Position Paper

Regulation of Bt crops in Canada

Phil Macdonald* and Stephen Yarrow

Canadian Food Inspection Agency, 59 Camelot Drive, Ottawa, Ontario, Canada K1A 0Y9

Received 2 January 2003; accepted 28 February 2003

Abstract

The Canadian Food Inspection Agency (CFIA) regulates environmental releases of plants with novel traits, which include transgenic plants such as Bt crops. Bt crops are regulated in Canada because they express insect resistance novel to their species. Commercialization of crops with novel traits such as the production of insecticidal Bt proteins requires an approval for environmental release, as well as approvals for use as feed and food. Environmental factors such as potential impacts on non-target species are considered. Insect resistance management (IRM) may be imposed as a condition for environmental release of Bt crops to delay the development of resistance in the target insect. Bt potato and European corn borer-resistant Bt corn have been released with mandatory IRM. The CFIA imposes an IRM plan consisting of appropriate refugia, education of farmers and seed dealers, and monitoring and mitigation. Industry, regulators, government extension staff and public researchers provide expert advice on IRM.

Keywords: Plant novel traits regulation; Bt crops; Insect resistance management; Canada

1. Introduction

The application of biotechnology in the field of plant agriculture over the last two decades has provided crop developers with extraordinary opportunities to introduce novel traits into plants. One area of interest is the protection of crops from insect pests by the synthesis of insecticidal proteins. A popular strategy for achieving this end has been to transfer genes from the soil bacterium *Bacillus thuringiensis* (Bt) into crop plants (primarily into corn and potatoes) that synthesize insecticidal protein crystals. These proteins have specific insecticidal activity but are nontoxic to humans and other vertebrates (Gould, 1995). Although foliar Bt sprays have been registered in Canada for over 30 years and have a long history of safe use, the incorporation of the insecticidal protein into a crop plant where it is more or less continuously produced poses additional challenges with respect to potential adverse environmental effects, especially impacts on non-target insects. Evaluating the environmental impact of these novel crops requires thorough testing and risk assessment. In addition, a robust regulatory framework is required to allow for responsible deployment of the technology and effective risk management.

This paper addresses: the Government of Canada’s biotechnology regulatory framework: (1) the Canadian Food Inspection Agency’s (CFIA) role in conducting environmental risk assessments of plants with novel traits (PNTs), including Bt crops, prior to their release into the environment; (2) the role of the federal government, both interdepartmental and interagency, in regulating plant biotechnology; (3) the management of target insect resistance development, and (4) the CFIA’s plans for addressing future challenges in the area of plant biotechnology regulation.

1.1. Concerns about the environment

Concerns about biotechnology’s impact on human health and the environment prompted the development of Canada’s current environmental regulatory regime for biotechnology-derived products. Environmental concerns, and the need for risk assessments, arose from the potential risks of the modified plants themselves, as well as risks associated with the transfer of novel traits to related plants. Some of the potential areas of risk include the possibility of:
(1) The novel traits increasing the weedy or invasiveness of crop plants or related species, depending on whether the traits affect the competitiveness of the plants; (2) the spread of the novel genes and traits through hybridization with wild, sexually compatible relatives, potentially increasing the fitness levels of these wild species and causing the disturbance or loss of rare populations; (3) novel insect resistance traits that depend on the production of toxins adversely affecting non-pest insects and predator/prey relationships, perhaps leading to the loss of insect species, and (4) the evolution of pests with increased resistance that could necessitate the use of higher doses of pesticides or more toxic chemicals.

In the case of Bt crops, although all of the above are relevant, the last two considerations are of particular concern. It should be noted that environmental concerns are not unique to plant biotechnology. For example, so-called industrial agriculture, due to the predominant use of monocultures, synthetic chemical inputs and heavy, fossil fuel-run machinery, has raised a number of environmental concerns. Also, the conventional development of crop varieties has, in some cases, led to environmental problems or has posed risks to human safety. For example, "Lenape," a conventionally bred variety of potato, was withdrawn from cultivation in the United States due to its elevated and harmful levels of glycoalkoloids (Zitnak and Johnston, 1970). From another point of view, a significant proportion of today's weeds in Canada arose from plants once intentionally introduced for agricultural, horticulture or ornamental purposes. Purple Loosestrife became invasive in North America after its introduction in the early 1800's in ship ballast and as an ornamental plant.

The Government of Canada approaches the regulation of biotechnology products, like any new technology or product line, from a safety-based and science-based approach.

2. Plant biotechnology regulation in Canada

The responsibility for regulating plants with novel traits, including genetically-engineered plants, is shared between Health Canada and the CFIA. Health Canada assesses the food safety of PNTs, while the CFIA conducts livestock feed safety assessments and environmental safety assessments, the latter being the focus of this paper. This cooperative system has evolved in accordance with the following principles:

2.1. The product based approach

Before and after assuming regulatory responsibility for PNTs, a number of multi-stakeholder consultations were held to seek advice on the federal government's regulatory approach. One of the first of these consultations, in 1988, was at a workshop carried out in conjunction with the Canadian Agricultural Research Council (CARC), a not-for-profit consortium of researchers from industry, academia, federal and provincial governments. The workshop participants recommended that the regulatory scope should be focused on "those plants which possess characteristics, or traits sufficiently different from the same, or similar species, as to require an assessment of risk." This led to the recommendation that "the product, and not the process" be regulated, i.e., that it was the presence of a novel trait(s) in a plant that potentially posed environmental risks, and not how the traits were specifically introduced. However, the "product versus the process" approach was challenged early on by some industry members. Early resolution of this issue helped to clearly define the trigger for the environmental safety assessment—a trigger based on the presence of novel traits in the Canadian environment in general, and not just on PNTs modified through recombinant DNA techniques.

An example of an application of this trigger is that a plant product modified through the process of mutagenesis or conventional breeding (for example, through a wide cross with a species not present in Canada) may lead to a line of plants with a new insect tolerance. A similar trait may also be produced through the use of recombinant DNA techniques. In each instance, the resultant plant product requires an environmental safety assessment due to the presence of the novel insect tolerance trait and its potential for ecological impact through either significant effects on non-target species or gene transfer to the same or related species. The need for an environmental safety assessment exists regardless of whether the introduction of novel traits is achieved through mutagenesis and selective breeding or via genetic engineering techniques.

2.2. The step-wise approach to the regulation of PNTs in Canada

The approval process for PNTs in Canada closely follows the evolution of a new PNT as it progresses through each step in its development. Table 1 describes the progress of a PNT through the regulatory process.

2.3. The federal regulatory framework for biotechnology

The Federal Regulatory Framework for Biotechnology was approved by the Government of Canada in 1993. The framework was developed to steer the federal regulatory approach. Along with addressing genetically engineered plants, the framework dealt with the impact of biotechnology on other commodities such as processed foods, veterinary vaccines, livestock feed and fertilizers. These commodities were all in their developmental stages...
in the late 1980s and early 1990s. The Federal Framework allows for the benefits of biotechnology products and processes to be realized in a way that protects health, safety and the environment. The framework resulted from an agreement among federal regulatory departments and agencies to the following key principles relating to biotechnology: (1) to maintain Canada’s high standards for the protection of the health of workers, the general public and the environment; (2) to use existing legislation and regulatory institutions to clarify responsibilities and avoid duplication; (3) to continue to develop clear guidelines for evaluating products of biotechnology which are in harmony with national priorities and international standards; (4) to provide for a sound scientific baseline on which to assess risk and evaluate products; (5) to ensure both the development and enforcement of Canadian biotechnology regulations in an open and consultative manner, and (6) to contribute to the prosperity and well-being of Canadians by fostering a favourable climate for investment, development, innovation and adoption of sustainable Canadian biotechnology products and processes.

The framework uses existing legislation and institutions instead of the development of a “Gene Act” or the establishment of a “Biotechnology Agency.” This means that new products such as PNTs are regulated in the same manner, broadly speaking, as conventionally derived products.

The Government of Canada’s approach to regulating products of biotechnology is based on: (1) the characteristics of the product; (2) the use of science-based risk assessments, followed by risk management (e.g. insect resistance management plans (IRM)); (3) the protection of the health of people, livestock, and the environment, and (4) meeting performance standards.

This approach recognizes and builds on the knowledge, expertise and infrastructure already present in traditional products’ regulatory frameworks. The Federal Regulatory Framework for Biotechnology also provides for mechanisms which assist in the maintenance of efficient, effective and harmonized approaches to the coordination of regulatory policy development across government.

### Table 1

<table>
<thead>
<tr>
<th>Development stage</th>
<th>Regulatory process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production in a laboratory and growth chamber followed by further development of the PNT in a greenhouse, i.e. development under contained conditions</td>
<td>Contained—refers to PNTs produced and studied in laboratories, growth chambers and greenhouses. These are considered to be conditions of environmental isolation. Researchers must adhere to laboratory biosafety guidelines established by Health Canada and the Medical Research Council, as well as codes of practice established by their own institutions</td>
</tr>
<tr>
<td>Field trials in the environment under controlled conditions</td>
<td>Confined—refers to field trials of PNTs in the environment under controlled conditions. These trials are subject to regulatory oversight by the CFIA under the Seeds Regulations. Conditions must be designed to minimize the possibility of any environmental impact and include measures to prevent transfer of pollen to other plants, restrictions on use, storage and disposal of harvested or excess plant material, inspection by CFIA inspectors and, post-harvest land use restrictions. Field trials are generally designed to evaluate agronomic and environmental characteristics of PNTs over several years, prior to the selection of potentially commercially viable PNT lines</td>
</tr>
<tr>
<td>Development to the pre-commercial stage for broad environmental release without conditions. Bt crops subject to IRM plans</td>
<td>Unconfined—refers to growth of PNTs without confinement conditions. Data generated from the confined trials contribute to the environmental safety assessments necessary prior to CFIA authorization for unconfined environmental release under the Seeds Regulations. Assessment criteria include altered weediness potential, potential for out-crossing, altered plant pest potential, impacts on non-target organisms and impact on biological diversity</td>
</tr>
<tr>
<td>Registration and marketing</td>
<td></td>
</tr>
</tbody>
</table>

As the new products of modern biotechnology were being developed in the 1980s, concerns were also emerging regarding the food safety aspects of these products. These concerns centred on the potential production of new or elevated levels of toxins or allergens resulting from genetic modifications, through either the inadvertent introduction of genes that could produce allergenic or toxic material, or through epistatic effects or other downstream interactions.

The sale of food in Canada is controlled by several regulatory mechanisms under the Food and Drugs Act and Regulations. For example, Health Canada assesses the safety of novel food products before they are sold and the CFIA plays an inspection and enforcement role. In October 1999, the Novel Food Regulations were promulgated to clarify and build on the powers of the Food and Drugs Act. These regulations address foods that, among other things, are derived from plants, animals or...
microorganisms that have been genetically modified to exhibit novel characteristics (for example, PNTs). Over the years of regulating these new products, the CFIA and Health Canada have built a strong relationship that harmonizes and complements their respective roles relating to environmental and human safety.

3. The environmental assessment of Bt crops in Canada

3.1. Unconfined release

Before Bt crops may be authorized for unconfined release, they must be fully assessed for environmental safety by the CFIA. Key to the environmental assessment approach of the CFIA is the development of ‘‘biology documents’’ for each crop species to be used as a comparator for novel varieties intended for unconfined release. These biology documents provide a snapshot of the agricultural, agronomic and environmental behaviour of each crop species in the Canadian environment, e.g. details on how the plant grows, reproduces, interacts with related and unrelated species, and how it is cultivated in Canada. This approach provides a backdrop for the environmental assessment of the modified form of the crops and assists in teasing out the potential differences in environmental interactions compared to the unmodified versions of the crop. Biology documents of both the canola species, B. napus and B. rapa, in addition to potato, corn, wheat, flax, and soybean, have been developed largely by the applicants themselves but with additional CFIA-directed reviews by Canadian crop experts. These biology documents serve as companion documents to the unconfined release guidelines, and are posted on the CFIA web site at http://www.inspection.gc.ca/english/plaveg/pbo/bio/biodoces.shtml. The CFIA’s approach of developing these biology documents as an adjunct to unconfined release information requirements has been internationally recognized. This approach has led to the OECD’s Working Group on Harmonization of Regulatory Oversight in Biotechnology to develop similar ‘‘consensus documents’’ that describe the biologies of key crop plants from a global environmental perspective.

In meeting the extensive information requirements for applications to the CFIA for unconfined release into the environment applicants will have conducted experiments at the confined release stage. These experiments are expected to contribute data which will address the five key criteria of environmental safety assessments: altered weeding potential, potential for out-crossing, altered plant pest potential, impacts on non-target organisms and impact on biological diversity. The generation of data to be considered for a determination of environmental safety must be produced using statistically valid experimental designs and protocols (i.e., equivalent to the standards required for inclusion in peer-reviewed research publications). Further information can also be submitted in an application based on the scientific literature and recent unpublished research from around the world. Proponents are also required to submit details of field trial protocols, including experimental designs and sampling procedures, that are consistent with the proposed use of the PNT. All this information, is supplied to the CFIA to initiate a review and decision for authorization of the release. CFIA officials also use pertinent information generated from the Agency’s own research, either conducted in-house or contracted out, on specific key environmental areas.

The unconfined release assessment focuses on real or potential interactions of the PNTs with the wider agricultural and ecological environment. The basis for these assessments is the comparison of the potential impacts of the PNTs on the environment with the unmodified crop species’ progenitors or counterparts. This concept of comparing new or modified products with existing familiar products is known as ‘‘substantial equivalence.’’ This determination does not mean that a specific modified and unmodified plant are identical in every way. It does mean, however, that the novel product and the conventionally derived product have been found, through testing and analysis, to be equally safe for their respective uses in the environment. The assessment is to determine whether there are significantly different or altered interactions with other life forms resulting from the PNTs novel gene products and which could potentially cause the plant to become a weed of agriculture, become invasive of natural habitats or be otherwise harmful to the environment.

To date, insect resistance traits approved in Canada are in corn, potatoes and cotton. Only corn and potatoes are cultivated in Canada but insect tolerant cotton is approved for livestock feed (cottonseed oil and meal) and human food use (cottonseed oil). In all cases the insect tolerance is based on the introduction of the Bt toxin. Fig. 1 shows the Bt toxins that have been introduced into crops in Canada and their target insect pest species.

3.2. Molecular characterization

A full molecular characterization is integral to the assessment of a Bt crop since it can indicate what additional information may be required for a full risk assessment. Molecular information usually spans the continuum from the presence of the introduced genes, the expression of DNA in the form of messenger RNA to the presence of the Bt toxin and any other novel proteins that may confer the novel traits. In the case of tissue specific expression, information on protein production levels in different parts of the plant can indicate different levels of exposure of novel proteins to various elements of the environment. For example, in the case of
the corn line MON 802 (developed by Pioneer Hi-Bred and Monsanto), which expresses the insecticidal protein Cry1Ab, molecular characterization demonstrated the absence of the Bt protein in pollen. As a consequence, pollen need not be considered as a route of exposure to the Bt toxin. As a contrast, Event 176 corn, originally developed by Ciba Seeds/Mycogen, expresses the Cry1Ab toxin at significant levels in the pollen, and thus exposure to the toxin via pollen was considered in the assessment of ecological impacts.

3.3. Phenotypic characterization

CFIA evaluates growth habit, vegetative vigour, overwintering capacity, flowering period, plant height, insect and disease susceptibility, other than resistance to the target pest, and yield and quality and reproductive and survival biology as part of the environmental assessment of Bt crops. As with traditional plant breeding, the use of biotechnology to introduce novel traits into plants has the potential to cause epistatic, pleiotropic or other unintended effects. In the case of Bt crops, the novel trait is a toxin and this component is analysed during the molecular-based characterizations. There may be cases, however, where the novel trait could disrupt certain aspects of a plant’s physiology. For example, the product developer may have introduced a novel gene that expresses a novel protein that may inadvertently alter a related biochemical pathway involved in the synthesis of existing proteins. Alternatively, the actual process of genetic modification may inadvertently disrupt existing genes and their functions. These secondary effects can be considered by examining the plant’s broad phenotypic or physical characteristics in comparison to non-modified counterparts. Inadvertent physiological disruptions, if significant, are likely to manifest themselves in a way that could cause changes in one or more of the plant’s physical attributes such as height, yield, habit, composition, levels of endogenous toxins, time to flowering, seed dormancy, fertility, disease resistance, etc. Demonstrating that the plant is behaving in the same manner as the conventional unmodified plant contributes a great deal towards accounting for the possibility of any potential secondary effects.

3.4. The use of indicator species for evaluation of toxicity

The toxicity of plant-expressed Bt toxins is addressed using indicator species to represent the usual routes of exposure. Indicator species, selected on the basis of this novel trait/exposure information, can determine potential effects on non-targets as a whole. Species selected can include mammals, insects, birds, fish and soil organisms, amongst others. As an example, Monsanto’s corn line MON 810 expresses Cry1Ab to impart resistance to the European corn borer. The developer exposed the insecticidal Bt protein produced in the plant to pollinator insects (honeybees), predaceous insects (green lacewing larvae, ladybird beetles) and parasitic Hymenoptera. No discernable effects were detected at more than tenfold higher dosages than would be expected from field exposure.

Other common indicator organisms using during the toxicity assessment include parasitic wasps, springtails, earthworms, mice and the bobwhite quail.

3.5. Impacts on the monarch butterfly

In the summer of 1999, a report in Nature (Losey et al., 1999) described a preliminary laboratory-based experiment, from Cornell University, where larvae of the monarch butterfly died after being fed milkweed leaves covered with pollen from a type of Bt corn (N4640-Bt field corn). As milkweed is the larvae’s sole food source, the Cornell researchers and some environmental groups expressed concern about the broader impact of Bt corn on monarch populations. The CFIA had concluded that there were no significant environmental risks associated with the use of the Bt corn lines that have been approved for use in Canada. These conclusions were reached based on the following: (1) molecular characterization indicating expression levels in the plant tissues; (2) toxicology of the expressed protein; (3) the indicator species studies; (4) knowledge of corn biology and agronomics, and (5) the dose of Bt toxins that a lepidopteran larvae would receive through inadvertent consumption.

Following the Cornell study, the CFIA, in cooperation with Environment Canada, funded further research to examine the effect of Bt corn pollen on monarch butterfly larvae. This research, conducted at the University of Guelph, focused on field-based studies rather than laboratory-based studies. The purpose was to
confirm the results of the safety review with field data. This preliminary study indicated that there was no significant impact on monarch butterfly populations from field exposure to an approved event that expresses significant levels of Cry1Ab in pollen (Event 176). This result has now been confirmed through an extensive series of papers produced by a cooperative network of researchers. These publications can be found at the Proceedings of the National Academy of Science USA’s website at http://www.pnas.org under the banner Special Edition for September 14, 2001.

Related research at the University of Illinois regarding the effects of a Bt corn line on the larvae of black swallowtail butterflies (which also depend on weeds often adjacent to corn fields) has also demonstrated that the corn pollen had no effect on the survival of the caterpillars in the field (Wraight et al., 2000).

3.6. Insect resistance management (IRM)

Bt-based foliar sprays have been available to growers for many years as useful and effective insecticides. For example, Bt foliar sprays are registered for control of the European corn borer on hybrid seed corn production, and another is registered to control cabbage looper on pepper production. Bt foliar sprays are also registered for use on both potatoes and tomatoes.

Widespread use, or misuse, of Bt-based pesticides may, as with any other extensive use of a pesticide system, render the technology ineffective due to the development of resistance by the pest insects (Gould et al., 1997; Tabashnik, 1995). This applies to both foliar spray forms or crop plants modified to produce their own Bt. As Bt crops synthesize an on-going, high dose of the toxin, selection pressure for resistant insects is high. As a consequence, the CFIA requires the application of resistance management plans for the Bt corn and potato lines authorized for unconfined release in Canada. Fig. 2 describes the components of an insect resistance plan.

The IRM plans for both corn and potatoes are based on high dosage or high Bt expression in plants (resulting in high pest insect mortality) and the use of so-called refugia—areas of non-Bt producing corn or potato plants that serve as refuges for susceptible pest insects (Sears and Schaasfma, 1998). Should resistant insects occur, they would be able to mate with susceptible insects available in the refuge to produce susceptible/resistant hybrids that will also be susceptible to the Bt plants, thus eliminating the resistance genes. Although the majority of the scientific community agrees that the refugia strategy promises to be effective in theory (viewed more favourably for corn than potatoes at this time), definitive evidence has not yet been widely reported. For this reason, the CFIA mandates growers to implement an IRM plan based on refugia and other key criteria, with the responsibility for compliance resting on the developers of the Bt crop. Long term unconfined release of Bt corn and Bt potatoes are authorized contingent on the following criteria: (1) refugia must comprise at least 20% of the Bt crop acreage, must be in close proximity to the Bt crop and must be managed in a way to support viable populations of the target pest insect; (2) education tools for IRM must be developed and provided to all growers and company field personnel; (3) scouting programs must be implemented to detect resistant pest insects at the earliest time possible, and any detections must be reported to the CFIA immediately; (4) integrated pest management practices

---

**Fig. 2. IRM—Roles and responsibilities.**
must be promoted, such as crop rotations and alternative pest control measures, and (5) continued research on the refugia-based IRM plan must continue and the results be made available to the CFIA.

The above IRM plans have been imposed by the CFIA on the Colorado potato beetle resistant potatoes and European corn borer resistant corn lines authorized to date for environmental release in Canada. Investigations have demonstrated a high level of compliance by the corn growers who have embraced Bt technology in high numbers (Powell et al., 1999).

4. Conclusion

4.1. CFIA’s evolving role in the regulation of plant biotechnology

The CFIA approved the first confined field trials in 1988. The regulation of unconfined release of PNTs has been conducted since 1994. The influence, however, of plant biotechnology on agriculture, the environment, commerce and Canadian society continues to grow and change, and is already posing new challenges to the regulatory system. The CFIA, in cooperation with the other federal regulatory departments and agencies, is moving forward to address these challenges.

4.2. Further IRM issues

A number of new developments are planned by the biotechnology industry and plant breeders to introduce novel insect resistance traits beyond the current Bt-based resistance traits. Some of these developments involve variations on Bt technology (e.g., to provide resistance to the corn root worm pest), while others include the introduction of genes that express proteinase inhibitors, chitinase endotoxins and fungal-based insecticidal proteins. It is quite likely that combinations of these novel traits could be introduced into various crop plants. Not only could these pose potential hazards to non-target organisms, but they will also raise substantial challenges to IRM plans.

The CFIA has, since its inception, gained substantial experience in protecting the Canadian environment from significant adverse effects from the release of PNTs. The stringency of federal standards and the strength of its regulatory scientific knowledge have allowed Canada to make sure that technologies like Bt crops can be deployed responsibly. The Government of Canada’s confidence in the environmental safety assessment process for PNTs is balanced, however, by the CFIA’s commitment to continuous improvements that reflect evolving science and the on-going challenges posed by new products derived from plant biotechnology.

References


