian cell culture, 15.000 l scale	1,5 g/l; 20 batches	5 bioreactors

Source: Baez (2004), modified.

Finally, potential humanitarian benefits to developing countries are frequently mentioned by manufacturers and scientists, that is to say the availability and applicability of drugs might be improved (e.g. in case of oral vaccines, storage conditions in case of PMPs in kernels) (Ma et al. 2005).

3 North America: commercialisation being stalled

Most commercial activity has so far centred in North America. More than 370 experimental field trials in the USA and in Canada with GM crops producing PMPs or PMIs[4] are a good indicator for commercial interests. Another indicator are clinical trials: 16 PMPs were recently reported to be in various steps of clinical trials (Pharma-Planta 2005, Sauter and Hüsing 2006) with about 10 products – including veterinary drugs – getting closer to market stage (see Table 3)[5]. Very recently, a poultry vaccine from plant cell culture was the first PMP that achieved regulatory approval.[6] Horn *et al.* (2004) anticipates market approval for 12 products from plants including vaccines, antibodies, and enzymes by 2009. Some enzymes and other substances are already produced on a small scale through molecular farming for commercial use as fine chemicals (Spök and Klade 2005).

Table 3: Plant-made pharmaceuticals approaching market stage.[a)]

Product	Application	Plant host(s)	Status[b)]	Company
Biopharmaceuticals for humans				
CaroRxTM	AB carries prophylaxis	Tobacco	II	Planet Biotechnology, USA
Gastric lipase	Therapeutic enzyme	Maize	II	Meristem Therapeutics, France
Human intrinsic factor	Dietary	Arabidopsis	II	Cobento Biotech AS, Denmark
AB	AB cancer vaccine	Tobacco	II	Large Scale Biology Company, USA
Hepatitis antigen	Oral vaccine against Hepatitis B	Potato	II	Arizona State University
Biopharmaceuticals for animals				
	Vaccine against feline parvovirus	Tobacco	Advanced	Large Scale Biology Company, USA
Human lactoferrin	Anti-infection, anti-inflammatory and iron-binding properties	Rice	Advanced[c]	Ventria, USA
Human lysozyme	Anti-infection, anti-inflammatory and iron-binding properties	Rice	Advanced[c]	Ventria, USA
HN protein of Newcastle Disease Virus	Poultry vaccine	Plant cell culture	Advanced	Dow Agro Sciences, USA

[a)] *This table only includes PMPs which are in the advanced stages in terms of clinical testing;*

[b)] *For human biopharmaceuticals: phase of clinical trials;*

[c)] *Already commercially available as fine chemicals.*

Source: company websites.

4 www.isb.vt.edu/cfdocs/fieldtests1.cfm; www.inspection.gc.ca/english/plaveg/bio/mf/sumpnte.shtml.

5 This also includes two products from EU based companies, Meristem Therapeutics and Cobento, the former of which is partly conducting field trials in the USA.

6 www.dowagro.com/newsroom/corporatenews/2006/20060131b.htm.

Consequently, the North American biotech industry is now keen to obtain a green light for commercial production, which would include open field production in food crops. Therefore, they are eager to establish a regulatory framework that would allow for commercialisation. The United States Department of Agriculture (USDA) and the Canadian Food Inspection Agency (CFIA) have become active quite early in the process. Support for this technology has come from certain growers' organisations, e.g. National Corn Growers Association (2001) and patients' alliances, e.g. IAPO (2005)[7]. Confronted with strong pressure from the food industry, environmentalists and consumer organisations regulators are however proceeding slowly and with care (Cassidy and Powell 2002, Ellstrand 2003, Jones 2003, Miller 2003, Kamenetsky 2003, UCS 2003).

Given the US preference for maize as a production platform, the key policy issue obviously is the risk of contamination, i.e. if pharm maize would end up in the food or feed chain (California Council on Science and Technology 2003, Felsot 2002, Pew 2002). Environmentalists and consumer organisations are highlighting health and environmental risks and the food industry is – on top of that – also concerned about the impacts of perception – recalling the consequences and costs of recent cases of accidental contamination (see further below). These concerns had been amplified by initiatives to grow pharm maize in the corn-belt region.

Canadian authorities are embarking on a more precautionary way. Unlike in the USA, they are explicitly recommending the use of non-food crops for PMPs and are limiting the size of experimental field trials to one hectare per province and year (CFIA 2003).

The sensitivity of certain actors results from contamination incidents, especially the case of StarLink (EPA 2000, Ellstrand 2003, Freese 2002, Spök, et al. 2003) and ProdiGene (Cassidy and Powell 2002, Choi 2002a, 2002b, Jones 2003):

StarLink is a GM maize variant harbouring the bacterial protein Cry9C. This protein is specifically toxic to a variety of pests and thereby renders the maize insect resistant. In 1998 the US Environmental Protection Agency (EPA) did not exclude the possibility of an allergic potential and granted a tolerance exemption for feed and industrial use only (i.e. not human food). The EPA required a buffer zone of 200 m between the GM and any conventional maize to avoid pollen contamination. StarLink maize and maize derived from the buffer zone were to be processed separately from food maize. Despite such safety measures Cry9C was detected in Taco Chips in September 2000 and subsequently also in maize flour. USDA eventually detected Cry9C in 9 to 22% of all maize samples. Given the huge variety of processed maize products millions of people are assumed to have consumed contaminated maize products before those products were recalled and removed from supermarket shelves. Despite a considerable number of consumer reports about allegedly allergic symptoms, in no case could actual allergic symptoms be attributed to the GM maize. Nevertheless, call-backs and compensations were reported to amount to billions of US $.

It was later revealed that contaminations occur via commingling after harvest. Commingling might happen for instance, if storage facilities, equipment and machinery are used for both GM and conventional maize varieties without properly cleaning them in between. Farmers or wholesalers handling such material might also be not aware to keep these types of maize separate. In fact, it turned out that some of the farmers and farm workers had not received appropriate information and training on both sowing and trading restrictions. In addition, there were indications of pollen flow to conventional maize varieties.

While the StarLink case was about maize grown for feed use on large acreages the ProdiGene incident was about pharm maize grown on small areas. In 2002 USDA's Animal and Plant Inspection Service (APHIS) staff recorded two cases of violations against conditions for deliberate re-

[7] www.ncga.com/news/CC/volume10/ccVol10n03.html.

lease of GM pharm crops. In both cases GM maize volunteers resulting from field trials of the US molecular farming company ProdiGene were detected in conventional soybean fields.

In the Iowa case, volunteers[8] were detected in a late stage of development. Given the possibility of pollen flow to surrounding maize fields, more than 60 hectares of maize had to be incinerated.

In Nebraska, ProdiGene did not remove the volunteers despite the order to do so was issued by inspectors of the USDA-APHIS. Thus, the volunteer pharm maize was harvested together with the soybean plants. About 14.000 tons of soybeans were put in quarantine by APHIS. ProdiGene reportedly bought the entire batch of soybean. The US Food and Drug Administration (FDA) stated only minimal risks if at all. Nevertheless, economic damages in this case were considerable: fines and financial damage were reported to have amounted to some 3 million US $ and eventually led to the bankruptcy of ProdiGene. In this case total economic damage was small compared to StarLink but, according to several commentators, the incident nevertheless caused a severe setback for the molecular farming industry.

4 European Union: late on the scene

In the EU commercial R & D activities in molecular farming have been increasing over the last five years: at present, at least 24 companies are active in this field, most of them specialised into this technology (see Table 4). Recently, with Syngenta, Bayer and BASF, EU-based multinational companies moved into the arena. Cobento and Meristem Therapeutics might be among the first to market a biopharmaceutical for use in humans from plants (see Table 3). Meristem is producing its gastric lipase in open field production using maize (presently on 20 hectares in France) and anticipates full scale production on 1.000 hectares following market authorisation in 2009 (Burtin 2006). The gene for the enzyme lipase was derived from dog and the product is intended to be used for treating Cystic Fibrosis.

Pharma-Planta, a research consortium under the European Commission's 6th Framework Programme is pioneering academic research activities in partnership with a small number of European firms[9]. The European Technology Platform "Plants for the Future"[10] which is advising the European Commission on research topics for the upcoming 7th Framework Programme, set a particular focus on industrial crops, including molecular farming (Plants for the Future 2004, 2005). These activities have very recently brought molecular farming onto the radar of EU regulators and risk assessors.

[8] A crop which sprouts unexpectedly in a surprise location. Birds and animals often plant them in their droppings, or the seeds are carried by wind or humans to new locations. In the case of maize, kernel might remain in the soil, survive the winter and sprout in the next growing season. If the field is being used for some other cultivars, the maize might be a weed.

[9] www.pharma-planta.org.

[10] EU Technology Platforms are led by industry and serve as frameworks for stakeholders, to define research and development priorities, timeframes and action plans on a number of strategically important issues where achieving Europe's future growth, competitiveness and sustainability objectives is dependent upon major research and technological advances in the medium to long term. The European Technology Platform „Plants for the Future" is coordinated by European Plant Science Organisations and EuropaBio and is advising the European Commission on biotechnology and plant genomics.

Table 4: European companies and organisations active in molecular farming.[a)]

Company/Organisation	Plant host(s)	Products/Indications
Agrenvec, Spain	Brassica (viral expression)	Contract manufacturing
BASF, Germany	Brassica, tobacco	Poly unsaturated fatty acids
Bayer Crop Science, BioScience, Germany	n.sp.	Antibodies etc.
Cobento Biotech, Denmark	Arabidopsis	Human intrinsic factor transcobalamin protein
CropDesign, Belgium[b)]	Maize, rice	Contract manufacturing
ERA Plantech, Spain	Protein bodies in most plant tissues and species	Product-neutral productivity improvements
Fraunhofer IME, Germany	Tobacco, corn, rice, wheat, tomato, plant suspension cells	Antibodies, vaccines (injectables and oral administration), enzymes for oncology and infectious disease
greenovation Biotech GmbH, Germany[g)]	Moss	Monoclonal antibodies and other complex proteins
Icon Genetics AG, Germany[d)]	Tobacco, Nicotiana benthamiana, spinach, red beets	Interferon, somatotropin, restriction enzyme, single-chain antibodies, monoclonal antibodies, antigens, glucocerebrosidase, thaumatin, albumin, DNAse, RNAse inhibitor, insulin
LemnaGene S.A., France[f)]	Lemna spp.	n.sp.
Maltagen Forschung GmbH, Germany	Barley, malt	Lactoferrin, lysozyme, human serum albumin, hepatitis vaccine, edible vaccines
Meristem Therapeutics, France	Maize, tobacco	Gastric lipase (MERISPASE®); albumin; human collagen; human lactoferrin; human IgA (x4); dust mite allergens; murine IgM (monomeric); human plasma proteins
Novoplant GmbH, Germany	Tubers, rape seed, flax seed, peas	Orally administered antibodies for animal health
ORF Genetics, Iceland[e)]	Barley, lettuce	Growth factors, proteases, antibodies, vaccines
Phyton Biotech, Germany	Plant cells	Amongst others: growth hormone receptor antagonist for treating acromegaly, cancer, diabetes
Pharma-Planta Project European Community	Maize, tobacco (various plants)	Antibodies, vaccines, others
PlantBio Products, Spain	Chloroplast transformation	Bioplastics
Plantechno SRL, Italy	Rice, wheat, tomato, maize, poplar, Agaricus, barley	Enzymes
Planton, Germany	Potato	Contract manufacturing
Plant Research International, The Netherlands	Platform technologies applicable in all plant hosts (tobacco, potato, tomato, rice, others)	Antibodies as a model: vaccines for oral application and targeted delivery
SunGene, Germany[c)]	Rapeseed, potato, tagetes, Arabidopsis, tobacco and tomato	Secondary metabolites e.g. carotenoids and vitamins for food, feed and health
Syngenta, Switzerland	Safflower etc.	Biopharmaceuticals for a range of indications, including antibodies, enzymes and other protein therapeutics
UniCrop Ltd, Finland	Camelina sprouts	Model proteins: monoclonal antibodies, immunoglobulin fusion protein; human serum albumin, enzymes

[a)] *Sources: Ma et al. (2005), Sauter and Hüsing (2006) modified and updated;*

[b)] *Acquired by BASF in 2006;*

[c)] *Joint venture of BASF Plant Science, the Institute of Plant Genetics and Crop Plant Research;*

[d)] *Recently acquired by Bayer;*

[e)] *Iceland is not a member of the EU but belongs to the European Economic Area;*

[f)] *Recently acquired by the US company Biolex Therapeutics;*

[g)] *Licence agreement with Bayer.*

Abbreviations: n.sp.: not specified.

5 Pharm crop risk issues differ

In principle most of the potential risks discussed for first generation GM crops[11] would apply to molecular farming as well. Nevertheless, three reasons are suggested here as to why risks associated with molecular farming could have different characteristics:

Firstly, unlike first generation GM crops, PMPs are designed to have a biological effect on man and/or higher animals, hence the hazard characteristics of the introduced protein might be of concern.

Secondly, an entirely different breeding rationale applies. Plants will be optimised e.g. for maximum yield, special morphology and growth habit suited to a specific harvesting method that can be used with the PMP application, absence of metabolites that may compromise product integrity or quality during bioprocessing (Davies 2005). Pharm crops are considered production facilities that have to be optimised for maximum yield of the target substance. Human and environmental exposure could therefore be increased compared to first generation GM crops. Depending on the expression system maximum yields of up to 25 and 31 % of total soluble protein (TSP) (Daniell *et al.* 2005, Fischer *et al.* 2004) and 80% TSP (Gleba *et al.* 2004), Marillonnet *et al.* 2004) have been achieved (the latter of which in greenhouse experiments). This would constitute a 700 to 5.000 fold increase in transgene products compared to first generation GM crops (Spök 2006).[12]

Thirdly, the likelihood of unintended secondary effects might be higher, and the hazard characteristics of GM plants might thus be of concern. Unintended secondary effects are already a big issue with single gene insertions of first generation GM crops, but the number and significance of genomic changes in the forthcoming generation of crops increase the likelihood of unintended effects and the associated uncertainties, all of which will need to be addressed in regulation. This is because these plants are likely to include several genetic modifications at the same time. Resistance genes might be introduced to avoid problems with pests, pathogens, and weeds which would otherwise require applying pesticides and herbicides. These substances might cause concerns as drug contaminants. Moreover, genetic modification for easy and unambiguous visual identification of seeds and plants are suggested which would enable a simple differentiation of plants, seeds or fruits not intended for consumption (Commandeur *et al.* 2003, Ellstrand 2003). In addition, molecular confinement technologies are being introduced involving several complex changes in the plant genome. Molecular confinement aims at avoiding gene dispersal via pollen or rendering plants infertile (Daniell 2002).

Whether this would translate into higher health and environmental risks would, however, depend on the particular case and also on the category. With many PMIs there might be no intention of a biological effect in humans or animals. Nevertheless, hazardous properties could also be associated with this category. Avidin, for instance, which is presently produced as a fine chemical, is toxic to many insects and might cause Vitamin H deficiency in higher animals and humans. Aprotinin, to take another plant derived fine chemical, is considered a reproductive hazard. In contrast, enzymes like lipases or trpysin might pose less health risks in case of food contamination, because both types of enzymes are ubiquitous in nature (Freese 2002). Moreover, trpysin is considered safe and used in food production in the USA and elsewhere. Health risks might not necessarily be restricted

[11] Mostly herbicide tolerant and insect resistant crops.

[12] The yield of 80% of TSP was achieved using a production system that is not intended for open field cultivation. It nevertheless shows what is technically feasible at present. For open field cultivation, yields of 10 to 35% might be more realistic – but might also be optimised as technology improves.

to toxic or allergenic effects, though. For instance, a human hormone could have detrimental effects if contaminating the food chain. A vaccine, e.g. a virus protein, might lead to desensitization. If so, those affected would perhaps not develop a desired immune response when vaccinated (Kirk *et al.* 2005). Consequently, the hazards might very much depend on the particular case.

Exposure, another key issue in risk assessment, will not only depend on the amount of protein produced but also on the area of land used for cultivation. Commercial production of large amounts of PMPs could take place on 10 to 1.000 hectares (see Table 2), which is in the range of larger US field trials with first generation GM crops. Beyond possible contamination accidents exposure is, therefore, more likely restricted to workers processing or handling the crops. Environmental exposure will also be different due to the higher concentration of proteins/unit area. Environmental exposure and spread could, however, be diminished by molecular, physical and organisational confinement measures while worker's exposure could be reduced by protective measures. Unintended secondary effects (see further below) might be of less concern in the case of small cultivation areas, especially if confinement measures are effective.

Regulatory and industry experts are thus framing the issue as a confinement problem. US and Canadian regulators have been working together with industry on a variety of physical and organisational confinement measures that can be applied to avoid outcrossing, spillage of seeds or biomass, and commingling with food or feed crops (see Table 5) and researchers are working on molecular confinement mechanisms that aim at avoiding gene dispersal by a variety of mechanisms (Daniell 2002). Most of the molecular confinement mechanisms being proposed (USDA 2003), however, are 'leaky', i.e. not working 100%, and still far from being used for commercial production (Ellstrand 2003). Organisational and physical confinement measures can fail due to human error. It has therefore been proposed that a combination of several different confinement measures have to be applied at the same time to establish a redundant system which would provide a sufficient level of safety.

What is considered by the biotech industry and regulatory experts as sufficient risk mitigation measures might, however, not be sufficient for the food industry or consumer and environmental groups, and perhaps also for the general public. Beyond and independent of any health or environmental harm, considerable economic damage might occur in case of contamination of the food and feed chain. Given the lessons of the StarLink and ProdiGene incidents, serious economic consequences might result from accidental commingling even in case there are no or very little health or environmental risks. Anxieties of civil society and the food and feed sector might also be sparked by discussions to use the remainders of biomass after the pharmaceutical component has been separated, e.g. for feed purposes instead of expensive incineration, also referred to as "dual-use" (Freese 2002).

Table 5: Physical and procedural confinement measures proposed.

- Distinct visual markers
- Time shift in planting compared to food/feed crops nearby
- Cultivation in remote areas
- Fencing, restrictions to enter
- Extended isolation distances (e.g. 1600/800 m for normal pollinating maize), fallow zones, temporal shifts in planting (e.g. 21 days for maize), other plants as pollen barriers, detasseling (maize), covering of inflorescence
- Dedicated equipment, machinery and processing facilities
- Preliminary on-farm processing
- Post-release monitoring
- Procedures for
  - seeding, transplanting, side-maintenance, harvesting, seed cleaning
  - storage, drying and processing of biomass
  - disposal of biomass e.g. autoclaving, incineration etc.
  - handling and cleaning of machinery, equipment and containers
  - monitoring during growing seasons and post-harvest land use
  - dealing with non-compliance with terms and conditions for confinement
- Records and reporting of all activities dealing with the cultivation and transport to processing facility, documentation and logs for seeds and biomass
- Training of staff and workers to adequately handle the plant material
- Emergency response/contingency plans
- Strict control of compliance to measures imposed – either by regulators or by other independent institutions (third-party audits)
- Test for GMO detection in raw agricultural commodity

Source: BIO (2005), Burtin (2006), CFIA (2003, 2004a, 2004b, 2004c, 2005), Spök et al. (2004)

6 EU regulators might need to role up their sleeves

Pharm crops will be operated similar to pharmaceutical production facilities and will be further improved accordingly. Risk characteristics are likely to differ from first generation GM crops and risk mitigation requirements will become a focal issue. These characteristics are likely to pose a number of challenges to policy makers and regulators in the EU (drawing on Spök and Klade 2005):

Obviously, there will be a need to review and update current risk assessment approaches and guidelines established for first generation GM crops. Possible challenges for risk assessors include the applicability of the concepts of substantial equivalence and familiarity which both play key roles in the risk assessment of presently marketed GM crops. Familiarity refers to experiences gathered with the host crop in conventional agriculture (Barret and Abergel 2000). This concept might however be less applicable if non-food/non-feed plants with which there is less experience are used, for instance safflower in Canada. Likewise, the concept of substantial equivalence might be considered less instructive. A GM crop that is considered substantially equivalent to a conventionally bred crop is deemed to be as safe as the conventional crop. If the conventional comparator has a history of safe use or consumption this establishes a relative safety that is considered acceptable. Substantial equivalence is normally being established by drawing on a comparative analysis encompassing a range of plant ingredients as well as morphological and agronomic parameters. Identified differences should then guide the risk assessment. If pharm crops, as explained above, had been subjected to multiple and perhaps more substantial changes of the genotype it might be either difficult or less significant to establish an equivalence status by just drawing on the presently used small range of analytes and characteristics. Moreover, if opting for non-food/non-feed crops one would most likely end up with a crop where there is less knowledge and experience in agricultural and environmental terms compared to presently used staple crops and where there is no long-established safety for consumption and use.

Furthermore, especially with PMPs another step might be added to risk assessment: to thoroughly assess and to advise on the appropriate level of confinement measures which could include all kind of molecular confinement measures but also the physical and organisational measures listed in Table 5.

Second, the perhaps most important goal of regulation might be the avoidance of any cross contamination of the food and feed chain as well as the question of "coexistence" between these kind of industrial crops and food and feed crops. In case of using food crops for open field production of PMPs and perhaps also PMIs there might be a need for mandatory and harmonised coexistence rules at the EU level supplementing or replacing the present EU guidelines. These rules might need to include threshold limits in case of accidental contamination and for liability reasons. The present EU harmonised threshold limits of 0,9% and 0,5% for GM crops in conventional food might not be considered acceptable from both a health and a public perception point of view. Conversely, it is difficult to envisage a zero tolerance policy, as it is presently pursued for molecular farming by the USDA (USDA 2006, Howard and Donnelly 2004). Even thorough on-site risk mitigation measures and extended safety distances of up to 1,6 km for maize producing PMPs (USDA 2006) are not considered to be a hundred percent effective by many commentators. Similar concerns are voiced by Canadian regulators (CFIA 2005). According to some commentators zero tolerance would not even be feasible if only non-food/non-feed crops would be used. Given the huge differences that can be assumed for the hazardous properties of the various kinds of

PMPs that can be envisaged, substance-specific threshold limits would be more likely. In analogy to the limit values for pesticide residues[13] limit values will need to be harmonised across the EU, either for specific substances or for particular categories of PMPs, as differences in limits between Member States would hamper food and feed trade. Furthermore, this would not only be an issue of contaminating conventional or organic crops – it would also pertain to GM food/feed crops. Such a scenario would render food control a more complex business.

A related issue would be the question of liability which is of course of paramount interest for the food and feed industry as well as for farmers (Smyth *et al.* 2002). As shown for the StarLink and ProdiGene incidents liability issues are not just academic speculation. Whether and under what particular conditions biotech companies, farmers or food producers could be held liable for any health, environmental and economic damage that might occur is an especially significant question. In comparison to first generation GM farming this would also be an issue for farmers and food producers using GM crops.

Given these constraints molecular farming companies and even regulators might opt for an additional authorisation under EU Regulation 1829/2003[14] for use as food and feed. Such a permit would relax the contamination threshold, ease potential liability cases and open the possibility to use remainders of production as feed. On the other hand, given the safety requirements embedded in this legislation and the difficulties of the EU level procedures for market authorisation of GM crops and food this is not likely to be an easy ride and might only be feasible for certain PMIs rather than for PMPs.

The need for keeping food/feed and pharm crops separate would, however, not be a concern of food and feed producers only. With PMPs it might well work the other way round as manufacturers can be expected to avoid contamination of their drugs, e.g. with food and feed crops, pests and pesticides to maintain the purity and safety standards important for a validated drug production process. In certain areas concerns might, however, differ between food and drug producers. For instance, outcrossing of normal food or feed maize into pharm maize, might be a particular concern for seed producers of pharm crops. Pharm maize seed production might therefore require safety distances and other measures to maintain the purity of the seeds. At commercial production stage the same contamination of pharm crops might be of less concern – especially if the PMP will be purified from the green plant material. Furthermore, for PMI producers aiming at bulk products there might be fewer incentives for confinement. Consequently, confinement triggered by these self-interests might provide additional but still limited reassurance to food and feed producers.

Therefore, it has to be questioned whether the presently established coexistence framework for GM and non-GM agriculture in the EU, based on non-mandatory EU recommendations and Member State legislation might be considered sufficient to deal with this kind of industrial crops. Even before the first PMP will be commercially cultivated in the EU: if this technology takes off in the USA, Canada or any other country exporting food or feed to the EU, EU regulators and food control might have to deal with questions of threshold limits earlier than expected.

Repeated reports of GM crop contamination of EU imports have kept regulators and consumers and environmental NGOs alert and are less likely to maintain or regain consumer trust in presently used segregation systems: e.g. in case of maize Bt10 (Macilwain 2005) and most recently contaminations

[13] Regulation (EC) 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC.

[14] Regulation (EC) 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed foresees a mandatory authorisation procedure prior to marketing any food or feed from GMOS in the EU.

by GM rice lines one of which originates not from commercial production but from US field trials (Pew 2006) while the other might come from illegal cultivation in China (Marris 2006). In these cases a zero contamination policy applies in the EU as these GM lines are not authorised for commercial production. The potential higher risks of commingling and contamination in developing or less industrialised countries might be a particularly neglected issue as producers are increasingly conducting their field trials in countries such as Chile, Cuba, India, South Africa (because this makes it possible to get more than one harvest per year and ironically because of the more difficult regulatory environment and the less favourable public perception in the EU).

Furthermore, there is no equivalent procedure in the EU to what is envisaged in the US as a commercialisation track for molecular farming. The EU Directive 2001/18/EC[15] foresees two different authorisation tracks: time- and area-limited field trials (Part B) and placing on the market of GM crops including import, transport, processing, handling, storage and cultivation (Part C). Part B procedures are national and authorisation can be granted by the respective Member State only, though derived products must not be used for commercial purposes. Part C foresees a centralised procedure involving all Member States in both risk assessment and decision making and authorisations would allow for commercialisation in all EU Member States. Both procedures might not be entirely appropriate for PMPs.

Many PMPs and perhaps also PMIs (e.g. fine chemicals for research and diagnostics) are intended to be produced on a small scale only and could be produced on areas that compare to large scale field trials of GM crops. Thus, it can easily be envisaged to cultivate, transport and process these plants within one Member State. Cultivation or processing of such plants might be conducted in-house or by contractors under supervision of the manufacturer. Such seeds and plants are unlikely to be traded on the market.

Given the US experience companies might in fact be keen to stay under strict regulatory oversight during the commercial production stage.[16] Thus, companies might in fact be happy with Part B type authorisations. However, according to EU law this would only work until the commercialisation step has been reached.

Part C authorisation procedures would allow for commercialisation and would be more proportionate for the increased rigour of their risk assessment and the mandatory monitoring. In the complex EU policy environment, though, there might be continued unpredictability around eventual authorisation decisions.

National Part B procedures would thus be more straightforward but would not be considered sufficient in terms of risk assessment and monitoring and perhaps not as acceptable, if there is any chance that possible contamination might effect commercial food and feed products intended for other EU countries.

Therefore, a separate authorisation track might be envisaged for PMPs and certain types of PMIs. Given the sensitivity of the issue it is however difficult to envisage such a procedure becoming established at any national level without the involvement of the EU or other National Authorities. One would perhaps not need such a separate track in case of PMIs and if no health or environmental concern could be identified (and an authorisation as food and feed becomes feasible) as well as in

[15] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC establishes a mandatory authorisation procedure for import, handling, processing and cultivation of GM crops.

[16] www.bio.org/healthcare/pmp/factsheet4.asp.

case of production of PMPs under containment[17]. Table 6 highlights how the different characteristics of PMPs would translate into different requirements for authorisation.

Table 6: Anticipated market authorisation requirements for GM plants used in the production of pharmaceuticals

	GM food and feed crops Field trial stage – Part B[f)]	Molecular farming[e)]	GM food and feed crops Commercial stage – Part C[g)]
Scale/area	Normally in the range of 0,5 to 20 hectares In rare cases: beyond 100 hectares	PMPs: a few to more than 1000 hectares	Unlimited
Authorisation	One Member State only	Not absolutely required in more than one Member State	Entire EU
Derived products can be used for commercial purposes	NR	R	R
Trading of seeds and propagating material	NR	NR	R
Import	R[b)]	R/NR[c)]	R
Transboundary transport	R[b)]	R/NR[c)]	R
Processing, Handling	R[b)]	R/NR[c)]	R
Cultivation in more than one Member State	R[b)]	R/NR[c)]	R
Supervision of on-site requirements	R[d)]	Confinement and containment measures might need strict supervision	n.a.
Monitoring	Not mandatory	More extended monitoring requirements might be needed	Mandatory[a)]
Risk assessment	National Competent Authority; requirements might differ between Member States	Could be both	EFSA and National Competent Authorities; requirements are harmonised at EU level
Regulatory oversight	National Competent Authority	To be established	European Commission
Decision making procedure	Member State level	To be established	EU level

[a)] *General surveillance applies, requirements for case-specific monitoring requirements have to be decided for each application;*

[b)] *Only for non-commercial purposes;*

[c)] *Depending on the particular case. Not necessarily required as transport, processing, handling and cultivation could be conducted in one Member State only;*

[d)] *Supervision might differ between Member States;*

[e)] *Anticipated requirements for molecular farming;*

[f)] *Requirements and responsibilities in case of field trials with GM crops (Directive 2001/18/EC, Part B);*

[g)] *Requirements and responsibilities in case of placing on the market of GM crops (Directive 2001/18/EC, Part C).*

Abbreviations: R/ NR: required/not required; n.a. not applicable.

Source: Compiled on the basis of Spök and Klade (2005).

[17] Containment or contained production in this article refers to physically closed buildings and appropriate measures to avoid any release of the GMO or viable parts of it to the environment. Contained use of GMOs is regulated in the European Union under Council Directive 90/219/EEC of 23 April 1990 on the contained use of genetically modified micro-organisms.

A separate track for molecular farming that would for instance restrict cultivation to one country or even to a particular region in one country might also help to tackle an inherent European problem – the diversity of European agricultural environments, of agricultural structure and practice. Both aspects are constantly creating problems with the centralised EU procedure of environmental risk assessment and monitoring requirements and contributed to extended timelines in market authorisations. If cultivation would be restricted to a particular region, environmental risks assessment and measures to be taken could be tailored to the specifics of this regional environment.

Finally, most of what is said above pertains to open field cultivation; however, there are alternative production approaches using contained facilities, using e.g. plant cell culture, duckweed, moss or root exudation (see Box 1). Contained production would drastically reduce the risks of food and feed contamination while lacking some of the advantages of open field production. Furthermore, whereas confinement measures for open field production of PMPs are likely to be discussed and agreed at the EU level, commercial production under contained conditions is still under regulatory oversight of the particular Member State according to EU Directive 90/219/EEC.[18] Greenhouse production would also be an alternative option, for they are normally considered as contained facilities. Greenhouse space for contract cultivation is presently available up to some 30 hectares[19] which would be sufficient for producing significant quantities of several high-value proteins.

Box 1: Contained production approaches in plant molecular farming

Plant cell culture

Plant cell lines, mainly from tobacco cultivars are grown in a very similar way as mammalian cell lines. In the last 15 years production of more than 20 different recombinant proteins have been demonstrated including antibodies, hormones, growth factors and cytokines. Purification of the target protein might be simpler compared to agricultural-scale production (Doran 2000, Hellwig et al. 2004). The first commercially approved PMP, a poultry vaccine is being produced from plant cell culture (see fn 6).

Root exudation

The formation of hairy roots can be induced by genetic modification and enable root tissue to be cultured in liquid medium. A variety of plant metabolites have been produced from hairy roots and excreted into the liquid medium which makes purification easier. Proteins produced so far include antibodies, phosphatase, ricin B fusion protein (Fitzgerald 2003, Gleba 1999, Guillon et al. 2006).

Moss

A particular moss variety which is very susceptible to transformation with recombinant DNA is cultured in bioreactors. Proteins can not only be secreted into the medium but also – via additional genetic modification – being modified to change from plant to human glycosylation pattern (Decker *et al.* 2003, Schaaf et al. 2005).

Lemna

Lemna or duckweed are small plants growing on the surface of ponds, lakes and rivers. The plant has been genetically modified to produce twelve monoclonal antibodies including small peptides and large multimeric enzymes (Fitzgerald 2003, Gasdaska et al. 2003).

[18] See fn 17.

[19] E.g. http://www.bevoagro.com/index.html.

Some PMPs, however, (e.g. allergens for diagnostics or medical therapy, vaccines, or hormones) might call for higher levels of containment than others. Member States might have different opinions about what would constitute an appropriate level of containment for a particular substance. There might even be different ideas about the borderline between contained production and deliberate release. For instance, a commercial production using net-houses, as is envisaged with potatoes in Denmark (Berglund 2006) might be considered by one Member State a rather unproblematic authorisation under the contained use Directive 90/219/EEC, whereas others might classify the same practice as deliberate release that would require an application under Directive 2001/18/EC obtained after going through a much more cumbersome EU procedure (Ball, Haas, personal communication). Such differences will need to be reviewed and perhaps harmonised by EU regulators.

7 Towards an open debate – facing complexity at various levels

Previous sections have illustrated the different characteristics of molecular farming and its associated health and environmental risks compared to first generation GM crops. Increased activities in European R & D and the proximity to market stage of first products of plant molecular farming are now drawing the attention of EU regulators to this issue. As analysed above, several challenges are posed to regulators in order to allow for commercialisation of molecular farming in the EU including, e.g. avoidance of contamination of the food and feed chain, set up of coexistence measures including threshold limits, establishment of an authorisation track that is appropriate for commercial open field production, and to better define what would constitute a contained production. Risk assessors are also called on to reconsider their assessment concepts and approaches and to include confinement measures as a particular focus of their risk assessment tasks.

While the study on which this paper is based was being conducted, EU risk assessors and regulators became active. Working groups have been established and workshops organised in the context of the European Food Safety Authority (Schoonejans 2006), the European biotech industry association EuropaBio (Barber, personal communication), the European Plant Science Organisation[20], and the Institute for Prospective Technology Studies of the EU Joint Research Centres. So far, most of these activities were designed as expert or technical meetings. Neither environmental/consumer NGOs nor food industry representatives participated in these activities. Given the sensitivity of the GMO issue in the EU a public debate will inevitably follow. Some of the issues associated with molecular farming definitely would require such a broad debate, for instance whether at all and under what particular conditions commercialisation in food/feed crops and open field cultivation should be possible. In that sense the recent hearing at the German Parliament (Deutscher Bundestag 2006) where different stakeholder groups and members of parliament could respond to and discuss the findings of a technology assessment project on molecular farming (Sauter and Hüsing 2006) can be considered a first move towards broadening the debate.

[20] www.epsoweb.org/Catalog/epso%20workshops/EPSO%20handout%20300106.pdf.

Moreover, a broad European debate on risk, benefits and regulatory issues might be complicated by conflicting values. Molecular farming is linked or is likely to be linked to the policy arenas of renewables, greening of industry or – more generally – to sustainable development on one hand and the debate on agricultural problems and reform in the EU on the other hand.

The former issue often is about substituting traditional chemical production processes by processes that are more environmentally sound, e.g. biotechnological processes. In case of PMPs, molecular farming is basically substituting one kind of biotechnological process by another. In case of non-proteinous PMIs, which would be produced on a larger scale as plant-metabolites, a different picture might emerge. With the help of genetic engineering these substances might be produced more efficiently and the properties might be tailored to the application intended. Thus, they might in fact serve to render renewables more competitive than before. However, even in this case, the potential environmental advantages might conflict with the specific environmental and health risks associated with open field production. In that sense molecular farming would find itself located at the crossroads of two debates: the risk debate on agricultural biotechnology and the sustainability debate on renewables and greening of industry. Some ten years ago a similar but less controversial 'crossroad' issue, the production of enzymes from genetically modified microorganisms triggered a major conflict among the Green Party in Germany (reviewed in Spök et al. 1992) and led to a difficult debate about how to value factual environmental benefits vs. hypothetical risks.

The latter issue is not only of hypothetical nature: in the USA some rural states where cropland is abundant and jobs are rare anticipate that pharm crops will generate economic benefits. In the EU, which is struggling with heavily subsidised agricultural production, industrial crops are considered as an interesting option to diversify European agriculture. In that context pharm crops have been explicitly welcomed by some commentators (e.g. APA 2005). Individual farmers who – in some Member States – are receiving compensations for not cultivating parts of their land are nevertheless coming under pressure and might be tempted to explore other agricultural products, especially if these products would promise a higher added value. As this analysis suggests, a higher added value by cultivating pharm crops might, however, be restricted to a few contract farmers and relatively small areas. GM crops for PMIs that would be grown on a larger scale might in fact provide an interesting alternative though, if the problem of coexistence can be solved.

In the EU, industrial crops are likely to become a particular focus in the context of the 7th EU framework programme. The recent revival of the biofuel debate is also likely to impact the whole issue of industrial crops. Given that food crops such as maize, wheat and rice are envisaged for the production of biofuel some of the coexistence and contamination issues might be very similar to those discussed for PMIs.

Beyond these complexities there is another issue that deserves particular attention. Molecular farming also sits at another crossroads, between "green" (agricultural) biotechnology and "red" biotechnology (use of genetic engineering for medical and pharmaceutical purposes). From this setting an interesting situation emerges as publics have generally been more supportive of red biotechnology than green biotechnology (Gaskell et al. 2001, Nielsen et al. 2002). Thus new lines of reasoning and new value conflicts might be expected. There is preliminary evidence from public perception studies that consumers would be more supportive for PMP or PMI production compared to first generation GM crops (Elbehri 2005, Einsiedel & Medlock 2005, Kirk & McIntosh 2005). No evidence is available from European countries, though. This crossroad situation is also reflected by a more complex pattern of policy actors. The biotech (molecular farming) industry might receive support from certain growers' and patients' associations, whereas the environmental and consumer organisations might be backed up by the food and feed industry. Unprecedented support might meet unprecedented opposition. Given the turn towards industrial crops in the EU with the economic potential on one hand and the sensitivity of the GMO issue in the EU on the other, policymakers might therefore need to walk another tight rope in order to harness the benefits of this new technology.

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