Canadian Food Inspection Agency | Agence canadienne d'inspection des aliments

Health Canada | Santé Canada

Canadian perspective on unintended effects (for novel foods and feeds)

Luc Bourbonnière and Jordan Bean, HC
Annie Savoie, CFIA
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Unintended Effects

- Codex Alimentarius *Guideline for the Conduct of Food Safety Assessment of Foods derived from Recombinant-DNA Plants* describes Unintended Effects as:
  - with the objective of conferring a specific target trait (your intended effect), additional traits could be acquired or existing traits could be lost or modified (unintended effects)(Section 3, Par.14)
  - An inherent and general phenomenon of any genetic modification technique including conventional breeding (Section 3, Par.14)
  - May be deleterious, beneficial, or neutral with respect to the health of the plant or the safety of foods derived from the plant (Section 3, Par.14) (also applies to livestock feeds)

Unintended Effects

- For recombinant-DNA (rDNA) plants, unintended effects can result from the random insertion of DNA sequences
  - > May cause disruption or silencing of active genes, activation of silent genes, or modify the expression of active genes (Section 3, Par.15)
  - > May result in new or altered patterns of metabolites (Section 3, Par.15)
  - > May also arise through subsequent conventional breeding of the rDNA plant (Section 3, Par.14)

Unintended Effects

- Divided into two groups: predictable and unexpected (Section 3, Par.16)
  - Predictable: Knowledge of the target trait (intended effect) gives hypothesis to potential unintended effect (e.g., overexpression of *N*-acetylglyphosate transferase (GAT) → increase in *N*-acetylated amino acids)
  - Unexpected:
    - Unrelated to the specific nature of the target trait, due to random occurrence of a genetic change (e.g., disruption of an active gene by insertion of a DNA sequence results in the expression of a novel fusion protein)
    - Due to an unknown interaction of the target trait with the endogenous system (e.g., protein-protein interaction when novel protein overexpressed, 'white leaf' phenotype in maize due to high lysine levels)

Safety Assessment (Section 3, Par.17)

- The safety assessment of a rDNA plant should include data and information to:
  - Reduce the possibility that food derived from a rDNA plant would have an unexpected, adverse effect on human health (also applicable to the health of livestock with feeds derived from the same plant)
- The safety assessment should involve:
  - Methods to identify and detect unintended effects
  - Procedures to evaluate their biological relevance and potential impact on food safety (and livestock feed safety)
- No individual test can detect all possible unintended effects or identify (with certainty) those relevant to human health (or animal health)

Pre-market Assessment of Novel Foods/Feeds

- Health Canada and the Canadian Food Inspection Agency (CFIA) conduct mandatory pre-market assessments for all novel foods and feeds, respectively

- Novel food safety assessment
  - A comparative approach based on Codex guidance

- Novel feed safety assessment
  - Also uses a comparative approach based on Codex principles with considerations to the inherent differences between consumers (i.e., human versus animal) and the type of plant material being consumed by livestock (e.g., meal vs oil)
  - The assessment also considers safety to humans by the potential transfer of residues into human food, i.e., meat, milk and eggs, and via worker/bystander exposure, and to the environment

Regulatory trigger for Novel Foods/Feeds

- Regulations are product-based, not process-based
- Canadian regulatory system is unique in that it can capture products derived from any breeding technique if it introduces a novel trait, removes an existing trait or alters an existing trait beyond normal variation (creating a novel food/feed)
- Data and information grouped into two parts of the novel food/feed assessment:
  - Molecular characterization and characterization of the trait
  - Phenotypic characterization

Pre-market Assessment of Novel Foods/Feeds

- Molecular characterization and characterization of the trait:
  - Examines how the organism was intentionally modified to achieve a target trait(s), i.e., intended effect
  - Based on data showing the actual modification(s) in the organism , one can predict changes to the phenotype (e.g., constitutive, tissue-specific expression of a novel protein)
  - As mentioned, prior knowledge of the target trait, including potential interactions with endogenous metabolic systems and its mode of action, may help predict potential unintended effects
    - Currently for the "new generation of traits" (e.g., RNAi), there is more emphasis regarding the mode of action of a trait during the assessment

Pre-market Assessment of Novel Foods/Feeds

- Molecular characterization and characterization of the trait (i.e. what we look at)
  - Description of the novel trait
    - Mode of Action (i.e., how the novel trait works)
  - Description of the genetic modification(s)
    - Method of transformation
    - Description of genetic elements intended for insertion into recipient organism/intended genetic modification(s) to recipient organism (e.g., site-directed mutagenesis)
  - Characterization of the genetic modification(s)
    - Description of insertion site(s)/site(s) of modification
    - Data confirming integrity and copy number of genetic elements within insertion site(s)/site(s) of modification
    - Bioinformatics analyses of genetic sequence flanking insertion site(s)

Pre-market Assessment of Novel Foods/Feeds

- Phenotypic characterization:
  - Examine the inherent qualities (e.g., nutritional composition, endogenous allergenicity, etc.) of the organism including the target trait and compare these qualities to its unmodified counterpart
  - Discern differences between the qualities of the organism and its counterpart and identify the biological relevance of these differences (if any) to human and animal health
  - Based on any predictable potential unintended effects, examine specific qualities to disprove or accept the null hypothesis (i.e., introduction of the target trait did not cause a specific unintended trait)

Pre-market Assessment of Novel Foods/Feeds

- Phenotypic characterization (i.e., what we look at)
  - Expression patterns of any intended novel substance (e.g., RNA, protein)
  - Nutritional composition (i.e., plant-specific key analytes and metabolites)
  - Expression of endogenous allergens (if applicable)
  - Chemical considerations (e.g., uptake of heavy metals, susceptibility to mycotoxin-producing fungi)
  - For novel feeds, efficacy of the plant as a livestock feed compared to its counterpart

Insertional Effects

- Health Canada and the CFIA recently published a paper:
  - *A comparative analysis of insertional effects in genetically engineered plants: considerations for pre-market assessments*[1]
    - An examination of the genetic changes collectively known as insertional effects and their potential to give rise to unintended traits
    - Comparison of insertional effects with genetic changes that occur in plants both spontaneously and as a result of conventional breeding practices

1 Schnell J, Steele M, Bean J, Neuspiel M, Girard C, Dormann N, Pearson C, Savoie A, Bourbonniere L, MacDonald P. 2015. A comparative analysis of insertional effects in genetically engineered plants: considerations for pre-market assessments. Transgenic Res. (1): 1-17. Epub 2014 Oct 26.

Insertional Effects paper

- Conclusions
  - Genetic changes are an unavoidable consequence of genetic engineering, but introduction of unintended effects is not
  - Genetic changes similar to insertional effects occur spontaneously and during conventional breeding of plants (plant genomes are constantly changing!)
  - Impact of genetic changes:
    - low potential that changes will result in a phenotypic change, and
    - low potential for any phenotypic change to have an adverse effect on the plant, food/feed safety
  - This greater understanding of the nature and impact of genetic changes can be used to further refine pre-market assessments of genetically engineered plants and foods/feeds derived from them

In conclusion

- The current safety assessment paradigm is designed to consider unintended effects and to evaluate the impact on health and safety
- From Canada's experience in assessing novel foods and novel feeds, unintended effects are rarely observed, and when they were noted, they did not impact on health and safety
- Based on our review of insertional effects, can we further fine tune our assessment of GM crops, e.g., retransformation?

Questions

- For additional information regarding Health Canada's pre-market assessment of novel foods including those derived from PNTs:
  - Website: http://www.hc-sc.gc.ca/fn-an/legislation/guide-ld/nf-an/index-eng.php
  - Contact: Mr. Luc Bourbonnière, Section Head of Novel Foods Section, Health Canada (luc.bourbonniere@hc-sc.gc.ca)

- For additional information regarding the CFIA's pre-market assessment of novel feeds including those derived from PNTs:
  - Website: http://www.inspection.gc.ca/animals/feeds/regulatory-guidance/rg-1/chapter-2/eng/1329298059609/1329298179464?chap=6
  - Contact: Ms. Annie Savoie, National Manager of Biotechnology and Microbiology Section, CFIA (annie.savoie@inspection.gc.ca)

Thank you


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