# Development and Implementation of the Canadian Approach to Regulation of Plants with Novel Traits

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## Abstract

The Canadian Federal Framework for Biotechnology Regulation sets down principles for the regulation of biotechnology products. One principle is that existing legislation and regulatory expertise should be used. Agriculture and Agri-Food Canada has a long history of regulation of plant products, both with respect to variety registration under the *Seeds Act*, plant import and export under the *Plant Protection Act* and livestock feed safety and nutritional efficacy under the *Feeds Act*. Health Canada on the other hand using the *Food and Drugs Act* has a long history of expertise in evaluating food safety. These two Departments are responsible for evaluating the safety of Plants with Novel Traits(PNTs).

The *Canadian Environmental Protection Act*, another key piece of legislation, contains the definition of "Biotechnology" used by all federal departments. It also contains a requirement that any person "manufacturing or importing" into Canada a "Substance New to Canada" must notify Environment Canada (unless this requirement is met under other legislation, as is the case with PNTs under the Seeds Act) and provide them with information that allows a determination of environmental safety. It is here that the concept of regulating "novel" products is firmly entrenched. Any plant that is novel (New to Canada) is therefore subject to notification and assessment, no matter how that plant was derived. Novelty is determined at the species, trait and use levels, and at the level of gene constructs in the case of those PNTs derived through recombinant DNA (rDNA) techniques. Novel herbicide tolerance in a crop species is an example of a novel trait that can be introduced into a crop plant species through use of a variety of techniques including wide crosses, mutation breeding and rDNA.

There is a step-wise approach to the regulation of PNT. Prior to authorization for release into the environment for "confined" field testing, they are subject to an environmental assessment. A more in depth assessment prior to authorization for "unconfined" release is required before they can be released commercially. In the case of crop plants that are used for food and for livestock feed, approval for food safety (Health Canada) and livestock feed safety must also be obtained.

## Introduction

This paper discusses the regulation of "Plants with Novel Traits" (PNTs) in Canada, with particular attention paid to environmental safety. While this discussion is spe-

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cific to plants, the approach is equally applicable to other organisms and biotechnology products.

A fundamental consideration in developing the Canadian regulatory approach has been, where possible, to use existing agricultural statutes and expertise, and not to duplicate regulatory efforts under different legislation. The Federal Departments involved in regulating PNTs are Agriculture and Agri-Food Canada using the *Seeds Act, Plant Protection Act* and *Feeds Act,* and Health Canada using the *Food and Drugs Act.* Environment Canada under the *Canadian Environmental Protection Act (CEPA),* regulates new substances not regulated by other Acts of Parliament. The *CEPA* is not triggered when these other Acts require notification and an assessment of whether the new substance is toxic prior to its manufacture or importation into Canada.

In the *CEPA* the definition of "biotechnology" used by Canadian regulatory agencies is as follows:

"Biotechnology means the application of science and engineering in the direct or indirect use of living organisms or parts or products of living organisms in their natural or modified forms".

This definition is clearly much broader than recombinant DNA technology alone, and can be interpreted to mean the application of any technology (science and engineering) to living organisms, their parts or products.

It is the *CEPA* that lays the foundation for assessing the safety of new or "novel" substances in Canada, and Health Canada and Agriculture and Agri-Food Canada under their legislation have embodied this concept through the development of regulations and safety assessment procedures for the food, livestock feed and environmental safety assessment of "Plants with Novel Traits" (PNTs).

## Regulate what? - thoughts in retrospect

The development of new plant types through rDNA techniques has generated a great deal of discussion about weeds and weediness. Keeler (1989) suggested that the greatest hazard expected from plant agricultural biotechnology is the anticipated production of serious weeds. A brief consideration of weeds and weediness then can serve as a useful example for determining which plants are novel and so require a safety assessment.

A weed may be considered a plant in a place where humankind considers it shouldn't be, and these places may include agricultural and non-agricultural habitats (Rissler and Mellon, 1993). Others consider a weed to be a plant that is objectionable and unwanted in ecosystems disturbed by humans (Baker, 1965). In our assesment of PNTs, we consider whether a plant may be objectionable (weedy) in managed ecosystems, or an aggressive plant that displaces other species in natural ecosystems in which case it is considered invasive. For example, wild oat (*Avena fatua*) is a very successful weed of arable agricultural lands in Canada, but has not been invasive of natural habitats. Purple loosestrife (*Lythrum salicaria*) is invasive of natural wetlands and has caused considerable ecosystem changes in some parts of Canada, but would not be considered a weed. Both species were introduced into North America, and both have characteristics that are well suited to the environments they inhabit, one managed and constantly disrupted by humankind, the other unmanaged, or natural.

A "confounding" aspect on the discussion about "weediness" has been the much raised concern about "risk" of outcrossing, especially when the novel trait introduced into plants is a novel herbicide tolerance, i.e., "transgenic herbicide tolerant crop plants." Of course, from "nature's" perspective the risk of outcrossing is a benefit, not a hazard. Within a species, and on occasion but at low frequencies, among related species and genera, outcrossing provides a mechanism to quickly share genes that could be advantageous in a given environment. Outcrossing is natural and normal, nonetheless the biosystematic study of a species and potential for gene flow both within the species and among related species is essential if we are to assess "unintended" undesirable effects resulting from release into the environment of PNTs of that species. Cultivated oat (*Avena sativa*) with a novel herbicide tolerance could pass the trait to its close and weedy relative wild oat (*A. fatua*) which in an agroecosystem where it is controlled by herbicides would benefit from an additional herbicide tolerance trait; an undesirable "unintended" but anticipated effect. If herbicide tolerance is designated as a characteristic of weediness, then such a plant could be considered more weedy. Herbicide tolerance obtained from a close relative by *L. salicaria* is likely to have no consequence unless challenged by the herbicide; an "unintended" event with no effect, unless it is decided to intervene through eradication measures (management) that might include the use of herbicides.

Focusing more closely on novel herbicide tolerance in crop plants, Mikkelsen *et al.* (1996) reported introgression of genes from transgenic cultivated BASTA herbicide-tolerant *Brassica napus* into its close and weedy (in Denmark) relative, *B. campestris (B. rapa)*. Accepting in this discussion that herbicide tolerance is a characteristic of weediness, then the resulting BASTA-tolerant *B. campestris* plants may clearly be more weedy and problematic (in some environments). But what if the BASTA-tolerant *B. napus* had been developed through means other than rDNA, for example, through a wide cross with embryo rescue, mutation breeding or somaclonal variation? Would not the potential for increased weediness in *B. campestris* be the same? Should not such a crop variety be evaluated for potential negative environmental impact in the same manner as an rDNA derived plant? In Canada we developed a *B. napus* variety through somaclonal variation to exhibit tolerance to imidazolinone herbicides. Considered as a PNT since there were no distinct stable populations (variety) of the species with this herbicide tolerance in Canada, it was subjected to the same regulatory safety assessment as *B. napus* varieties developed to exhibit novel herbicide tolerance through rDNA technologies.

The National Academy of Sciences (1987) suggests that "no conceptual distinction exists between genetic modification of plants and microorganisms by classical methods or by molecular methods that modify DNA and transfer genes." Regal (1994), however, arguing that rDNA technology is *not* basically the same as traditional domestication, introduced a pragmatic perspective to the discussion by suggesting that most genetic engineering projects involve the introduction of non-adaptive traits into ecologically incompetent hosts, but that the technology has more potential to be "misused" (Regal's emphasis) than does traditional breeding. It is those projects in which novel adaptive traits are added to an ecologically competent host that could create unusual, ecologically high-risk organisms.

Clearly, through the use of today's sophisticated "classical" crop development technologies, it is possible to develop new crop plant types that may be substantially non-equivalent with respect to both environmental and food safety to their counterparts we have been using for years. From these considerations comes the principle that it is the nature of the organism and the environment into which it will be introduced that determines whether the organism should be evaluated, not the process by which the product is obtained.

It is for these reasons that the Canadian regulatory approach has been designed to consider novelty, and so can be considered truly "product"-based.

## Determining whether a plant is novel

Health Canada considers that "Novel foods may include;

- products and processes that have not previously been used before as food or to process food in Canada,
- food containing microorganisms that have not previously been used as food or to process food,
- products and processes that have previously not been used before as foods that result from genetic modification and exhibit new or modified characteristics that have previously not been identified in those foods, or that result from production by organisms exhibiting such new or modified characteristics, or
- food that is modified from the traditional product or is produced by a process that has been modified from the traditional process."

Agriculture and Agri-Food Canada embodies the same concept within the proposed definition of a novel trait in a plant as: a characteristic that;

- has been intentionally selected, created or introduced into a distinct stable population of cultivated seed of the same species through a specific genetic change, and,
- based on valid scientific rationale, is not substantially equivalent, in terms of its specific use and safety both for the environment and for human health, to any characteristic of a distinct, stable population of cultivated seed of the same species in Canada, having regard to weediness potential, gene flow, plant pest potential, impact on non-target organisms and impact on biodiversity."

Whether or not a plant has novel traits is determined using the concepts of "familiarity" and "substantial equivalence." Familiarity can be thought of as a "coarse" filter or decision tree;

1. has the plant species already been grown/released into the environment in Can-

ada?

2. is the trait similar to those already introduced into the plant species previously released in Canada?
3. has the development method been used before in the plant species previously released in Canada?
4. will cultivation practices be similar to those previously used for this plant species in Canada?

If the answer is "no" to any of these, then the plant is novel and a review is required. If the answers to all questions is "yes", the "fine" filter or decision tree of substantial equivalence when compared to similar plants in use in Canada is applied. The following points address substantial equivalence:

1. In the case where the trait has been introduced via rDNA methodologies, are the specific genetic elements the same as those previously approved by Agriculture and Agri-Food Canada in the same species? and
2. Is it known that this plant will not result in altered environmental interactions compared to its counterpart(s); this based on data or sound scientific rationale? Consider;
   - potential for the PNT to become a weed of agriculture or be invasive of natural habitats
   - potential for gene flow to wild relatives whose hybrid offspring may become more weedy or more invasive
   - potential for the PNT to become a plant pest
   - potential impact of the PNT or its gene products on non-target species, including humans
   - potential impact on biodiversity

If the response to either of these is "no," then the plant is considered a PNT and is subject to an environmental assessment. If "yes," then it is regulated in the same way as its counterparts. Under this system, responsibility is placed on the developers of new plant types; they must know their products.

## The safety assessment of plants with novel traits

Safety assessments of PNTs in Canada follow very similar steps to those applied by other national regulatory agencies. A thorough characterization of the PNT is essential. How were the novel attributes introduced? If genes were introduced from other species, what are the attributes of donor organisms, e.g., toxicological and allergenic properties ? What new proteins are produced? What are the properties of these new proteins, and at what levels, in what tissues, and how stable is their production? A complete characterization should meet the requirements of all regulatory agencies, and from this, concerns specific to the environmental, food and livestock feed safety questions are then identified. The fundamental components of the environmental assessment are a consideration of the biology and ecology in Canada of the host plant species, and the novel attributes of the PNT. Do the new proteins alter the biology/ecology of the novel plant? Do the new proteins themselves result in different interactions with other organisms in the environment? Comparing the novel plant with counterparts in use in Canada is key to the assessment process, and for this purpose a series of "biologies" of crop plant species in Canada is being developed. These describe the potential for outcrossing to plants of the same or related species, weediness, invasiveness and pest potential in Canada, and set baseline standards with which the PNTs of these species can be compared. Concerns arising from the characterization about food and livestock feed safety and efficacy are addressed through consideration of the properties of any new proteins, and through a determination of substantial equivalence with respect to the known attributes of the crop plant.

## Regulated release of plants with novel traits into the environment

The importation of a PNT into Canada requires an import permit under the *Plant Protection Act.* Release of PNTs into the environment then follows a stepwise approach. Developers of PNTs follow Medical Research Council guidelines (Anonymous, 1996) for research conducted in "contained" facilities, such as properly constructed greenhouses, growth chambers and laboratories.

Preliminary field releases are conducted under "confined" conditions which minimize the potential for movement of plant, pollen and seed outside of the test site. The biology of the host species plays a key role in determining confinement conditions, especially the reproductive isolation requirements. Authorization from Agriculture and Agri-Food Canada is required to field test PNTs under confined conditions. The guidelines, "Confined Testing of Plants with Novel Traits in Canada," detail the information that must be submitted and fall into five sections;

1. information about the persons responsible for the proposed release
2. information about the host plant species (not required if already published as part of the "biology" series)
3. information about the novel traits
    - how they were introduced into the plant
    - information on all donor organisms
    - information about novel proteins
4. information about the proposed testing site
    - exact location
    - proximity to ecologically important sites
    - presence of endangered species

5. trial protocol
   - duration of trial
   - proposed isolation measures
   - seeding and harvesting procedures
   - monitoring timetables
   - proposed post-trial cropping and monitoring plans

Agriculture and Agri-Food Canada informs all Canadian provincial authorities about the trials planned within their jurisdictions, and time is given for provincial government officials to ask further questions or raise objections. Following a favorable outcome of the assessment, the confined trial is authorized with specified conditions. Table 1 shows the number of submissions (specific plants with novel traits) by plant species and that have been approved from 1988 to the present time. Table 2 shows submissions by trait, and Table 3 submissions by development method.

Before a PNT may become commercialized it must undergo an environmental evaluation to determine its environmental safety when grown without conditions of confinement. "Assessment Criteria for Determining the Environmental Safety of Plants with Novel Traits" and species "biology" companion documents provide information on how to make a submission for authorization for "unconfined" release(Table 4). A complete characterization of the products as previously described is essential. The information requirements have been developed to consider five assessment criteria;

1. potential for the PNT to become a weed of agriculture or be invasive of natural habitats,
2. potential for gene-flow to wild relatives whose hybrid offspring may become more weedy or more invasive,
3. potential for the PNT to become a plant pest,
4. potential impact of the PNT or its gene products on non-target species, including humans, and
5. potential impact on biodiversity.

These criteria are addressed through the PNT characterization, and focus on the potential for altered environmental interactions resulting from both intended and unintended modifications to the biology of the host plant, and from the novel proteins themselves.

Developers of PNTs are encouraged to seek authorization for unconfined release before they intend to conduct multi-location replicated cooperative yield trials since otherwise they will be subject to confined field testing regulations. Prior to commercialization the PNT must also have received approval from Health Canada if it is to be used as food, and from Agriculture and Agri-Food Canada if it is to be used as livestock feed. At no time during the development process may any material derived from plantings of these PNTs be used as food for humans or for livestock feed unless these required approvals have been received from Health Canada and Agriculture and Agri-Food Canada.

## Conclusion

The Canadian approach of regulating "Plants with Novel Traits" as described offers the benefits of both environmental responsibility and regulatory resource efficiency. Novel plants with similar attributes, no matter how derived, are assessed for environmental, food and livestock feed safety, yet efficiencies are achieved by removing the necessity of assessing the safety of the same product types over and over again simply because they result from specific development technologies. The step-wise approach allows for flexible timing of environmental, food and feed safety authorizations as the novel product approaches commercialization. Together, the "novel substance" approach and "step-wise release" result in a minimum of regulatory burden on developers of Plants with Novel Traits while maintaining responsible regulatory oversight of these products.

## References


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**Table 1** Authorized submissions for confined release by plant species

| | 1988 | 1989 | 1990 | 1991 | 1992 | 1993 | 1994 | 1995 | 1996 |
|---|---|---|---|---|---|---|---|---|---|
| Alfalfa (*Medicago sativa*) | - | 1 | 2 | 2 | 6 | 7 | 6 | 8 | 26 |
| Broccoli (*Brassica oleraceae*) | - | - | - | - | - | - | | 1 | 1 |
| Brown mustard (*B. juncea*) | - | - | - | - | - | - | 1 | 2 | - |
| Ethiopian mustard (*B. carinata*) | - | - | - | - | - | - | - | - | 1 |
| Cherry (*Prunus avium*) | - | - | - | - | - | - | - | - | 1 |
| Canola (*B. napus*) | 8 | 21 | 26 | 29 | 23 | 51 | 59 | 58 | 53 |
| Canola (*B. rapa*) | - | - | - | - | - | 7 | 11 | 12 | 19 |
| Corn (*Zea mays*) | - | - | 2 | 1 | - | 6 | 8 | 18 | 13 |
| Flax (*Linum usitatissimum*) | 2 | 4 | 3 | 2 | 3 | 3 | 4 | 4 | - |
| Grape vine (*Vitis vinifera*) | - | - | - | - | - | - | - | - | 1 |
| Japanese trefoil (*Lotus japonicus*) | - | - | - | - | - | - | 2 | - | - |
| Potato (*Solanum tuberosum*) | - | - | 3 | 4 | 5 | 7 | 12 | 14 | 19 |
| Soybean (*Glycine max*) | - | - | - | - | 1 | 3 | 2 | 4 | 2 |
| Strawberry (*Fragaria x Ananassa*) | - | - | - | - | - | - | 1 | 1 | 1 |
| Tobacco (*Nicotianum tabaccum*) | - | 1 | 3 | 1 | 2 | 5 | 4 | 1 | 4 |
| Tomato (*Lycopersicon* sp.) | - | 1 | 1 | - | - | - | - | - | 1 |
| Barley (*Hordeum vulgare*) | - | - | - | - | - | - | - | 1 | - |
| Wheat (*Triticum aestivum*) | - | - | - | - | - | - | 2 | 3 | 1 |
| TOTAL | 10 | 28 | 40 | 39 | 40 | 89 | 113 | 127 | 143 |

**Table 2** Authorized submissions for confined release by novel trait

| | 1988 | 1989 | 1990 | 1991 | 1992 | 1993 | 1994 | 1995 | 1996 |
|---|---|---|---|---|---|---|---|---|---|
| Novel herbicide tolerance | 5 | 23 | 29 | 30 | 26 | 51 | 65 | 63 | 60 |
| Male sterility/restoration | - | - | - | 3 | 3 | 6 | 11 | 9 | 9 |
| Insect resistance | - | - | - | 1 | 3 | 9 | 13 | 21 | 16 |
| Nutritional change | 2 | 2 | 2 | - | 1 | 11 | 2 | 3 | 10 |
| Modified oil composition | 1 | - | - | - | 1 | 9 | 8 | 23 | 19 |
| Virus resistance | - | - | 3 | 5 | 3 | 5 | 9 | 9 | 9 |
| Stress tolerance | - | - | - | - | 5 | 7 | 14 | 13 | 21 |
| Fungal resistance | - | - | - | - | - | 2 | - | 4 | 9 |
| Pharmaceutical | - | - | - | - | - | - | 1 | 2 | 4 |
| Industrial proteins | - | - | - | - | - | - | - | - | 3 |
| Genetic research | 2 | 3 | 6 | 4 | 2 | 1 | 4 | 14 | 5 |

note: cumulative totals are greater than actual submission numbers as individual submissions may include more than one novel trait

**Table 3** Authorized submissions for confined release by development method

| | 1988 | 1989 | 1990 | 1991 | 1992 | 1993 | 1994 | 1995 | 1996 |
|---|---|---|---|---|---|---|---|---|---|
| Biolistics | - | - | 2 | - | 1 | 4 | 8 | 20 | 14 |
| Mutagenesis | - | 2 | 2 | 2 | - | 2 | 2 | 3 | 1 |
| Direct DNA uptake | - | - | - | - | - | 3 | 2 | 2 | 1 |
| *Agrobacterium tumefaciens*-mediated transformation | 10 | 26 | 36 | 37 | 39 | 73 | 93 | 92 | 108 |
| Hybridization | - | - | - | - | - | 7 | 8 | 10 | 19 |
| TOTAL | 10 | 28 | 40 | 39 | 40 | 89 | 113 | 127 | 143 |

note: PNTs derived through hybridization are those in which a novel trait has been introduced from a related species, e.g., from *Brassica napus* into *B. rapa*

**Table 4** Unconfined release of Plants with Novel Traits authorized to July 1, 1996

| | | | | |
|---|---|---|---|---|
| HCN92, canola (*Brassica napus*) | AgrEvo | Herbicide-tolerant | Tr | Env/Food/Feed |
| GT73, canola (*B. napus)* | Monsanto | Herbicide-tolerant | Tr | Env/Food/Feed |
| NS738/1471/1473, canola (*B. napus*) | Pioneer Hi-Bred | Herbicide-tolerant | Mu/So | Env/Food/Feed |
| MS1/RF1, canola (*B. napus*) | PGS | Novel hybrid system | Tr | Env/Food/Feed |
| GT-40-3-2, soybean (*Glycine max*) | Monsanto | Herbicide-tolerant | Tr | Env/Feed |
| NL Russet Burbank, potato (*Solanum tuberosum*) | Monsanto | Bt insect-resistant | Tr | Env/Food/Feed |
| GT200, canola (*B. napus*) | Monsanto | Herbicide-tolerant | Tr | Env |
| High lauric acid canola (*B. napus*) | Calgene | Modified oil | Tr | Env/Food/Feed |
| Event 176, Corn (*Zea mays*) | Ciba Seeds /Mycogen | Bt insect-resistant | Tr | Env/Food/Feed |
| Corn (*Z. mays*) | Pioneer Hi-Bred | Herbicide-tolerant | Mu/So | Env/Food/Feed |
| HCN28, canola (*B. napus*) | AgrEvo | Herbicide-tolerant | Tr | Env |
| Corn (*Z. mays*) | Northrup King | Bt insect-resistance | Tr | Env |
| Corn (*Z. mays*) | BASF | Herbicide-tolerant | So | Env |
| Corn (*Z. mays*) | AgrEvo | Herbicide-tolerant | Tr | Env |
| CDC Triffid, Flax (*Linum usitatissimum*) | University of Saskatchewan | Herbicide-tolerant | Tr | Env/Feed |

Note; Tr = derived through rDNA, Mu/So = derived through mutation and somaclonal variation, So = derived through somaclonal variation, Env = environmental safety assessment resulting in unconfined release authorization, Feed = feed safety assessment resulting in livestock feed use authorization, and Food = food safety assessment resulting in food use authorization.