Plant Biotechnology Journal (2008) **6**, pp. 213–225 doi: 10.1111/j.1467-7652.2007.00309.x

Review article

Regulating innovative crop technologies in Canada: the case of regulating genetically modified crops

Stuart Smyth[1,*] and Alan McHughen[2]

[1]*College of Biotechnology, University of Saskatchewan, 51 Campus Drive, Saskatoon, SK, Canada S7N 5A8*
[2]*Department of Botany and Plant Sciences, University of California, Riverside, CA 92521, USA*

Received 27 September 2007; accepted 11 October 2007.
**Correspondence* (fax 306-966-8413; e-mail stuart.smyth@usask.ca)

Keywords: biotechnology, genetic engineering, genetic modification, plants with novel traits, rDNA, regulations, risk.

Summary

The advent of genetically modified crops in the late 1980s triggered a regulatory response to the relatively new field of plant genetic engineering. Over a 7-year period, a new regulatory framework was created, based on scientific principles that focused on risk mitigation. The process was transparent and deliberately sought the input of those involved in crop development from non-governmental organizations, industry, academia and federal research laboratories. The resulting regulations have now been in place for over a decade, and the resilience of the risk-mitigating regulations is evident as there has been no documented case of damage to either environment or human health.

Introduction

The perceived magnitude of risk in modern society appears to have increased to previously unimaginable levels, when, in reality, the actual risk may not have changed as much as our knowledge of exposure to risk. The varieties of risk to which modern societies are exposed are certainly more extensive than in the past, but the absolute incidence of risk may not have changed substantially. It is, more often than not, our perception of exposure to hazards that is increasing.

Risk and the magnitude of risk change over time, yet human exposure to risk appears to be relatively constant over time. Exposure to a specific risk, or even a class of risk, can appear, and then increase or wane over time, but the overall exposure to risk has remained relatively constant through the ages. Although exposure to risk in areas of food safety, nuclear contamination and climate change may be increasing, the risk of exposure to global warfare, starvation and enslavement has decreased significantly.

One fundamental factor that remains unchanged when risk is being assessed is the need for a governance strategy adapted to the changing nature of risk. Risk strategies are inevitably diverse, both in their objectives and implementation. This article offers insights into the challenge by examining the risks that have manifested themselves within and around the field of agricultural biotechnology. We begin by providing a review of the regulatory system for conventionally bred varieties in Canada. This is followed by a description of the process for developing specific regulations for genetically modified (GM) crops, and a synopsis of the present regulatory systems.

Canadian regulatory regime for conventionally bred crop varieties

The traditional governance system for crop agriculture has its foundation in an extensive, horizontally based, public/private regulatory system (Smyth *et al*., 2004). Risks are managed by various stakeholders depending on the stage of variety development. Private or public breeders are responsible for managing any risks in their research programmes, as long as the materials remain in isolated conditions (e.g. in laboratories or under glass). Once the breeder has developed a cultivar that is genetically stable and unique, it is ready to be examined for registration and the formal system takes over.

In the production system, the public sector has tended to establish the general environment for private actors to effect transactions. The Food and Drugs Act (1985) sets rules for human consumption[1], the Feeds Act (1983) sets maximum

[1] Health Canada sets policies and standards for food safety. However, if a modified plant is to be used as animal feed and has the potential to introduce harm to humans when the animal is consumed as food, it is the Canadian Food Inspection Agency that enforces this aspect of the policies and standards.

tolerances of nutrients for livestock feed, the Seeds Act (1985) specifies the performance standards for new germplasm and the Canadian Grain Commission sets and monitors the standards for the seeds trade.

These three Acts are designed to establish standards for risks related to plant agriculture. The main quality attributes of the Seeds Act are uniformity, stability and uniqueness. However, this Act also establishes thresholds for environmental safety risk aspects, such as gene flow, invasiness, weediness and impact on non-target organisms. The Feeds Act defines the thresholds for the potential risks caused by allergenicity, toxicity, digestibility and dietary exposure relating to animal feeding. The Food and Drugs Act establishes risk thresholds for allergenicity, toxicity, metabolization, nutrition and dietary exposure relating to human consumption. The integration of these three Acts into the regulatory framework for new plant varieties is designed to identify all potential risk categories and to ensure that any new plant variety is benchmarked to existing varieties already determined to be safe for human and animal consumption.

The Seeds Act is the first point of quality assurance, as new varieties must, on average, at least equal the quality (in set parameters) of contemporary commercial varieties. All new varieties of grain and oilseeds generally flow through the same system in Canada, with higher levels of oversight on those that involve novel traits (novel traits are described below in greater detail). The variety registration system stipulates that any new variety developed within 30 agricultural crops has to receive variety approval prior to the import of seed, advertisement for sale or sale of seed. This process is in place to ensure that the new variety being submitted for approval exceeds or is at least equal to existing varieties. This is carried out to ensure that the overall quality of the variety is constantly improving, a manifestation of the 'merit system'.

When the crop breeder develops a new cultivar, he or she begins field trials, the purpose of which is to provide the evidence to evaluate the environmental risks of the new cultivar and to assess its agronomic merit (e.g. yield, disease resistance, time to maturity, quality and any other traits). Most new cultivars require 3 years of field trials to gather this data; however, it is possible to take only 2 years in clear cases.

Once the field trial data are gathered, they are submitted to the variety recommending committee. At this point, the public/private aspect of variety registration comes fully into effect, as the merit assessment of new variety applications is conducted by official recommending committees. There are 21 recommending committees recognized by the Canadian Food Inspection Agency (CFIA). These committees comprise government and industry representatives, and evaluate the agronomic, grain quality and disease rating data, make performance comparisons, and come to a decision as to whether the merits of this particular cultivar meet (or exceed) the quality standards for the particular variety. If the decision is in favour of the new cultivar, the breeder receives notification that the committee supports the registration and commercialization of the new variety. When the new cultivar has been evaluated and supported for registration by an appropriate recommending body of experts, a dossier is submitted to the Variety Registration Office (VRO) within the CFIA. The VRO reviews the submission data and has the authority to request additional information from the breeder prior to granting variety approval. The VRO retains final authority to grant variety approval in Canada.

There are four variety approval options when making approval decisions (CFIA, 2000). The typical option is to grant national approval to the new variety, meaning that there are no restrictions on the sale of seed or the production of the crop anywhere in Canada. Regional registration can be granted to ensure that a crop variety is only produced within a defined geographical area. The geographical separation between the Western prairie crop area and the lower Ontario and Quebec growing area often defines the regional approval. Contract registration is granted to varieties that are required to be segregated from other similar varieties for crop safety reasons (see Smyth and Phillips, 2002 for more details on segregation systems). Finally, interim registration can be approved that establishes a fixed duration for approval of the variety.

Once a variety is approved, the Canadian Seed Trade Association manages the seed multiplication system, specifying the tolerances for substandard materials, and the retail seed business, by overseeing the sale of seeds by registered name. After harvest, the Canadian Grain Commission takes over quality assurance for much of the product, setting and enforcing grades and standards for the trade. Within this context, spot markets have relatively efficiently managed the commercialization of a large number of new varieties over the years (Kennett *et al*., 1998).

Regulations are not static in nature and, early in 2006, the CFIA engaged in a review of the framework for seed variety registration. The review is a three-pronged approach in that it proposes to identify problems, discuss options to address the problems and assess the alternatives (CFIA, 2006a). The review process initiated by the CFIA was a very open and consultative process. At the time of writing, the CFIA was approaching the end of a 5-month online consultation process aimed at eliciting input from diverse interests.

This public/private governance framework minimizes the risks associated with the approval of new crop varieties. The

role of the various recommending committees is essential, as it ensures that experts working with that specific crop type are those that make the initial recommendation regarding approval. This recommendation is not made by arms-length bureaucratic scientists, but by a variety of individuals with hands-on experience. This integration into the regulatory framework has resulted in a variety approval system that consistently works towards improved safety and quality, and therefore risk reduction.

Developing regulations for plants with novel traits

To deal with the potential risks that may develop following the application of new genetic technologies to the science of plant breeding, Canadian regulators established a new classification of plants. The Canadian regulations for the initial innovative crops were based on science, and all subsequent regulatory changes have continued to be based on science. The regulations are based on the end product that is established, not the process used to create the product. To this end, Canada developed regulations for plants with novel traits (PNTs). Plants that are classified as PNTs are those that have been modified via genetic engineering or mutagenesis, as well as those that do not have a history of production and safe consumption in Canada (CFIA, 2004a).

However, some rDNA developed plants are not PNTs, which creates some confusion for crop developers. This differs from the US regulatory system. Most jurisdictions trigger regulatory scrutiny for every new rDNA insertion into a plant's genome, but the CFIA triggers regulatory scrutiny only when a plant acquires a new trait, even if it is not a product of rDNA. Plants developed using traditional breeding, not rDNA, have triggered regulatory review for expressing novel traits. A recent example is a conventionally bred barley variety expressing low phytate from the University of Saskatchewan. A plant developed using rDNA, but not expressing a novel (or, in this case, unapproved) trait, would be exempt, even if it is a new or different transformation or insertion event. For example, if a transgenic PNT were assessed and approved, a cultivar derived from a subsequent plant of the same species, transformed with the same DNA construct and expressing the same traits as the approved variety, would not trigger regulatory scrutiny as a PNT, as it would not be novel. However, the developer would still have to fulfil variety registration requirements prior to commercial release, and would retain the obligation to report any subsequent unusual or unexpected observations.

The regulation of products created via biotechnology is the responsibility of the CFIA, Environment Canada and Health Canada (Table 1). Using legislation from four different Acts, the CFIA is responsible for plants, animal feeds, fertilizers and veterinary biologics. The Office of Food Biotechnology (OFB) has been established within the CFIA to co-ordinate the safety evaluation of novel foods. Environment Canada acts as a regulatory safety net for products of biotechnology, where it has the regulatory mandate for all animate products of biotechnology for uses not covered under other federal legislation. Environment Canada regulates biotechnology within the scope of the Canadian Environmental Protection Act (1999). Through the Food and Drugs Act, Health Canada oversees the regulation of foods, drugs, cosmetics, medical devices and pest control products. All safety assessments are conducted on the basis of scientific principles developed through expert international consultations with the World Health Organization (WHO), Food and Agriculture Organization (FAO) and the Organization for Economic Co-operation and Development (OECD) (Harrison, 2001).

All novel trait products, prior to receiving registration approval, are thoroughly tested by the CFIA, Environment Canada and Health Canada officials using scientific principles.

Table 1 Legislation governing biotechnology

Agency	Product	Act
Canadian Food Inspection Agency (CFIA)	Plants with novel traits	Seeds Act
	Novel fertilizers and supplements	Fertilizers Act
	Novel livestock feeds	Feeds Act
	Veterinary biologics	Health of Animals Act
Environment Canada	All animate products of biotechnology for uses not covered under other federal legislation	Canadian Environmental Protection Act (1999)
Health Canada	Novel foods	Food and Drug Act
	Pest control products	Pest Control Products Act

Source: CFIA (2005a).

Officials from all departments work together on a new variety application. Officials do not re-perform the scientific experiments and research information that is submitted by the applying company; rather, they analyse all of the data that is submitted and may re-perform portions of the experimentation to corroborate results. Frequently, government officials will ask the submitting company to provide them with additional information regarding specific segments of the application, which may result in the company conducting additional scientific experiments. On review of all the information, the variety is accepted if all conditions are fully met and rejected if any condition is not deemed to be acceptable.

The next section focuses on the scientific/governance aspect of the development of these new regulations, and identifies the risks that the regulatory framework strives to address. This is followed by a discussion of the process used to develop the regulations, identifying the objectives of the framework and the collaboration involved in the development process.

Scientific/governance approach to the initial GM crop regulations

By 1986, transformed plants with new transgenic traits were available and ready for field testing. The science of transgenic plants was well in advance of the governance capacity, as there was no regulatory protocol in place at this time. The number of field trials was relatively small, and those conducted in 1986 and 1987 followed the protocol used for all previous field trials with new crop varieties. By the spring of 1988, federal permits were required to plant a field trial with a transgenic plant variety. Following the initial permits, the governance process was conducted by the use of periodic directives issued by federal regulators. These directives were issued following considerable contact and discussion with the industry stakeholders.

The trials were conducted to gather the data required by the Seeds Act, Feeds Act and the Food and Drugs Act, as described above. The regulators also needed evidence on the characterization of the transformation system, the nature of the carrier DNA, genetic material delivered to the plant, the components of the vector and a summary of all genetic components. In addition, the regulator required an array of data to assess the inheritance and stability of the genetic modification (e.g. Mendelian segregation) and a description of the novel traits [e.g. Southern analysis and qualitative enzyme-linked immunosorbent assay (ELISA) of the gene expression levels]. (See www.inspection.gc.ca/english/plaveg/bio/subs/subexe.shtm for a detailed list of what this involves.)

Once confined field trials had been authorized, they were undertaken following a strict set of guidelines and standards, which, although national in application, were drawn from international evidence of the appropriate risk management procedures and the latest international biosafety evidence. Although the regulators were responsible for auditing and enforcing the rules on trials, these trials were usually managed directly by the research firm or by a contractor (in Canada, the various research farms operated by Agriculture Canada have managed many of the trials under contract with the companies).

By 1992, the breeders conducting field trials had gathered sufficient data to demonstrate intergenerational stability, agronomic efficacy and commercial promise, and began to develop their regulatory package of evidence to present to the regulators to assess the safety of the products. In Canada, this required extensive data on the toxicity of the novel gene products (e.g. a series of toxicity studies with humans, animals and non-target species). The product proponents also had to provide scientific studies on the nutritional aspects of the novel trait and plant for both humans and livestock, and comparisons of the amino acid sequences of the novel trait with known allergen proteins. Finally, the proponents were required to provide a package of studies on the environmental impact of the novel traits on soil, weeds, wild relatives and non-target organisms. McHughen (2000) published a photographic histogram of the volume of data required to satisfy regulators of the health and safety of transgenic crops (in his case, a transgenic flax variety) – the pile of studies and reports exceeded 3 ft (91.5 cm) for the transgenic product vs. an average of about 30 pages for a conventionally bred variety.

The results of the field trials, food, feed and environmental reviews were then examined by the appropriate regulators. In Canada, Health Canada undertook the food safety review, whereas the environmental and animal health reviews were conducted by forerunner agencies of the CFIA. In each case, they had enabling standards embedded in legislation or regulation which needed to be made specific for each product or technology. The process involved extensive negotiation between the regulator and the product proponent, supplemented with reference by the regulator to experts in other national regulatory systems and to those outside the regulatory system.

Finally, the initial GM crop varieties (three new trait canola varieties) were assessed by a committee of researchers operating under the authority of the Seeds Act. They analysed the candidate varieties against standard, commercially grown 'check' varieties. The committee then authorized them for sale to farmers. Most other countries do not have this regulatory step.

At this point, a blended public–private quality control system took over.

For the initial GM canola varieties, this was administered by the Western Canadian Canola Rapeseed Recommendation Committee (WCCRRC), a committee of more than 30 public and private breeders that evaluates new varieties against the 'check' varieties and recommends varieties for release. This standard has been backstopped by the Canola Council of Canada trademark on canola, which specifies that products must have at most 2% erucic acid and 30 μmol of glucosinolates per 100 g of dried meal. Furthermore, the new variety approval system periodically raises the standard for new varieties by choosing a new 'check' variety as the base, which sets oil and meal properties, grain yields and disease resistance.

The regulatory approval process was completed in February 1995 when the Pest Management Regulatory Agency submitted recommendations for approval for two varieties of GM canola to the Expert Committee for Canola. Agriculture and Agri-Food Canada approved the two varieties for unconfined release in March 1995, meaning that large-scale commercial production of GM crops could occur in Canada.

Although the scientific risks were resolved by the close involvement with the academic community and industry in developing a regulatory directive on the biology of the species to establish familiarity, this did not address all the risks. Canada was not alone in having to develop a regulatory framework for transgenic crops, as the USA and Europe were also heavily engaged in this. Many of the breeders involved in the industry at this time recognized that new regulations were inevitable, and that close collaboration with the regulators would be advantageous. Although there were scientific risks that needed to be addressed through regulation, Canada also had to develop this regulatory framework to remain competitive at an international level. The actions of the USA and Europe meant that, if Canada commercialized transgenic products without a thorough regulatory framework, the perceived lack of regulation could be viewed as a safety concern, thus denying market access to Canadian products. To ensure that trade barriers did not arise, it was recognized that a thorough risk analysis and approval system would be an essential component of advancing the industry of transgenic plants.

One important observation from the development of regulations for these first-generation GM crops was that the regulators were openly accepting of industry and academic stakeholder involvement. At the time of commercialization, the mid-1990s, the regulators operated from the perspective that, once the scientific risks were satisfactorily addressed, the technology was allowed to proceed unimpeded by regulatory interference.

The process of developing PNT regulations in Canada

This section discusses the interaction between science and governance that occurred as the regulatory framework was developed in Canada.

The initial workshop to address the regulatory framework that would be required for the successful commercialization of transgenic crop technologies was organized in 1988 by the Canadian Agricultural Research Council (CARC), entitled 'Regulation of Agricultural Products of Biotechnology' (Canadian Agricultural Research Council, 1988). There were 108 attendees for this workshop, 65 from the various government agencies and research organizations, 27 from numerous private industry firms, 14 from Canadian universities and two from the United States Department of Agriculture (USDA).

The objectives of this workshop focused on an assessment of the current position of agricultural biotechnology in Canada. The first objective was to engage in a current assessment of the regulatory environment for agricultural biotechnology products in Canada. The second objective was to identify how this Canadian situation compared with those in the USA and Europe. The final objective was to define what regulatory concerns existed at this point in time from the perspective of the industry and the regulators.

This workshop produced the following key recommendations designed to improve the regulatory process, and which provided the basis for the development of the PNT regulatory framework.

1. Those plants which possess characteristics or traits sufficiently different from those of the same or similar species should require an assessment of risk.

2. The product, not the process, should be regulated.

3. The categories of novel herbicide tolerance, novel pesticidal properties, novel stress tolerance and novel compositional changes were raised as categories of concern (Canadian Agricultural Research Council, 1988).

Over the next 3 years, the Director of the Animal and Plant Health Directorate, within the Food Production and Inspection Branch of Agriculture Canada, convened periodic *ad hoc* meetings of varying representation to discuss pertinent issues. It was not until 1992 that a formalized structure was put in place to deal with the regulatory changes that would be required. It was decided in April 1992 that a standing advisory committee would be established with the following mandate.

1. To provide information and guidance on the regulation of plant biotechnology.

2. To assist in the development of a consistent regulatory approach.

3. To assess and evaluate regulatory requirements for field testing and commercialization of GM plant material (Agriculture Canada, 1992).

The Plant Biotechnology Advisory Committee also had a formalized representation, and the membership consisted of representatives from 11 various agriculture-related societies and associations[2].

In 1992, the Food Production and Inspection Branch contracted with Dr Wally Beversdorf (Chair of the Department of Crop Science at the University of Guelph) to develop a draft protocol and assessment criteria for the unconfined release of PNTs. This initiative, when taken in consideration with a series of workshops held across Canada between January and March 1993, produced a draft set of regulations. A workshop was held on November 8–10, 1993 in Ottawa to discuss the draft regulations. The draft regulations were shared with attendees prior to the workshop and were entitled, 'Assessment Criteria for Determining Environmental Safety of Genetically Modified Plants'.

The workshop consisted of numerous presentations from a variety of stakeholders that had been invited to participate in the workshop. The objectives of the workshop were to build consensus on the approach to regulate PNTs, to ensure consistency with existing regulations, to ensure the sharing of information and to develop working relationships (CFIA, 2001).

The principles of the federal regulatory framework were identified as follows: to build on existing legislation and institutions; to uphold health and environmental safety standards; to harmonize with national priorities and standards; to use risk-based assessments and methodologies; to assess products, not processes; and to develop a favourable climate for investment, development and innovation by adopting sustainable products and processes.

Much discussion was given to the concept of substantial equivalence for products derived by biotechnology, especially the difference between 'familiarity' and 'substantial equivalence'. Familiarity was described as an extensive knowledge of factors relating to the production of a particular crop species that allowed for decisions pertaining to safety to be made; substantial equivalence applied to those new crop types whose safety could not be identified from a standard risk assessment.

[2] Membership consisted of the Canadian Seed Growers Association, Canadian Seed Trade Association, Crop Protection Institute, Genetics Society of Canada, Canadian Society of Agronomy, Confederation of Canadian Faculties of Agriculture and Veterinary Medicine, Plant Biotechnology Institute, Expert Committee on Weeds, Canadian Society on Botany, Canadian Phytopathological Society and the National Seed Potato Bureau.

Unfortunately, because there is no standard accepted definition of substantial equivalence, and agencies use different definitions, a firm decision was not made by Canadian regulators pertaining to the use of substantial equivalence in regulatory actions. This inconsistent definition contributed to the ongoing confusion over the use of the term. This confusion was witnessed in the report of The Royal Society of Canada (2001). Canada has a *de facto* application of substantial equivalence, in that regulators apply regulations to the resulting product, not the process used to create the product, which is contradictory to the wording in CFIA regulations.

The CFIA states that '... a plant with a novel trait is one that is not "substantially equivalent" to existing plants of the same species cultivated in Canada ...' (CFIA, 2005b: p. 1); however, this is incorrect, as the progeny of approved PNTs are not considered to be novel. The Royal Society report was widely criticized in the scientific community, partly because it assumes *a priori* that transgenic plants are suspect, and so suggests that scientific evidence must be presented to prove them safe. This is faulty on two points: first, there is no scientific reason to suppose that plants developed using rDNA are any more risky than plants developed using other technologies; and, second, science cannot prove something safe. Health Canada, on the other hand, states that '... substantial equivalence is not to be used as a decision threshold and GM-products should be subject to a rigorous scientific assessment of their potential for causing harm ...' (Health Canada, 2001: p. 1). In fact, Health Canada goes on to identify that substantial equivalence is not uniformly applied in federal regulations. Ultimately, although substantial equivalence for PNTs was not defined within the developing regulations, some form of it has been practiced by the regulators.

Key recommendations for the draft regulations were that time should not be a factor in approving these new technologies, but, rather, safety should be the chief concern and should be proven regardless of the time taken to do this. International acceptance of the products was identified as crucial for commercial success for these new crop technologies. Participants acknowledged that there were risks, but that the focus must be given to identifiable, science-based risks, not hypothetical socio-economic risks. The final recommendation dealt with the importance for regulatory harmonization within North America. Harmonization would ensure that the ultimate regulatory framework would not hinder the competitiveness of this emerging industry in Canada (CFIA, 2001).

In March 1994, a follow-up workshop was convened by the Plant Products Division (PPD) of Agriculture Canada with the objective of reviewing the regulations that had been

redrafted following the November 1993 workshop. The PPD wanted an expert review of specific guidelines that had been developed to provide for the unconfined release of new canola and flax varieties prior to the regulations being released (Agriculture Canada, 1994). The PPD called the members of the Plant Biotechnology Advisory Committee[2] together to provide their insights. Although this workshop focused on the unconfined release for canola and flax, the group also held initial discussions regarding the unconfined release for corn, soybeans, potatoes and *rapa* canola. The feedback from the committee members was incorporated into the document released for public comment, and the biotechnology industry believed that they had cleared the final regulatory hurdle.

In June 1994, those involved in the development of the regulatory framework were surprised and alarmed when the Feed Section of the PPD informed participants of the Plant Biotechnology Advisory Committee that they would initiate the development of their own regulatory guidelines for the use of GM plant material in livestock feed. The Feed Section sought participation by experts to form the Transgenic Plants as Livestock Feed Advisory Committee. Membership of this committee consisted of 16 experts from various involvements in biotechnology. (Environment Canada was sporadically engaged in the regulatory process at this time.) A workshop was held in Ottawa on September 21–22, 1994, and draft guidelines were developed and sent out for public comment on November 22, 1994. Twenty-five comments were received and incorporated into a revised draft of the regulations that was sent back to the members for comment. Comments were due back from committee members by March 15, 1995. It is interesting to note that the first decision document approving the unconfined release of a PNT crop (Agrevo's ammonium-tolerant canola) was approved on March 10, 1995, as this was 5 days prior to the end of the above comment period and well in advance of the final approval of regulations developed by the Feed Section. The second was given to Monsanto's Roundup® herbicide-tolerant canola on March 24, 1995. Figure 1 summarizes the involvement of the various regulatory actors over the process.

The 7-year process of developing the regulations for PNT crops was time consuming; however, the process was scientifically justified and successful, as there have been no documented problems resulting from 12 years of commercial PNT crop production in Canada. The scientific risks and the governance aspect of risk management were captured within the PNT regulatory framework. However, the process was not without challenges, as was identified by the lack of any defining characteristics regarding substantial equivalence. The regulatory mandate was, to a certain degree, unfocused, as was evidenced by the late involvement of the Feed Section. Regulatory integration of the Feed Section needed to occur in harmony with the larger actions of the PPD. The result of this scattered approach to developing PNT regulations was that the commercial release of PNTs in Canada was delayed by 1 year.

Canada's present PNT regulatory framework

Greater understanding of GM crop types exists following 12 years of production. Unfortunately, this has not facilitated improvements in the regulatory approval process for GM crops. Although there has been consistency in the decision-making process, the continued use of case-by-case assessments has resulted in a situation in which there is no identifiable regulatory template for seed developers to follow. (Case-by-case is based on the trait that has been inserted; this means that the risks may vary and, therefore, so does the regulatory focus.) This has created a scenario in which no seed developer submitting an application package for regulatory approval of a new PNT knows what or how much scientific data are required. At present, breeders submit a volume of data that they perceive to be sufficient for approval according to the application form, but fully expect the regulators to request additional information. The problem that breeders have with this process is that they have no idea of how much information is required, nor a final decision timeline, as the data request process is open-ended, and the supply of additional data can frequently result in further additional demands from regulators.

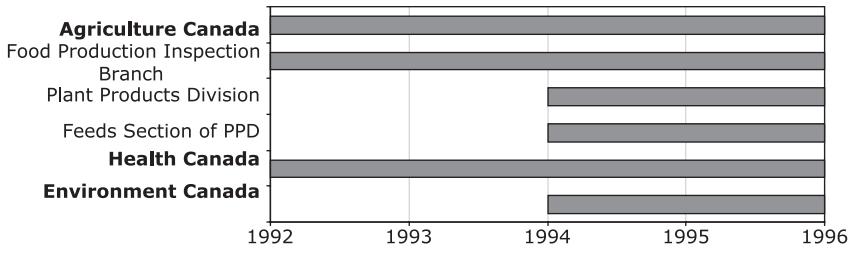

Figure 1 Regulatory actors involved in the development of regulations for plants with novel traits.

The following sections document the existing regulatory framework and highlight the specific aspects of the system that act as regulatory barriers to the commercialization of innovative PNT crop varieties.

Canadian Food Inspection Agency

To date, in Canada, most commercialized genetically engineered plants have been considered to contain novel traits, and therefore have been assessed for safety. However, the approach used by the CFIA does not mean that all PNTs are developed through genetic engineering. Novel traits can be developed through various techniques (other than genetic engineering), such as mutagenesis, somaclonal variation and other forms of what, in other countries, are considered as 'traditional' breeding. Canada does not use the breeding process as a trigger for regulation, but instead focuses on the features of the product. For example, the non-rDNA somaclonal variant Clearfield canola was considered as a PNT and regulated as such, but Normandy flax, which was also bred using somaclonal variation, was not.

Because of this, government evaluators carefully assess potential impacts before these modified plants can be released into the environment. Environmental safety assessments examine five broad categories of possible impacts of a PNT.

1. The potential of the plant to become a weed or to be invasive of natural habitats.

2. The potential for gene flow to wild relatives.

3. The potential for a plant to become a plant pest.

4. The potential impact of a plant or its gene products on non-target species.

5. The potential impact on biodiversity (CFIA, 2004b).

Because of the above definition and the subsequent assessment categories, every herbicide-tolerant variety application that the CFIA receives is treated as a PNT, regardless of the technology used to create the herbicide-tolerant variety. Although there are very few crop varieties approved with stacked traits (corn, cotton and potato), a herbicide-tolerant variety that has additional traits stacked with it, such as drought tolerance, would be given consideration for variety approval under the following CFIA directives.

1. Directive 94-08: Assessment Criteria for Determining Environmental Safety of Plants with Novel Traits.

2. Directive 95-03: Guidelines for the Assessment of Novel Feeds: Plant Sources.

3. Directive D-96-13: Import Permit Requirements for Plants with Novel Traits, and their Products.

4. Directive 2000-07: Guidelines for the Environmental Release of Plants with Novel Traits within Confined Field Trials in Canada.

Using these directives, the CFIA assesses all PNT variety applications for environmental release and use as animal feed. It is no longer possible to obtain split approval for a crop variety in Canada, where the crop would be approved for use as animal feed but not human consumption. Figure 2 provides a flowchart of the CFIA's regulatory process.

In Stage 1 of the development of a new PNT variety that is intended for unconfined environmental release and/or use as a livestock feed, the plants are required to be grown in a contained facility (i.e. glasshouse or laboratory growth chamber). Growing conditions in these types of facility follow biosafety guidelines that have been established by Health Canada and the Medical Research Council. Research institutions may develop and require that codes of practice be followed in addition to the above.

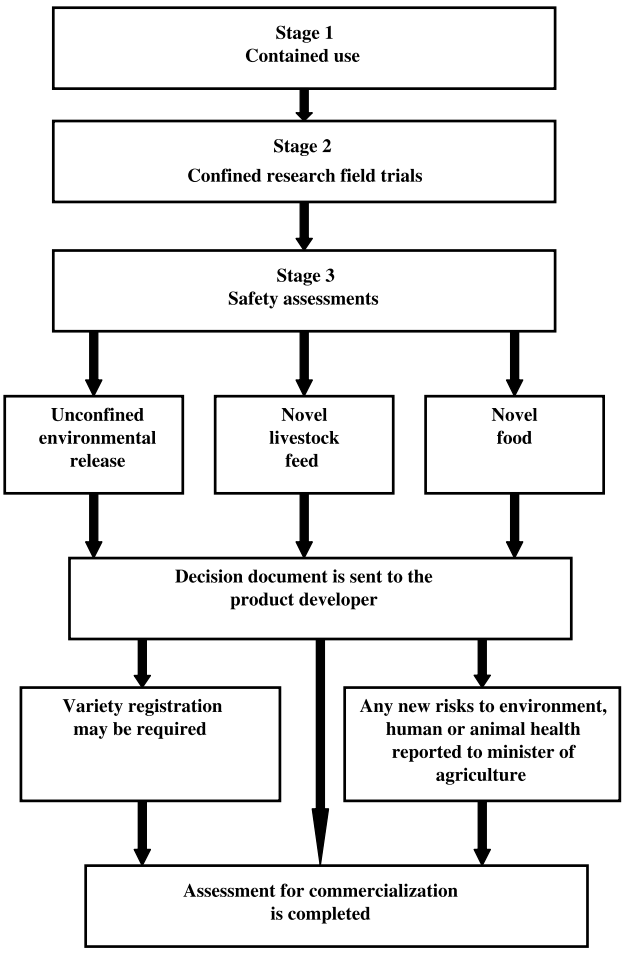

Figure 2 Regulation of plants with novel traits in Canada. Source: CFIA (2006b).

In Stage 2, the PNT variety developer must submit an application to the CFIA and receive authorization to conduct confined field trials in Canada. Directive 2000-07 is used to establish how many trials are allowed in Canada, the size of the plot and the isolation distances that are required. The CFIA notifies each province in which field trial applications have been received, and provincial authorities are given a 30-day comment period. The field trials are conducted over several years in various locations that represent potential adoption regions, and the data produced by these trials are used to provide information to the CFIA for the safety assessments in Stage 3.

The safety assessment for the new variety is conducted in Stage 3. This stage is designed to address the five priority categories listed above. To provide the necessary information to satisfy these questions, the product developer is required to submit scientific data that have been gathered from the field trials. The CFIA has a database of scientific studies that it can draw upon to review the data, and may commission additional studies if required. Peer-reviewed journal articles are also used as sources of relevant information. The scientific data that are required for the CFIA to undertake the safety assessment include: the identification and classification of the PNT; modification methods; description of the novel trait(s); environmental data; livestock feed data (nutritional, toxicity and allergenicity data) (CFIA, 2006b).

It is at this stage that the bottleneck in the system exists. The lack of a data 'roadmap' that could inform breeders about the specifics of what is required is becoming a barrier to commercialization. As the science of genetic engineering continues to advance, more knowledge about GM plants is available. This increase in knowledge about GM plants does not change the probabilities of a risk event, but does change the regulatory perceptions of a risk event. As the science of genetic engineering advances, so, too, should the regulation of the products, but the regulatory advances must be based on quantifiable increases in risk probabilities. This is not the case with the regulatory creep that is occurring in Canada.

Following the review of the scientific data, a decision document is drafted and sent to the product developer, as well as posted on the Internet. This document explains how the review took place, and provides a basis for the final decision that was rendered. If, at any point following this, additional scientific information becomes available regarding the crop variety, the product developer is required to report this information to the CFIA, who will undertake a re-evaluation based on the information. At this point, the CFIA regulation process is complete, and the product developer is eligible to apply to the CFIA for unconfined commercial production of the new PNT crop variety.

The requests for additional scientific data are coming too late in the regulatory process. This results in commercialization delays, which prevents producers from having the opportunity to adopt improved crop varieties. Smyth and Phillips (2001) estimated that, in the case of GM canola, a 2-year delay in commercialization would have cost the entire canola industry C$100 million.

Health Canada

Unlike the CFIA, which uses a product trigger, Health Canada defines novel foods as foods resulting from a process not previously used for food, products that do not have a history of safe use as a food, foods that have been modified by genetic manipulation, genetically engineered foods or biotechnology-derived foods (Health Canada, 2006a). Health Canada assesses the safety of all GM and other novel foods proposed for sale in Canada. Companies are required to submit detailed scientific data for review and approval by Health Canada before such foods can be sold, or used as animal feed if the modified feed has the potential to introduce harmful components into the portion of the animal being consumed as food.

Health Canada is also responsible for the environmental assessment of products regulated under the Food and Drugs Act, including novel foods. This activity is required by the New Substance Notification Regulations of the Canadian Environmental Protection Act (1999). Health Canada started working with Environment Canada in 2001 to develop new regulations to assess the impact on the environment and on human health of new substances used in these products. This process was known as Health Canada's Environmental Impact Initiative. However, it would appear that this initiative has stalled (Health Canada, 2006b), and that any harmonization or co-operation between the two departments has been delayed for a substantial period of time.

Health Canada does not review all foods new to the Canadian market, only those that are truly novel. Therefore, the concept of prior safe use as a food was introduced to exclude foods new to the Canadian market, which have a history of safe food use in other countries, from being the target of a novel food notification. Secondly, the concept of 'major change' was introduced into the novel food definition in order to avoid the potential of a minor processing change of triggering a novel food notification. This approach intended to restrict novel food notifications caused by the introduction of new processes only to those that were truly

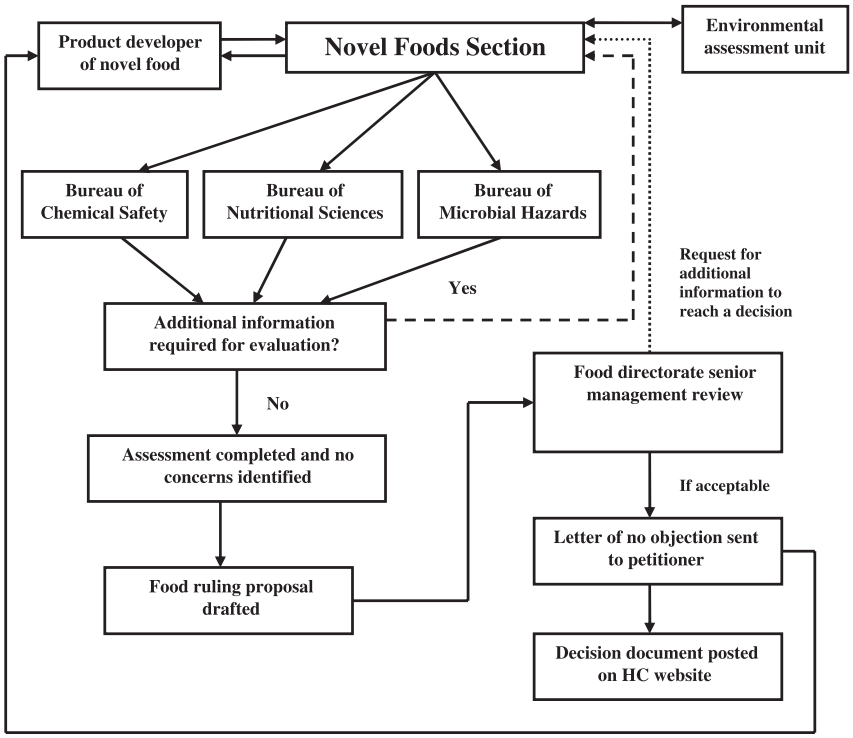

Figure 3 Novel food notification/submission. Source: Health Canada (2006d).

new and caused substantial changes in the composition of the food.

A major change with respect to a food is defined as a change peripheral to the manufacturer's experience or generally accepted nutritional or food science theory. This would place the modified food outside the accepted limits of natural variations for that food with regard to the following.
1. The composition, structure or nutritional quality of the food or its generally recognized physiological effects.
2. The manner in which the food is metabolized in the body.
3. The microbiological safety, chemical safety or safe use of the food (Health Canada, 2006c).

The challenge of this approach is that the transparency regarding the required submission of scientific data for regulatory approval is even less than that of the CFIA's process. The less precedence there is of the use of a novel food product, the less transparency.

Regulators at Health Canada take the data from the field trials conducted by the product developer that relate to the category for novel foods in Figure 1. This is when the nutritional, toxicity and allergenicity data are reviewed and assessed. Additional data are needed to satisfy risk assessments regarding dietary exposure, metabolization and microbiological safety. One salient feature of the Health Canada regulatory process is its use of experience from other jurisdictions. If a PNT product has a history of safe production and consumption in another country, this is admissible as data for regulatory approval in Canada. Health Canada is unique amongst the PNT regulatory bodies in this context, as the CFIA and Environment Canada will not allow a history of safe production and consumption elsewhere as admissible data. Figure 3 provides the Health Canada regulatory process.

Health Canada has established criteria for the assessment of novel foods that provide information to establish the safety of the novel food. Written notification is required at least 45 days prior to the sale or advertising for sale of any novel food. Health Canada is required to respond within 45 days of receipt of the notification regarding its acceptability for sale. If additional information is required to properly establish the safety of the product, such information will be requested in writing and the clock is stopped. The applicant is not permitted to sell or advertise the product until the additional information requirement is fulfilled and Health Canada has agreed to the acceptability of the product.

Once the Novel Foods Section of Health Canada receives the application for a new PNT food product from the product developer, there are four reviews required. The product developer needs to address environmental safety, chemical safety, nutritional changes/stability and microbial hazards.

Once the scientific review of the data is complete, Health Canada can request additional information, which then requires another scientific review of the new data. If there are no requests at this point, a draft ruling is developed by the

Novel Foods Section, which then goes up the bureaucratic ladder for review. Senior management within Health Canada has the right to request additional information from the product developer at this stage, and this process would trigger another scientific review. If the drafted proposal is acceptable, a letter is sent to the product developer about this, and the Decision Document is posted on the Internet. At this point, the product developer may safely market the PNT product or crop variety.

Again, it is the requests for additional information that act as a commercialization barrier. The risk spectrum would appear to be limitless when dealing with novel foods, and this greatly frustrates breeders. Many of the scientific advances in the detection of food risks now allow for testing to be performed at previously undetectable levels. This raises the cost of regulatory approval, as breeders have to conduct additional research to be able to quantify the new risk detection levels. This would not be an issue for breeders (or certainly less of one) if there were peer-reviewed articles in existence that quantified the need for greater risk detection levels. Unfortunately, these articles do not exist and the increased regulatory scrutiny would appear to be less risk-based.

Environment Canada

Environment Canada regulates products of biotechnology using the New Substances Notification Regulations of the Canadian Environmental Protection Act (1999). Environment Canada uses this legislation to anticipate and prevent the introduction of new substances that may pose unacceptable risks to human health and the environment. The New Substances Notification Regulations is a federal initiative designed to respond to concerns over recent growth in the diversity and quantity of commercially available substances. As part of a 'cradle-to-grave' management approach to toxic substances, the provisions for substances new to Canada are intended to ensure that no new substance is introduced into the marketplace before an assessment of its toxicity has been completed. 'Toxicity', as defined in the Canadian Environmental Protection Act (1999), refers to risk to human health or the environment (Environment Canada, 2007). Features of the new substances programme include criteria for identifying new substances, a mechanism for assessing new substances and, when necessary, the enabling powers to implement specific controls.

A 'substance' is defined by the Canadian Environmental Protection Act (1999) as including animate matter, i.e. organisms (Environment Canada, 2005). A 'new' substance is a substance that is not listed on the Domestic Substances List (DSL). The DSL is a compilation of substances that were in commerce between January 1, 1984 and December 31, 1986, according to the criteria set out in the Canadian Environmental Protection Act (1999). An eligible organism is one that was in use in Canada between 1984 and 1986, such that its entry into the environment was unrestricted. The DSL is the sole standard against which a substance is judged to be 'new' to Canada. With few exceptions, any substances not on this list are considered to be new, and Environment Canada must be notified prior to importation or manufacture. Although there are 35 existing biotechnology substances listed on the DSL, products derived from biotechnology are classified as 'new substances' under the Canadian Environmental Protection Act (1999).

The assessment process is initiated when Environment Canada receives a new substance notification prepared by the product developer that proposes to import or manufacture a substance. New substance notifications must contain all required administrative and technical data and must be provided to Environment Canada prior to manufacture or import. Notification information is jointly assessed by the Departments of Environment and Health to determine the potential adverse effects of the substance on the environment and human health. This assessment, which must be completed within a time specified by the New Substances Notification Regulations, will result in the following.

1. A determination that the substance is not suspected of being toxic.

2. A suspicion that the substance is toxic, which may require: (i) controls on, or prohibition of, import and manufacture; or (ii) prohibition pending submission and assessment of additional information determined to be required by the Departments.

3. Limiting the purpose for which a substance may be used to permit the waiver of information requirements (Environment Canada, 2005).

The regulations covering chemical or polymer substances have been in effect since July 1, 1994, and those covering biotechnology substances, including organisms or products of microorganisms, have been in effect since September 1, 1997.

Figure 4 provides a flowchart of Environment Canada's regulatory framework.

New substances that require regulation under the DSL are divided between Environment Canada and Health Canada. Health Canada reviews the scientific data that relate to human exposure and potential human toxicity risks. Environment Canada reviews the scientific data that relate to non-human risks. Following a review of the data, officials from both

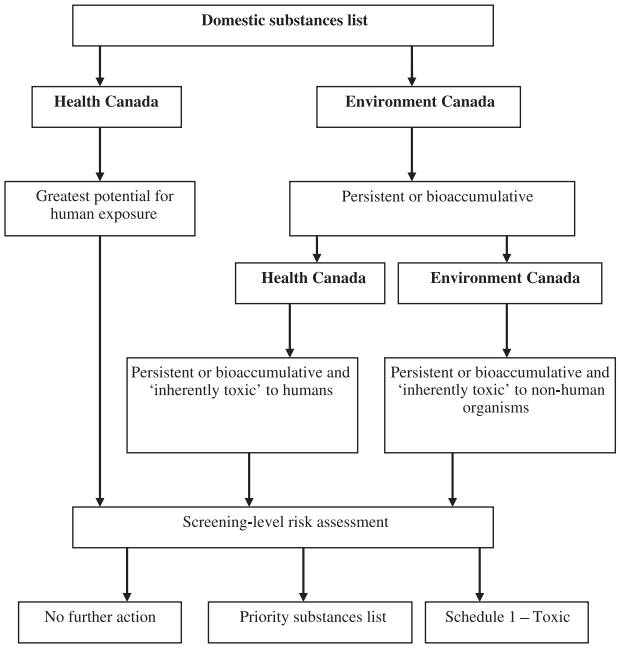

Figure 4 Domestic substances list regulatory process.
Source: Environment Canada (2005).

departments meet to determine the level of risk assessment, which can result in three potential courses of action. The first is that the new substance is deemed to be safe, which requires no further action to be taken by regulators. The second outcome is that a level of risk has been identified and the new substance is placed on the list of priority substances. The final outcome is that the new substance is identified as a toxic substance (e.g. polychlorobiphenyls, PCBs) and placed on the toxic substances list, which means that the substance is to be eliminated and prevented from entering the environment.

Of the three regulatory agencies, Environment Canada is the least engaged with the PNT process. The lack of transparency regarding scientific data requests applies largely to the CFIA and Health Canada. However, there have been concerns expressed by developers of microbial biotechnology regarding the Environment Canada assessment process; it has limited application to issues related to the PNT regulatory process.

Conclusions

The Canadian regulatory system for innovative crop-based technologies is founded in science, and has been proven to be efficient in ensuring that any risks have been prevented from becoming anything more than a statistical probability. The investment that was spent in drafting the regulations over a decade ago has provided a return many times over, as the adoption rates of GM canola, corn and soybeans has been very high, thereby providing benefits to Canadian producers with no documented damage to health or the environment. Although this process was necessary to commercialize the initial GM varieties, the time has come to revisit these regulations.

The rigours of the regulatory requirements, in terms of the cost of conducting the studies necessary to gather sufficient data to meet the demands of the regulators for aspects such as gene flow, allergenicity and toxicity, are pushing public researchers out of the variety development industry. Public research institutions have limited budgets and simply do not have the finances to undertake the expensive research required to satisfy regulators. The concern within the seed development industry is that the commercialization of new traits will only be performed by large multinational seed developers, thereby having a potentially large negative impact on the continuing development of crop varieties that are best situated for Canada, such as canola.

There is justified concern about the increase in regulatory requirements for GM crop varieties, as this increase in regulation is not justified by any increase in risk. The correlation between innovative GM or PNT crop varieties and increased risks to human safety has not been scientifically documented. As the scientific capability to detect an increasing number of potential risk factors increases, Canadian regulators are, in some ways, acting like a sponge by simply increasing all of the regulatory requirements without relinquishing any risk factors that have been consistently addressed through 15 years of research and commercial use. At some point, the regulatory system will have to decide which risk factors can be efficiently addressed, as the process of trying to address each and every existing and new risk factor will stretch the regulatory capacity far beyond economic efficiency, resulting in costly commercialization delays.

References

Agriculture Canada (1992) *Letter of Invitation to Participate*. *Mimeograph.* Ottawa, ON: Queen's Printer.

Agriculture Canada (1994) *Plant Biotechnology Advisory Committee: Summary of Proceedings*. Ottawa, ON: Queen's Printer.

Canadian Agricultural Research Council (1988) *Proceedings of the Workshop on Regulation of Agricultural Products of Biotechnology*. Ottawa, ON: Canadian Agricultural Research Council.

Canadian Food Inspection Agency (CFIA) (2000) *Procedures for the Registration of Crop Varieties in Canada*. URL http://www.inspection.gc.ca/english/plaveg/variet/proced/regenr_promode.shtml#4 [accessed on 12 February 2007].

Canadian Food Inspection Agency (CFIA) (2004a) *Directive 2000-07: Conducting Confined Research Field Trials of Plants with Novel*

Traits in Canada. URL http://www.inspection.gc.ca/english/plaveg/bio/dir/dir0007e.shtml [accessed on 25 April 2005].

Canadian Food Inspection Agency (CFIA) (2004b) *Directive 94-08: Assessment Criteria for Determining Environmental Safety of Plants with Novel Traits*. URL http://www.inspection.gc.ca/english/plaveg/bio/dir/dir9408e.shtml [accessed on 4 December 2004].

Canadian Food Inspection Agency (CFIA) (2005a) *Regulation of Agricultural Biotechnology in Canada*. Ottawa: Queen's Printer.

Canadian Food Inspection Agency (CFIA) (2005b) *How are Plants with Novel Traits Assessed for their Long Term Safety by the Canadian Food Inspection Agency (CFIA)?* URL http://www.inspection.gc.ca/english/sci./biotech/reg/equive.shtml [accessed on 12 February 2007].

Canadian Food Inspection Agency (CFIA) (2006a) *Seed Regulatory Framework Modernization Including Adjustments to the Variety Registration System*. URL http://www.inspection.gc.ca/english/plaveg/variet/revetu/prepo06e.shtml [accessed on 10 January 2007].

Canadian Food Inspection Agency (CFIA) (2006b) *Regulation of Agricultural Biotechnology in Canada an Educator's Resource*. URL http://www.inspection.gc.ca/english/sci./biotech/General/educ_postsece.shtml [accessed on 27 February 2006].

Canadian Food Inspection Agency (CFIA) (undated)*Workshop on Regulating Agricultural Products of Biotechnology*. URL www.inspection.gc.ca [accessed on 13 November 2007].

Environment Canada (2005) *A Guide to Understanding the Canadian Environmental Protection Act, 1999*. URL http://www.ec.gc.ca/CEPARegistry/the_act/guide04/s5.cfm [accessed on 22 February 2007].

Environment Canada. (2007) *Overview of CEPA 1999*. URL http://www.ec.gc.ca/CEPARegistry/gene_info/Overview.cfm [accessed on 27 February 2007].

Harrison, B. (2001) Regulating novel foods in Canada. *Presentation to the Conference on the Convergence of Global Regulatory Affairs: its Potential Impact on International Trade and Public Perception, March 19–20, 2001, Saskatoon, SK, Canada*.

Health Canada (2001) *Action Plan of the Government of Canada*. URL http://www.hc-sc.gc.ca/sr-sr/pubs/gmf-agm/substan_table_e.html [accessed on 19 February 2007].

Health Canada (2006a) *Genetically Modified (GM) Foods and Other Novel Foods*. URL http://www.hc-sc.gc.ca/fn-an/gmf-agm/index_e.html [accessed on 19 February 2007].

Health Canada (2006b) *Environmental Impact Initiative*. URL http://www.hc-sc.gc.ca/ewh-semt/contaminants/person/impact/about-impact/index_e.html [accessed on 6 March 2007].

Health Canada (2006c) *Guidelines for the Safety Assessment of Novel Foods*. URL http://www.hc-sc.gc.ca/fn-an/legislation/guide-ld/nf-an/guidelines-lignesdirectrices_e.html [accessed on 6 March 2007].

Health Canada (2006d) *Processing a Novel Food Notification/Submission in the Food Directorate*. URL http://www.hc-sc.gc.ca/fn-an/legislation/guide-ld/novel_notification-avis-nouveaux_e.html [accessed on 8 March 2007].

Kennett, J., Fulton, M., Molder, P. and Brooks, H. (1998) Supply chain management: the case of a UK baker preserving the identity of Canadian milling wheat. *Supply Chain Manage*. **3** (3), 157–166.

McHughen, A. (2000) *Pandora's Picnic Basket*. Oxford: Oxford University Press.

Smyth, S. and Phillips, P.W.B. (2001) Competitors co-operating: establishing a supply chain to manage genetically modified canola. *Int. Food Agribus Manage Rev*. **4**, 51–66.

Smyth, S. and Phillips, P.W.B. (2002) Product differentiation alternatives: identity preservation, segregation and traceability. *Agbioforum*, **5** (2), 30–42.

Smyth, S., Phillips, P.W.B., Kerr, W.A. and Khachatourians, G.G. (2004) *Regulating the Liabilities of Agricultural Biotechnology*. Wallingford: CABI Publishing.

The Royal Society of Canada (2001) *Elements of Precaution: Recommendations for the Regulation of Food Biotechnology in Canada*. URL http://www.rsc.ca//files/publications/expert_panels/foodbiotechnology/GMreportEN.pdf [accessed on 7 August 2007].

