

## Marketing AgrEvo's Genetically Modified Crop Plants Including Herbicide-Tolerant Corn and Canola

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### Abstract

AgrEvo is developing several crops which have been genetically modified by insertion of the *pat* or *bar* gene to be tolerant to the herbicide glufosinate-ammonium. When the herbicide is used with these herbicide-tolerant crops, it is called Liberty™ Herbicide, the tolerant crop is called Liberty Link™ and together they are referred to as the Liberty Link™ System. In Canada, Liberty Link™ canola was launched commercially in 1995, with all seeds from the harvest retained in Canada for domestic crush. In 1996, the goal is to have achieved regulatory clearances for Liberty Link™ canola in key countries so that the harvested seeds can enter commerce. In the United States, Liberty Link™ corn will be launched commercially in 1997, followed by soybean in 1998. AgrEvo is in the process of obtaining regulatory approvals for these crops in key export countries.

### The Liberty Link™ system

The Liberty Link™ crops, canola, corn, soybean, sugar beet, rapeseed, and rice, are being developed through partnership between AgrEvo and seed companies, universities or breeding specialists at Agriculture and Agri-Food Canada (AAFC). Liberty Link™ crops carry one or two genes that were added using a combination of recombinant DNA techniques and plant breeding. The herbicide tolerance genes (*phosphinothricin acetyltransferase* or *pat*; and *bialaphos-resistance* or *bar*) confer tolerance to the non-selective herbicide, glufosinate-ammonium (D/L-phosphinothricin) sold under the trade names Liberty™, Basta™, and Finale™. Some crops also contain a marker gene or gene which confers an additional commercially valuable trait. Genes were stably incorporated into the plant's genome using direct DNA uptake by protoplasts, particle acceleration or *Agrobacterium*-mediated transformation. The original transformants were then crossed to seed company, public or AAFC breeding lines to develop commercial varieties.

In the natural environment, *Streptomyces viridochromogenes* and *S. hygroscopicus*, common soil bacteria, produce phosphinothricin as a competitive strategy against soil microorganisms. In order to ensure their own safety, these bacteria also are equipped with the enzyme, phosphinothricin acetyltransferase (PAT), which acetylates and thereby inactivates this non-selective agent.

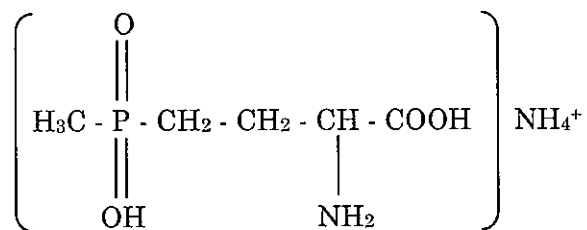
A chemically synthesized phosphinothricin analogue, known as glufosinate-ammonium (Fig. 1), is the active ingredient in the non-selective herbicide Liberty™.

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A synthetic version of the *pat* coding sequence was used to maximize the expression in plants which receive the gene. The native *bar* coding sequences was used in plants which received this gene.

Fig. 1 Glufosinate-ammonium (D/L phosphinothricin)



Together, the combination of Liberty™ Herbicide and Liberty Link™ crops is known as the Liberty Link™ system. Both the herbicide and the herbicide inactivation system are naturally occurring and have a long history of environmental exposure without negative effects. This adds to our confidence in the safety of the system.

It should be understood that the use of Liberty™ Herbicide in the Liberty Link™ System is optional. If weeds fail to develop, the farmer does not have to use the herbicide and he is left with a normal highly performing crop variety. If weeds develop, Liberty™ can be used as a post-emergence option. This allows the farmer to avoid tillage-based alternatives which can promote soil erosion. The grower is also free to use other available chemical control methods. It is clear from Liberty's origins that since the environment is naturally equipped to facilitate the herbicide's rapid breakdown, environmental safety is ensured. As a non-selective herbicide, the weed control provided by Liberty™ Herbicide is excellent. Seed quality at harvest is also excellent. In total, this Liberty Link™ System is a great step forward for producers allowing for broad spectrum control of problem weeds in crop production.

### Commercialization of Liberty Link™ crops

In order for Liberty Link™ crops to be cleared for commercial use, a process involving many steps has to be completed. The Environmental, Food, and Feed Safety must be assessed by government authorities in key production and export countries. In countries where the crop will be grown, the agronomic performance may be assessed for the purpose of Variety Registration. Finally, other government authorities review the Liberty™ Herbicide to determine that the herbicide residue in Liberty Link™ crops does not pose a hazard to the environment and/or consumers.

With regard to Liberty Link™ canola, whose seed for production is marketed under the name Innovator in Canada, all clearances were obtained in Canada in 1995. In addition, in 1995 the food and feed safety of Innovator products was positively assessed in the United States (U.S.), and clearance was granted for Canadian-grown Innovator to be imported into the U.S. for crushing and processing. The same data package has

been presented to additional international regulatory authorities who have also confirmed the safety of the Liberty Link™ System. In the United Kingdom (UK), food and feed approval was granted in 1996. A favorable review of the Innovator environmental safety package was given in the UK, and it is now under review within the European Union (EU). Japan has also concluded that Innovator canola can be imported into Japan for crushing without adverse environmental effects. Both food and feed reviews are underway in Japan with a response expected later this year.

AgrEvo's Liberty Link™ corn was approved in the U.S. in 1995. Registration of Liberty™ Herbicide for use on corn in the US is expected before the end of 1996. In 1996, Canada concluded that unconfined release of Liberty Link™ corn was safe in Canada. A favorable review of a Liberty Link™ corn environmental safety package was given in France, and it is now under review within the EU. Japan is currently reviewing the environmental safety. Food and feed reviews are pending in Canada, UK and Japan.

Some of AgrEvo's Liberty Link™ soybean transformants are under environmental review in the US. Further data are being developed for other soybean transformants and AgrEvo's other Liberty Link™ crops.

While regulatory clearance to market Innovator canola in Canada and in the U.S. was obtained in 1995, our key international trading partners in Japan and the EU had not yet reviewed the data packages, and were not in a position to endorse our safety documentation. To respect rather than jeopardize those international relationships, AgrEvo Canada voluntarily agreed to a limited introduction of less than 40,000 acres in 1995. In addition, a highly controlled closed-loop contract-to-crush system was implemented. Seed moved from our Prairie Pool partners directly to the farmer, back to the Pools at harvest, and to specific crushers who could guarantee that the oil and meal would stay in North America where our regulatory clearances were already established. This was a difficult and costly process, but one which enabled the technology to be introduced to the Canadian farmer while at the same time respecting a complex international regulatory environment. Overall, the whole Canadian canola industry believes this was a responsible approach, balancing the needs of the Canadian farmer and the international trading partners while moving the regulatory environment forward.

For AgrEvo, identity preservation was a useful tool for that time and place. However, advances in the regulatory systems of our key trading partners have removed the need. Acceptance of biotechnology products by our trading partners and the public continues to increase. Where a closed-loop contract-to-crush system was possible for canola, in the United States such a system would be unwieldy for corn and soybeans, and is not planned.

## Lessons learned

AgrEvo began the development process for canola and corn in the mid 1980s, long before regulatory guidelines were in place in most countries. This posed great challenges to the development team since they had to predict data requirements rather

than read them. While the risk was high, the international AgrEvo team worked together closely, and successfully captured the best ideas of a diverse range of specialists. In the end, this cooperative approach allowed AgrEvo to develop a canola data package that has stood up to international scrutiny while achieving the first commercialization of a crop product of biotechnology in Canada. At this time, AgrEvo is also enjoying a similar response to the first Liberty Link™ corn packages. The lesson learned from this is that there is no substitute for detailed advanced planning.

The common thread to all Liberty Link™ crops is the herbicide resistance gene and its product. AgrEvo has developed a safety data package about the gene (*pat*, *bar*) and the PAT protein that can be used in Liberty Link™ regulatory submissions. The data include a Western blot comparison of the molecular weight of the PAT protein expressed in different Liberty Link™ crops and in *Escherichia coli*. The data show that the molecular weight is comparable in all crops tested and has not undergone any post-translational modification. This equivalency allows bridging of a core PAT safety data package developed using few crop species to additional crop species and transformants so that redundant studies are not required for each new transformation event and each new crop.

As authorities gain experience with the review of genetically modified crops, flexibility may be afforded to the regulated community. AgrEvo has learned to pursue perceived flexibility in the regulations and policies. One example of this is the bridging to corn of PAT safety data developed using canola. Such bridging was forwarded when AgrEvo undertook Liberty Link™ corn food and feed safety assessment consultations with the Food and Drug Administration. Another example concerns the opinion from the United States Department of Agriculture's (USDA) Animal and Plant Health Inspection Service (APHIS) that Innovator canola brought into the U.S. by container truck for processing is not a regulated article. Since Innovator is not released into the environment during transport, AgrEvo was not required to obtain environmental clearance (determination of nonregulated status) for import.

One of the most important lessons learned is that continued active interface with the consumer positively influences acceptance of biotechnology products. We have pursued an open dialogue and shared information with government officials, concerned health professionals, growers, media professionals, and those who oppose biotechnology. The most useful interaction has been face-to-face meetings with concerned people. As we have grown canola, corn, and soybean under confinement since the early 1990's we have developed long-term relationships with growers, government officials and the media. They have shown great acceptance of the technology and have a high interest in its success. Because of the long-term relationships developed, we are certain we will be the first to know if a negative concern arises. In Canada, there were press releases with every Canadian clearance achieved for Liberty canola. With each successive clearance, the media coverage decreased. This is a positive sign for the acceptance of biotechnology products.

One challenge we have faced is that North American consumers are not knowledge-

able about existing food safety systems. This means that AgrEvo has had to assure the consumer that existing food is safe before beginning a dialogue regarding the safety of Liberty Link™ -derived products.

## The future

Today, there is growing international pressure from outside North America to advance safety reviews. Regions outside North America have a desire to be economically competitive in the biotechnology arena; to be a participant and not an obstacle. It is recognized that no one gains by making biotechnology a barrier to trade. AgrEvo is encouraged that there is a growing recognition of the great promise that agricultural biotechnology holds.

Looking into the future, AgrEvo plans to obtain regulatory clearances in key growing and export countries for our Liberty Link™ crops. We will continue international consultation efforts and pursue coordinated review of our submissions by key countries. Such efforts by AgrEvo and others will lead to experience gained by authorities and the regulated community; clarity of unique international data requirements; a harmonization of requirements between countries; and greater acceptance of bridging between data packages. Finally, these efforts are expected to result in the international recognition of some types of clearances so that redundant review is eliminated.

