THE COMMERCIAL ASPECTS OF THE DEVELOPMENT OF TRANSGENIC CROPS WITH HERBICIDE TOLERANCE

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ABSTRACT

In the next 20 years the world population is expected to rise by 50% creating a demand for double the quantity of food. All existing and new techniques for food will be required to achieve this including recombinant DNA technology. Transgenic herbicide tolerant crops are one of the first major results of this technology. They are now being grown commercially in most continents of the world and are delivering benefits in weed control, cost of production and reduced environmental impact. Nearly 7 million hectares of herbicide tolerant crops were grown in 1997 with significant increases expected in 1998. To date Europe has been very slow to accept this technology. The European regulatory process appears to be paralysed and many herbicide tolerant crops are held up within the process whilst the rest of the world encompasses this new technology.

INTRODUCTION

Much has been said and written about the development of genetically modified crops and crops with novel herbicide tolerances in particular. With such an emotive subject few of these contributions have come from a completely unbiased viewpoints. This paper is no exception.

These new products and their commercialisation must develop alongside rigorous regulatory processes and codes of practice. However, these should not be fixed. They need to evolve in line with increasing knowledge in this area of science. But such processes should go hand in hand with introduction and must not become the means of blocking crop improvements by groups who have vested interests in other systems.

BACKGROUND

In the next 30 years the greatest demand on global agriculture will be to produce the amount of food that the increasing population of the world will require. The available area of arable land per capita of population has decreased to less than 60% of that in 1961(Table 1). This is despite an increase in the area of land down to agriculture of over 400 million ha (over x13 m US maize area). By 2025 most estimates expect the world's population to increase by at least 50% . The understandable desire of developing countries to improve the diet of their populations will need food production to double.

Objectors to the use of recombinant DNA techniques in crop improvement claim that the world doesn't need them. Some of the most vociferous groups go further to claim that the requirement for food can be met by conventional techniques, and indeed by increasingly extensive techniques, thus allowing a move away from intensive agricultural systems.

Dennis Avery in last years Bawden Lecture put the case for technology far more succinctly than I am able to do *" ...viewed in this light, agricultural research and technology are the most vital investment we can make - for both people and the environment."* (Avery, 1997).

Table 1. World Population and land availability

	1961	1971	1981	1991	1996/7
Population (million)	3,085	3,777	4,523	5,365	5,848
Total Land Area (m ha)	13,043	13,043	13,043	13,043	13,048
As Agricultural Land	34%	35%	36%	37%	38%
As Arable Land	10%	10%	10%	11%	11%
Arable land/person (ha)	0.41	0.34	0.29	0.26	0.24

Source: FAO.

To double food production whilst producing even the same amount of food per unit of land will require at least the doubling of the area under cultivation. This will lead to corresponding devastating effects on global biodiversity. Opponents to improved technology in farming claim that extensive and organic solutions, and the consumption of less animal protein can produce the increases required. Supporters of such solutions to food demands are long on rhetoric but seem shy to produce supportive data. One reason might be that major governments like China do not seem to agree. China is importing increasing amounts of animal protein see Table 2.

Table 2 Import of Meat by China 1986 - 1996

Metric tonnes	1986	1990	1995	1996
Pig meat	10	229	1068	2,539
Chicken meat	5,000	65,000	253,000	308,000

Source: FAO.

A method of food production needs to be adopted which will be less damaging to biodiversity and the environment in general. The least impact on biodiversity must come from producing more food, without ploughing more land, and to achieve it using a more sustainable system. The alternatives are unthinkable or politically unachievable:

a) to dramatically increase the amount of (increasingly poor) land under the plough with a corresponding destruction of primary habitat;
b) to immediately reduce global population growth to zero;
c) to impose a global diet minimising the consumption of animal protein.

Pragmatically, we have no alternative but to use every option available to secure an adequate food supply for the expected increase in the world population and hope that the politicians generate the miracle for us not to need it.

To ensure a sustainable doubling of food production, on a similar area of land within the next 30 years, will require an integrated global strategy. This must include

- Focused breeding programmes to improve yield potential, pest/disease resistance and quality and to adapt crops for different environments e.g. reduced water availability
- Land use programmes to minimise loss of arable land through building and erosion
- Agronomy programmes to improve efficient use of nutrients and particularly water
- The political will to reduce global dependence on animal protein
- Contingencies for environmental and political disasters (to include sensible food stocks)

In practice, this means that any new technology that offers potential should be grasped and developed. Recombinant DNA techniques offer one of the major planks on which the achievement of these huge targets can be based.

THE DEVELOPMENT OF HERBICIDE TOLERANCE

Research is ongoing on a range of Herbicide Tolerance projects but there are principally two systems being commercialised which have been developed with the help of recombinant DNA:

Glufosinate-ammonium tolerance - Liberty Link - AgrEvo
Glyphosate tolerance - Roundup Ready - Monsanto

Work to develop tolerance to other herbicides by direct gene transfer has also been ongoing but to date with less commercial success. Bromoxynil tolerance in cotton and tobacco has been developed to the level of commercialisation by Calgene and Rhone Poulenc, respectively. The soil bacterium *Klebsiella ozaenae* yielded a gene which can detoxify bromoxynil by hydrolysing it to dibromohydroxybenzoic acid. The coding gene for this enzymatic process is known as *bxn.* For completeness some research has also been carried out with both asulam and atrazine. Although other companies have work ongoing in this area none is yet at a stage where commercialisation is imminent. The commercial appeal of the two major systems is based on their effectiveness as herbicides and excellent environmental profiles.

Glufosinate-ammonium

Glufosinate-ammonium is the ammonium salt of the amino acid Phosphinothricin. This in turn is derived from the natural compound L-phosphinothricyl-L-alanyl-alanine. This tripeptide was isolated from *Streptomyces viridochromogenes* and also independently from *Streptomyces hygroscopicus* where it was given the common name Bialaphos. Glufosinate-ammonium was then developed as a non-selective herbicide by Hoechst Ag. Ongoing work identified genes within both *Streptomyces* species which produce enzymes which rapidly de-toxify the herbicide thus protecting the organisms themselves. In the case of *Streptomyces hygroscopicus,* De Block *et al.* (1987) identified the bialphos resistance gene *(bar gene)* and in *Streptomyces viridochromogenes* Straunch *et al.* (1988) independently isolated the phosphinothricin acetyl transferase gene *(pat gene).* The *bar* and *pat* genes exhibit close homology and code for the enzyme which converts glufosinate-ammonium into the non herbicidally active N-acetyl-glufosinate.

Glyphosate

Glyphosate (n-phosphonomethyl glycine) is a synthetic phosphonated amino acid, used in herbicidal formulations as various salts, but most commonly as the isopropylamine salt. Glyphosate is a specific inhibitor of an enzyme, EPSPS (5-enolpyruvylshikimate-3-phosphate synthase; E.C. 2.5.1.19), an enzyme of the shikimate pathway of aromatic amino acid biosynthesis, which is present in plants, bacteria and fungi, but not in animals. Three methods of conferring tolerance have been researched since the early 1980's (Padgette *et al*, 1996); 1) Over-production of EPSPS, 2) Introduction of an EPSPS with decreased affinity for glyphosate, and 3) introduction of a glyphosate degradation gene.

The first widely adopted commercial crop, soyabean, involved the second of these approaches, being developed from a soyabean line, coded 40-3-2, expressing the CP4 type EPSPS isolated from *Agrobacterium* sp. Strain CP4. Effective expression of this gene was further enhanced by fusion to a chloroplast transit peptide (CTP) sequence which targets the expression of the enzyme to the chloroplast. In some crops, an additional method has been included, namely a gene coding for an enzyme, glyphosate oxidoreductase (GOX), from the bacterium *Achromobacter* sp., which catalyses the degradation of glyphosate.

MARKET SIZE

The area of genetically modified crops grown increased over 4 fold between 1996 and 1997. The rapid acceptance of herbicide tolerance in North America (Fig. 1) means that 63% of the global growth was with such crops (mainly soyabeans and canola). Although in 1997 nearly 75% of all genetically modified crops were grown in North America, China 14%, Argentina 11%, Australia, and Mexico all showed significant increases in the area of commercial crops grown. Estimates for 1998 cropping are for further major increases to occur globally despite some devastating climatic setbacks in North America.

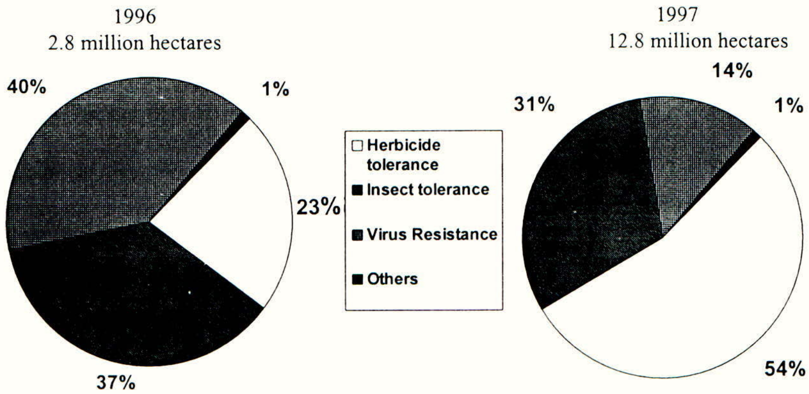
WHAT CONTRIBUTION CAN HERBICIDE TOLERANT CROPS MAKE?

For those opposing the genetic modification of crops, herbicide tolerant crops have become the focal point for their objection. From their viewpoint it would seem that very few crops are treated with herbicides and the need for weed control is simply global propaganda disseminated by multinational companies. Fifty years of research, development and practical usage throughout the world appears to have little impact on these irrationally held views.

Farmers do not spend money unless it is necessary and the registration and sale of herbicides is not be permitted if such products are not safe. The future targets for new herbicide development are, therefore, to produce even better and safer products which achieve the management of yield robbing weeds whilst minimising any adverse environmental impact. The challenge has always been to link effective weed control and best environmental profile with crop tolerance.

All crops are by definition herbicide tolerant to those products which can be used selectively on them. Crops genetically modified to be tolerant to a previously non-selective herbicide have allowed the search for this ideal package to be widened. The change to a genetically modified crop is that the specific gene which confers that tolerance has been introduced using recombinant DNA technology rather than selective breeding, mutagenesis or any other selection technique. The method by which a tolerance is achieved does not increase the risk of environmental problems arising from the growing of the crop. A conventional crop of oilseed rape is no more likely to cross with a closely related wild species than one on which has been conferred a novel herbicide tolerance.

Figure 1: Change in commercial hectares of transgenic crops 1996 -1997



Source: James 1997

Commercial benefits from Herbicide Tolerant crops

The major benefits which are claimed for transgenic herbicide tolerant crops are in concept the same as those for all herbicide use. However, the glyphosate and glufosinate-ammonium systems are closer to the criteria of an ideal herbicide package. Namely:

- short impact on the environment,
- targeted activity on weeds,
- novel mode of action,
- high crop selectivity.

The combination of these improved criteria should lead to the using of less chemical with better environmental profiles and the production of higher yields. If achieved, this combination which should be of interest to all who profess a desire to more sustainable production.

Data from commercial usage in North America supports the theory. In 1996 herbicide tolerant soya beans required 10 - 40% less herbicide (James, 1997) whilst improving overall weed control. At the same time yields are reported to have increased by 6% (Anon, 1998), soil moisture conservation improved, all with no increase in herbicide residue carry-over.

Herbicide tolerant canola in Canada also reduced herbicide requirements by up to 50% (Rogers & Merritt, 1997), whilst increasing yields by an average of 9% and improving grade 1 seed from 63% to 85% (James, 1997). It is estimated that in 1996 the overall benefits from herbicide tolerant canola in Canada amounted to $50/ha over conventional methods as a result of reduced costs and improved yield and quality. Add to this the improved environmental benefits it becomes clear why such an approach is being taken up in North America as rapidly as seed becomes available.

These benefits are seen with less certainty in Europe and more questions are being asked about the impact on wild species rather than the total environmental and commercial benefits. European agriculture is generally less dependent on soil active residual herbicides than North America. The rapid trend to low dose and more active molecules, which suit the systems of more intensive in-field advice, mean that the scale of benefits might not be as large. Nevertheless, such benefits will still exist. Developments in maize will mean the need for atrazine can be eliminated. In winter oilseed rape, a single timely autumn spray can effectively deal with weeds whilst permitting a non-yield robbing germination of weeds in spring to provide food for beneficials and desirable organisms. It is probably in sugar beet where this new technology is first set to deliver similar levels of improvement as has been seen in North America. Improvements in weed control and crop safety will result whilst at the same time reduce chemical usage by up to 30%, soil erosion by 11% (Van den Daele *et al.*, 1997) and moisture loss.

PRODUCT REGISTRATION IN EUROPE

The development of a new technology brings with it the need to establish appropriate regulatory processes. Through the EU90/219 and EU90/220 regulations, implemented in the UK jointly by the Department of the Environment, Transport and the Regions (DETR) and the Ministry of Agriculture Fisheries and Food (MAFF), advised by the Advisory Committee on Novel Foods and Processes (ACNFP) and the Advisory Committee on Release to the Environment (ACRE), the UK has a raft of regulations which manage the risks associated with genetic modification at all stages of research, development and commercialisation. It is only when the politicians (parliamentary, professional or amateur) became involved with the help of pressure groups that a scientific assessment of risk has started to become confused with ethics.

Thus, the leading biotechnology companies find themselves in the untenable position of still being unable to bring products to the market despite meeting all of the rigorous demands of regulatory procedure. At the moment there appears to be no method of appeal or legal enforcement which can change the anarchy which currently makes up the EU regulatory process. This rigid system should lead to a registration in 150 - 200 days. However, there is currently one submission which still has not fully cleared the system after 1,000 days. The current state of registrations in Europe is summarised in Table 4.

Regulatory Aspects in Europe

Much effort is being laid on the precautionary principle. Whilst sensible precautions should always be taken before the introduction of any new technology, the emphasis on any draconian precautionary principle would prevent the introduction of almost all new technologies whether high or low tech. We do not know with absolute certainty that the introduction of transgenic crops will be completely safe any more than we know that the wide-scale introduction of organic farming practices will not damage the environment (e.g. increase erosion, soil moisture loss and damage to soil flora/fauna as a result of an increase in ploughing and soil cultivation). On balance the EU regulatory system, plus member governments pro-active funding of additional research during the regulatory process, is an effective method of minimising risk to an appropriate level. If the balance is correct it can maintain the incentive for global companies to commit investment into such new technologies.

Table 4 : Summary of the Registration Status of Herbicide Tolerant Crops in Europe

Glufosinate Tolerance

Crop	Transformation	Company	Registration status	Variety status
Maize	T25 (pat)	AgrEvo	Marketing consent agreed – growing & import	up to 10 varieties in EU trials. First sales expected in 1999
Maize	T14 (pat)	AgrEvo	Awaiting 90/220 pt C marketing consent growing and import	
Maize	pat + cry1Ab,	Northrup King	Marketing consent agreed	
Maize	bar + cry1Ab,	Novartis	Marketing consent agreed	
OSR	Topaz (pat)	AgrEvo	Marketing consent agreed - import only	Innovator & Independence AgrEvo (Canada)
OSR	pHoe 6 pat)	AgrEvo	Awaiting 90/220 pt C marketing consent - growing & import	National list trials (UK & D)
Sugar -Beet	T 120-7 pOCAC/ 18 AC (pat)	KWS	Awaiting 90/220 pt C marketing consent - growing & import	Variety in UK NL trials

Glufosinate Tolerance + hybrid Production

Crop	Transformation	Company	Registration status	Variety status
OSR	ms1 rf1 (bar)	PGS /AgEvo	Marketing consent agreed for growing and import but not yet issued	Spring OSR: Archimedes (UK) NL2 PGS 3850 + up to 3 others (Canada)
OSR	ms8 rf3 (bar)	PGS /AgrEvo	Awaiting 90/220 pt C clearance	Winter OSR: 2 varieties in UL NL2 + a range of varieties in other EU countries

Glyphosate Tolerance

Crop	Transformation	Company	Registration status	Variety status
Soya	EPSPS	Monsanto	Marketing consent agreed - import only	c 100 already commercially available in N & S America
OSR	EPSPS + gox	Monsanto	ACNFP clearance Jan 1996 - marketing consent not yet sought	Various canola varieties (Canada) Winter OSR varieties in UK NL1 and NL2
Maize	EPSPS + cry1Ab + gox	Pioneer Gentique	Marketing consent agreed	
Sugar-Beet	EPSPS	Monsanto and various companies	Awaiting 90/220 pt C clearance	UK NL2
Fodder Beet	EPSPS gene	Monsanto	Awaiting 90/220 pt C clearance	UK NL2

The most vocal concerns from the sceptics relate to the environmental impact following the release of herbicide tolerant oilseed rape. In addition to the intensive research carried out by companies to meet the regulatory processes of the world, much additional work is ongoing. This is frequently jointly funded by both public and private purse. Current projects are assessing the risk of production of multiple herbicide tolerant volunteers - INRA, BRIGHT (Botanical and Rotational Implications of Genetically Modified Herbicide Tolerant Crops); production of interspecific hybrids - INRA; the impact of agronomy on the growing of transgenic crops - FACTT (Familiarisation and Acceptance of Crops with Transgenic Technology), the impact of herbicides on hedgerow flora - NIAB. If the questions raised by those concerned about the impact of herbicide tolerant crops are to be answered then this work and that being carried out by those developing the technology needs to be completed. With about 30 trials having been damaged or destroyed this year in the UK alone this is becoming increasingly difficult and expensive.

It is crucial that the food production industry improves it willingness to work together with food producers and government to form a better relationship with consumers. We should therefore welcome the formation of SCIMAC (Supply Chain Initiative for Modified Agricultural Crops) which brings together the key industry organisations. The founding objectives of this group are to manage the introduction of genetically modified crops in an open and responsible way thus underpinning consumer confidence.

Unfortunately, no amount of work, however good, will prove absolute risk. At some stage a decision needs to be taken to proceed or to stop. In the rest of the world this has already happened and the technology is developing rapidly. It is only in Europe where the political imperative has taken control of what should be a rational risk assessment. There is a disparity between the view of Europe and the rest of the world which can be summed up as follows:

'Farmers see GM crops as a means of competing on the world market when subsidies disappear. No one could believe EU farmers were not going to use GM crops *"How will you compete with those that do?"* they ask' (Bullock, 1998).

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