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Application of Laws, Policies, and Guidance from the United States and Canada to the Regulation of Food and Feed Derived from Genetically Modified Crops: Interpretation of Composition Data

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ABSTRACT: With the development of recombinant DNA techniques for genetically modifying plants to exhibit beneficial traits, laws and regulations were adopted to ensure the safety of food and feed derived from such plants. This paper focuses on the regulation of genetically modified (GM) plants in Canada and the United States, with emphasis on the results of the compositional analysis routinely utilized as an indicator of possible unintended effects resulting from genetic modification. This work discusses the mandate of Health Canada and the Canadian Food Inspection Agency as well as the U.S. Food and Drug Administration's approach to regulating food and feed derived from GM plants. This work also addresses how publications by the Organisation for Economic Co-operation and Development and Codex Alimentarius fit, particularly with defining the importance and purpose of compositional analysis. The importance of study design, selection of comparators, use of literature, and commercial variety reference values is also discussed.

KEYWORDS: *agricultural biotechnology, compositional analysis, GM crops, GM food regulation, GM feed regulation*

INTRODUCTION

It has been 20 years since the U.S. Food and Drug Administration (FDA) published its Statement of Policy on Foods Derived from New Plant Varieties.[1] This policy was precipitated by the seed industry request for its customers to market food derived from new plant varieties developed using recombinant DNA (rDNA) techniques, which is also known as bioengineering or genetic modification. Around the same time, Canada developed policy and ultimately published the Novel Foods Regulations, Division 28, of the Food and Drugs Act and Regulations (1999), as well as the Novel Feeds Regulations, of the Feeds Act and Regulations (1996).[2,3]

At the time of the 1992 FDA publication, there were many unknowns with rDNA technology. In the United States, three agencies/departments were involved: the U.S. Environmental Protection Agency, the U.S. Department of Agriculture Animal and Plant Health Inspection Agency, and the FDA. Ridley has delineated the responsibilities of these agencies/departments in the regulation of GM crops.[1(p 7, §IV.A.),4] The U.S. Federal Food, Drug, and Cosmetic Act (FDCA) does not provide for the FDA to preapprove foods prior to marketing. To note, in this paper, the term *food* includes feed because the FDCA defines food as food for humans or other animals.[5] Regulation of the safety of food falls under §402(a) of the FDCA. Food is adulterated, among other factors, if it bears or contains any poisonous or deleterious substance that may render it injurious to health. However, in the case in which the substance is not an added substance, such food shall not be considered adulterated under this clause if the quantity of such substance in such food does not ordinarily render it injurious to health. The FDCA does require the FDA premarket approval of food additives regardless of the technique used to add them to food, which are defined under §201(s) of the act as any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, that are not generally recognized as safe (GRAS).[6,7] Food additive petitions are required for food additives under §409 of the FDCA. However, the FDA is empowered with the precedent of making a determination on whether or not a substance is a food additive requiring a food additive petition.[8] Again, it is important to note that the FDCA includes feed additives with food additives.[1]

As part of the FDA's 1992 Statement of Policy, there were concerns of deleterious things happening because of the insertion into the plant of genetic material that had been manipulated in vitro (i.e., a transformation event). These concerns include, but are not limited to, the following: that the DNA may physically insert into a transcriptionally active site on the chromosome, so as to inactivate a host gene or alter control of its expression, or that the expressed product may interact with a gene product or metabolite in a deleterious way.[1(p. 7, §IV.A.)] As a response to congressional and public concern, the FDA provided guidance for plant breeders and developers (sponsors) to follow prior to marketing seed for food-producing plants. The sponsors were advised to consult the FDA early and often. As a statement to the guidance, the FDA anticipated that transferred genetic material, as with

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inherent genetic material, would usually be considered GRAS.[1] The FDA also decided that there would be a unified concurrent food and feed consultation. Health Canada used existing legislation (the Food and Drugs Act and the Feeds Act) to define novel food and novel feed and introduced a notification requirement for novel foods and feeds. Providing this definition was a foundation to the approval process.[2] Novel food is defined as a substance, including a microorganism, that does not have a history of safe use as a food and/or a food that has been manufactured, prepared, preserved, or packaged by a process that has not been previously applied to that food and causes the food to undergo a major change.[2] This definition also includes the following: a food that is derived from a plant, animal, or microorganism that has been genetically modified such that the plant, animal, or microorganism exhibits characteristics that were not previously observed in that plant, animal, or microorganism; the plant, animal, or microorganism no longer exhibits characteristics that were previously observed in that plant, animal, or microorganism; or one or more characteristics no longer fall within the anticipated range for that plant, animal, or microorganism.[2] A parallel definition was developed for novel feed.[3] For the purposes of this paper, the terms *genetically modified food* (GM food) and *genetically modified feed* (GM feed) are used to describe this third category of novel foods and feeds as defined in the Canadian regulations.[2,3] It is noted that defining "novel foods" and providing guidance documents serve a very important role in providing registrants with structure for obtaining and explaining scientific studies designed to evaluate the safety of new foods and feeds. As in the United States,[9] Canada has a policy of "no split approvals" in that both food and feed assessments for GM plants must be completed satisfactorily before Health Canada and the Canadian Food Inspection Agency (CFIA) issue their respective approval letters for the GM food and GM feed. Health Canada is responsible for establishing standards and policies governing the safety and nutritional quality of all food, including novel foods, sold in Canada. Concurrently, the CFIA is responsible for establishing standards and policies governing the safety and nutritional quality of all feed, including novel feeds, sold in Canada. Under the Canadian Novel Foods Regulations and the Novel Feeds Regulations, notifications are required, and a safety assessment is conducted by Health Canada and the CFIA before the novel food and novel feed, respectively, are permitted for sale in the marketplace.[2,3]

Other countries followed with laws and regulations governing feed and food derived from bioengineered plants. The European Union enacted two directives: European Directive 2001/18, which governs the commercial use of a GM plant (reproductive) as well as its release into the environment for growing or importing the plant (material), and European Directive 1829/2003, which covers food and feed made from or containing the GM plant.[10,11] Food Standards Australia New Zealand (FSANZ) regulates food produced using gene technology (i.e., GM) under Standard 1.5.2 of the Australian Food Standards Code.[12] Standard 1.5.2 contains two parts: Division 1 addresses the health and safety requirements prior to the sale of the GM food, and Division 2 covers the labeling and other information requirements (including food additives and processing aids) produced using GM technology. Japan relies on its 1947 law as well as its 1995 revision to regulate GM foods and feeds.[13] In 2004, the Joint Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) Food Standards Program of the Codex Alimentarius Commission published a consensus guidance titled "Foods Derived from Modern Biotechnology".[14] The stated purpose of the document was to provide a framework for undertaking risk analysis on the safety and nutritional aspects of foods derived from modern biotechnology.

On the basis of an overview of the country/union laws, the food and feed regulatory processes for GM crops can be viewed as two types of regulatory procedures.[15] The first type is the specific product-based procedure (characteristics of the GM product), as is evident in the United States and Canada. The second type is the process-based procedure (process of making the GM crop) that is evident in the European Union and Australia.[15] However, the common regulatory mandate of all countries is to ensure the safety of all domestic and imported foods intended for human or animal consumption. Compositional analysis of key components is a part of all safety assessments.[14−16]

Several terms are used in this work, and their definitions are as follows: *genetic engineering*, the process of transformation by recombinant DNA technology; *transformation event*, the introduction into a plant of genetic material that has been manipulated in vitro; *genetically modified (GM) or bioengineered*, food derived from a plant that is developed using a transformation event; *conventional counterpart*, a related variety, its components, and/or products for which there is experience of establishing safety based on common use as a food; and *experimental comparator*, the conventional counterpart.

OVERSIGHT OF GM FOODS AND FEEDS IN THE UNITED STATES AND CANADA

Safety assessments of GM foods and feeds in the United States and Canada are conducted on a case-by-case basis, according to the policies and regulations described in the previous section. It is recognized that each country has its own laws, regulations, and guidance, but the overall safety assessments meet the principles stated in the second edition of "Foods Derived From Modern Biotechnology", published by the Codex Alimentarius Commission in 2009.[17] These assessments are conducted by a team of scientific experts in a number of fields (e.g., molecular biology, chemistry, toxicology, nutrition, statistics, and microbiology).

Guidelines for preparing a submission for assessment have been published in both the United States and Canada. For example, the FDA published its "Guidance on Consultation Procedures Foods Derived From New Plant Varieties" in 1996.[18] Health Canada published "Guidelines for the Safety Assessment of Novel Foods" in 1993,[19] and the CFIA published "Guidelines for the Assessment of Plants with Novel Traits as Livestock Feed" in 1995.[20]

In Canada, notification to Health Canada or the CFIA is required before the sale of a GM food or feed, respectively. In the United States, the voluntary requests for consultations from plant breeders on bioengineered foods are coordinated by the FDA Center for Food Safety and Applied Nutrition and its Center for Veterinary Medicine.

The guidance and safety assessment in both countries follow the Codex framework of food safety assessment.[17] The relevant elements to address in the safety assessment are elaborated in the U.S. guidance, as follows: (1) the name of the bioengineered food and the crop from which it is derived; (2) a description of the various applications or uses of the bioengineered food, including animal feed uses; (3) informa-

tion concerning the sources, identities, and functions of introduced genetic material; (4) information on the purpose or intended technical effect of the modification and its expected effect on the composition or characteristic properties of the food or feed; (5) information concerning the identity and function of expression products encoded by the introduced genetic material, including an estimate of the concentration of any expression product in the bioengineered crop or food derived thereof; (6) information regarding any known or suspected allergenicity and toxicity of expression products and the basis for concluding that foods containing the expression products can be safely consumed; (7) information comparing the composition or characteristics of the bioengineered food to that of food derived from the parental variety or other commonly consumed varieties with special emphasis on important nutrients and toxicants that occur naturally in the food; (8) a discussion of the available information that addresses whether the potential for the bioengineered food to induce an allergic response has been altered by the genetic modification; and (9) any other information relevant to the safety and nutritional assessment of the bioengineered food. The information in elements 3−9 is used to assess both the intended and the potential unintended changes in the plant as a result of the genetic modification.[18]

COMPOSITIONAL ASSESSMENT OF FOOD AND FEED

The compositional analysis is an important element in the safety assessment of GM foods and feeds. It forms part of the weight-of-evidence approach in determining overall safety. The seller or petitioner submits detailed scientific reports to substantiate that the GM food and feed is as safe as that currently marketed.[21−23] The purpose of the compositional assessment is twofold: first, to verify that the expected changes resulting from the genetic modification have not negatively affected the safety and nutritional quality of the food and, second, to verify that detrimental unintended changes to plant composition have not occurred as a result of the modification (i.e., as a check for "unintended effects"). Unintended changes that could be detrimental may include increased or decreased levels of nutrients, antinutrients, secondary metabolites, and/or natural plant toxicants.

It is recognized that most plant varieties are a source of both food and feed. With maize, foods include products from the kernel such as flour, sugars, and syrups, whereas feeds include the forage, the kernel, and byproducts from food and biofuel processing. With soybeans, the oil and protein from the seed are food products, whereas the forage and meal left from the extraction of oil are feed products. Likewise, with cotton, the oil is a food, whereas the cottonseed from which the oil is extracted is feed.[5]

For the purposes of this paper, the focus is on unintended effects and composition analysis as a tool in the assessment. Because of the interrelatedness and complexity of plant metabolic networks, composition analysis has been used as a tool for the evaluation of unintended and unexpected effects of a transformation event. It is recognized that key nutrients may vary across crops on the basis of how food and feed from such crops are used in the diet. Because not all plant components are pertinent to a safety or nutritional review, the Organisation for Economic Co- operation and Development (OECD) has adopted the term *key* to delineate components that one should consider in evaluating whether a GM plant is as safe as its experimental comparator(s) (conventional counterpart(s)).[16] The OECD Task Force for the Safety of Novel Foods and Feeds has published crop-specific consensus documents that list the key nutrients, antinutrients, secondary metabolites, and natural toxicants.[24] For other crops, data on these components are extracted from the literature. The U.S. National Research Council (NRC) and the Institute of Medicine of the National Academies have published scientific reports on the nutrient requirements of domestic animals and humans, respectively, which serve as a standard for deriving key nutrients, antinutrients, and natural toxicants.[25−27]

The extent of the requirement for compositional data (e.g., the number of analytes to test, the number of field sites, years of data collection) may also be tailored, on the basis of familiarity.[28] The familiarity with the crop characteristics, and with the novel trait, can inform the overall data requirements. In some cases, bridging data and scientific rationales are acceptable, in place of new data. For instance, the grain of lysine corn (LY038) aside from containing elevated levels of lysine, has elevated levels of lysine catabolites, saccharopine, and α-aminoadipic acid. Studies from the scientific literature were accepted as evidence that these catabolites would not cause a human or animal safety concerns.[29]

Key Components. According to the OECD definition, key nutrients typically include proximates, amino acids, fatty acids, calcium, phosphorus, anti-nutrients that adversely affect metabolism, and toxicants that are harmful to health. Proximates, as related to a nutritional analysis, include the following: moisture (weight loss after drying), crude protein (N × 6.25), crude fat (usually ether extractable), ash [remainder after combustion in a furnace (500 °C)], and crude fiber (remainder after acid treatment and drying).[24,30]

Fiber as related to a nutritional analysis includes the following: crude fiber, total dietary fiber (that not digested by humans; important in human nutrition), acid detergent fiber (ADF) (cellulose + lignin; indigestible to animals), and neutral detergent fiber (ADF fraction + hemicellulose; important to animals).[24]

Key amino acids usually include the essential amino acids plus those that have been shown to be limiting to some species. Arginine, histidine, isoleucine, lysine, leucine, methionine (+ cystine), phenylalanine, threonine, valine, and tryptophan are usually considered essential for nonruminant animals. Glycine, tyrosine, and serine are also important. The most limiting amino acids for animals are lysine, methionine, and threonine.[24,26,27]

Minerals are important to nutrition. Major minerals include calcium, phosphorus, magnesium, potassium, and sodium. Trace minerals include iron, selenium manganese, copper, and zinc. Other than calcium and phosphorus, the key minerals vary with crop type and food and feed components of the crop. Fat-soluble vitamins include vitamins A, D, E, and K. Water-soluble vitamins include B_1, B_2, B_6, C, folacin, niacin, and pantothenic acid. Again, key vitamins depend on the crop and the food and feed components.[24]

Because antinutrients are crop specific, each crop has its list of antinutrients (Table 1).[24] Similarly, natural plant toxicants are crop specific, and each crop also has its list of toxicants, although not all plants include key toxicants (Table 2).[24]

Table 1. Crop Antinutrients Important to Animal Nutrition and Health[24]

antinutrient	property	action	common crop
phytic acid	binds minerals	bound minerals unavailable to the animal	maize
			soybean
			low erucic acid rapeseed
			grain sorghum
			cassava
			cotton
			barley
			soybean
lectins			soybean
tannins			grain sorghum
			cassava

EXPERIMENTAL DESIGN OF COMPOSITION STUDIES

Studies are usually conducted with the GM plant variety and its parent. Several field locations are selected, representing the geographic area where the bioengineered plant is expected to be grown. Within a location, plots of land are allocated to the experiment. Usually three or more blocks containing two or more plots are formed to ensure that the treated and control plants are grown under the same conditions. Precautions are taken to ensure that no cross-fertilization occurs, and external sources of variation are controlled.[31]

Harvest, Storage, Processing, and Analysis. Harvest, storage, and processing are conducted in such a manner to maintain the integrity of the experimental plant material. Compositional analysis is conducted using validated analytical methods, and the data are subjected to an appropriate statistical analysis, resulting in probability estimates.[31]

Data Presentation. Data for each plant component are usually assembled in tabular form and usually include a mean, *p* or *F* value, and available literature ranges. For consistency with recognized databases, component values are usually presented as a percentage of dry weight with the exception of fatty acids, which are usually given as a percentage of total fatty acids. Aside from a percentage of dry weight, amino acids are sometimes presented as a percentage of total protein.[31]

Evaluation of Composition Data. The first comparison is to the experimental comparator. If a statistically significant difference is found, further comparison to reference varieties and literature or recognized database ranges should be done. Recognized databases include, but are not limited to, those developed by the OECD,[24] U.S. Department of Agriculture,[32] International Life Sciences Institute (ILSI),[33] National Agricultural Research Organization,[34] and NRC,[26] as well as available data in peer-reviewed journals. If the level of a particular component does appear to be outside of what is expected on the basis of the published ranges, further examination of the unintended difference is warranted, to investigate possible unintended effects of the modification. An evaluation of the impact of the difference on food and nutritional safety should be conducted. Further compositional analysis or animal feeding studies may be needed to demonstrate the safety and nutritional quality of the food and feed derived from the GM plant.[17]

Weight of Evidence. As mentioned above, compositional assessment is part of the overall safety assessment. Conclusions are made on the acceptability of a bioengineered plant variety, based on all of the submitted evidence. Valid scientific rationale is acceptable to bridge data. For compositional data, although there may be significant differences between the bioengineered plant and its comparator for some of the constituents, literature ranges can help guide whether further assessment is needed or whether the plant composition is within the expected range for the constituents.

SUMMARY OF FOOD DERIVED FROM GM CROPS APPROVED FOR MARKETING IN CANADA AND THE UNITED STATES

Results of FDA Consultations (1995−2012). The second bioengineered plant with a completed consultation in the United States was a soybean bioengineered to be tolerant to the herbicide glyphosate.[23,31] Glyphosate, when applied, causes plant death because it inhibits the action of the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), which is essential for the biosynthesis of aromatic amino acids. To bioengineer the soybean tolerant, a gene is extracted from the soil bacterium *Agrobacterium* sp. strain CP4 that encodes an EPSPS (CP4 EPSPS), which is highly resistant to inhibition by

Table 2. Crop Natural Toxicants Important to Animal Nutrition and Health[24]

toxicant	property	action	common crop
gossypol	binds to amino acids and iron	amenorrhea and atrophy of uteri	cotton[44]
		reduced fertility	
		atrophy of muscles	
cyclopropenoid fatty acids: sterculic acid, dihydrosterculic acid, and malvalic acid	inhibition of desaturation of saturated fatty acids	poultry: reduced hatchability	cotton
		trout: increased incidence of liver tumors	
cyanoglycosides	yields hydrocyanic acid that inhibits cytochrome oxidase	muscle fasciculation and death	cassava
			grain sorghum
			forage legumes

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glyphosate. The bioengineered soybean expresses a relatively low level of CP4 EPSPS and that renders soybeans tolerant of commercially relevant levels of glyphosate. The philosophy is simple from a scientific building-block point of view. Plants require protein for their structure and as enzymes to facilitate a multitude of metabolic reactions (in this case, one enzyme of many facilitating the formation of aromatic amino acids). Scientists estimate that soybean plants express more than 46000 different proteins to carry out their life function.[35,36] Proteins are the expression product of genes. Proteins are made of building blocks called amino acids, and there are 20 common amino acids. What makes proteins unique is the sequence of amino acids. A lack of one or more of the amino acids, such as the aromatic ones (tyrosine, tryptophan, and phenylalanine) in this case, results in all proteins not being expressed. However, in the case of the glyphosate-tolerant glyphosate soybean, another protein, CP4 EPSPS, is expressed by the plant to perform the same function as the inhibited EPSPS (i.e., facilitate the biosynthesis of the aromatic amino acids). Thus, the glyphosate plant functions normally.[23,25]

Although the FDA has completed consultations on nearly 100 GM crops, the intended effects of the modifications and the number of different genes used to modify these crops are small.[31] Herbicide resistance involves adding genes to overcome the effects of glyphosate, glufosinate, imidazoline, sulfonylurea, and bromoxynil, respectively. There are many insect-resistant GM varieties, mostly proteins from *Bacillus thuringiensis*. Other GM varieties include several with plant-incorporated protectants (PIP) and some with new traits affecting ripening/softening, nutrient accumulation, and markers.

The FDA has completed almost 100 GM crop consultations representing even more transformation events. Maize was the subject of the most consultations, followed by soybean, with oilseed rape, cotton, and 13 other crops, respectively.[31]

The intended effects of the transformation events for new crop varieties were herbicide tolerance, pesticide resistance, both, or other, including virus resistance, nutritional enhancement, and markers.

The newly expressed proteins and their intended effects in maize include three proteins conferring herbicide tolerance, nine proteins conferring insect protection, and five that are enzymes with specific purposes of enhancing or inhibiting metabolism or catabolism.

The newly expressed proteins in soybean include five herbicide-tolerant proteins, one insect-protected protein, and one protein that results in an improved nutritional event. One transformation event included an insert that produced no new protein, but caused accumulation of a fatty acid.[31,37]

The newly expressed proteins for cotton include four that exhibit herbicide tolerance and six that show insect protection.[31]

The newly expressed proteins for the remaining crops are as follows. There are four herbicide-tolerant proteins: two that confer herbicide tolerance for oilseed rape, radicchio, and rice, a third that confers herbicide tolerance to oilseed rape, and a fourth that confers herbicide resistance to GM flax. There are two insect-protected proteins and these are expressed in potato and tomato varieties. Eight viral coat proteins providing viral resistance are expressed in a variety of crops, including cantaloupe, papaya, potato, plum, and squash. Tomatoes and cantaloupes were the recipients of gene products causing delayed ripening. For all of the GM/bioengineered plants involving transformation events in 17 different crops that have been evaluated in the United States, all have shown that they are "not materially different in composition, safety or any other relevant factor of varieties now grown, marketed or consumed in the US".[31] In addition, completed consultations are crop specific for transformation events, and further consultation on those transformation events when crossed using conventional breeding practices with non-GM or other transformation events that are the subject of completed consultations are not required.[1,18] In addition, reviews of the composition of GM crops have concluded that for the GM plants assessed to date, no meaningful differences in composition attributed to the transformation event have been detected.[38−41] The reviews have focused on soy and maize, modified for insect protection and/or herbicide tolerance (the most common and most studied material). The reader is referred to the FDA Consultation Inventory (http//www.fda.hhs.gov/bioconinventory) for a current list.

Results of Novel Foods Reviews in Canada. In Canada, as of February 2013, over 100 novel foods and feeds have also been assessed, and the developers of these foods and feeds have been issued letters of no objection/approval, in accordance with the Novel Food Regulations and the Novel Feed Regulations. These foods and feeds are listed on the Health Canada and the CFIA Web sites, respectively (http://www.novelfoods.gc.ca; http://www.inspection.gc.ca).

Many crops from which food and feed are derived have been genetically modified using genetic engineering and are legally marketed in Canada and the United States. The scientific regulatory authorities in both countries have done thorough scientific reviews of the GM crops before they were marketed. Detailed analytical compositional analyses of these GM crops, designed to detect unintentional adverse effects, have been completed by sellers or petitioners prior to release for food and feed use. No such adverse effects have been discovered.[31,41−43]

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Notes

The authors declare no competing financial interest.

W.D.P., PAS, retired in 2010 following 40 years of service with the U.S. Food and Drug Administration (FDA), Center for Veterinary Medicine. This paper reflects the views of the author and should not be construed to represent the FDA's views or policies.

ABBREVIATIONS USED

ADF, acid detergent fiber; CFIA, Canadian Food Inspection Agency; EPSPS, 5-enolpyruvylshikimate-3-phosphate synthase; FDA, U.S. Food and Drug Administration; FDCA, Food, Drug, and Cosmetic Act; FSANZ, Food Standards Australia New Zealand; GM, genetically modified; GRAS, generally recognized as safe; NRC, National Research Council; OECD, Organisation for Economic Co-operation and Development; rDNA, recombinant DNA; WHO, World Health Organization

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