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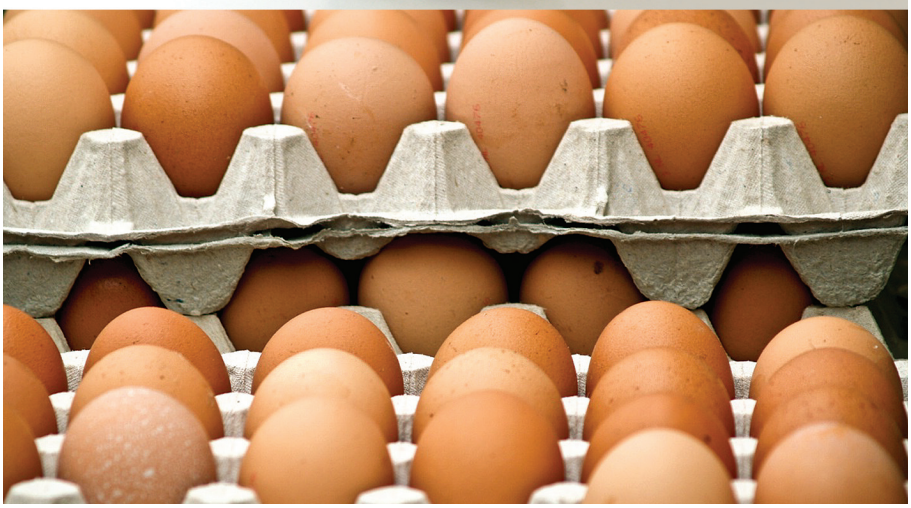
Safety of Meat, Milk, and Eggs from Animals Fed Crops Derived from Modern Biotechnology

Animal Agriculture's Future through Biotechnology, Part 5

Summary

As the global land area of biotechnology-derived crops modified for agronomic input traits such as herbicide tolerance and/or insect resistance continues to increase, these crops have become an increasingly important source of feedstuffs for farm animals, and it is important to review the safety of meat, milk, and eggs derived from animals fed these crops. Once the safety of the newly expressed protein has been established, then nutritional equivalence between biotechnology-derived (often referred to as "biotech") crops and conventional varieties can be established through analysis of nutrient composition. Performance, health, and nutrient use by farm animals are similar when fed either conventional or biotechnology-derived crops, and/or their coproducts. Furthermore, no biologically relevant differences in the composition of animal products, including meat, milk, and eggs, have been reported between farm animals fed diets containing commercially available, biotechnology-derived crops and those fed diets containing conventional genetic counterparts. No intact or immunologically reactive fragments of transgenic plant proteins or deoxyribonucleic acid (DNA) have been detected in samples of meat, milk, eggs, lymphocytes, blood, and organ tissue from production ani-mals fed biotechnology-derived crops modified for agronomic input traits.

The regulatory processes in place to assess the safety of biotechnology-derived crops have been effective in safeguarding public health. To date, there has been no authenticated case of an adverse health-related incident associated with the consumption of food or feed derived from modern biotechnology. The review of the currently available data concludes that meat, milk, and eggs produced by farm animals fed biotechnology-derived crops are as wholesome, safe, and nutritious as similar products derived from animals fed conventional crops.



Photos courtesy of SXC.hu: meat (Yucel Tellici, photographer), milk (Zsuzsanna Kilian, photographer), and eggs.

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INTRODUCTION

Animal products such as meat, milk, and eggs are significant sources of high-quality food for humans and represent approximately one-sixth of their food energy and one-third of their food protein on a global basis (CAST 1999). Diets for farm animals may contain forages (e.g., pasture, hay, and silage), crop residues (e.g., maize stover and rice straw), cereal grains, and food and fiber coproducts (e.g., soybean, canola and cottonseeds meals, cottonseed hulls, and corn distillers' dried grains). Between 1996 and 2006, the land area of biotechnology-derived crops modified for agronomic input traits such as herbicide tolerance and/or insect resistance increased dramatically (Figure 1; James 2005), and biotechnology-derived varieties of corn, soybean, cotton, and canola now are widely used as feedstuffs for both monogastric and ruminant livestock production systems.

For example, during 2005, biotechnology-derived soybean represented more than 60% of soybean plantings worldwide (Table 1), and in the United States, at least 70% of the corn and soybean crops currently fed to farm animals are obtained from biotechnology-derived crops. It also should be noted that more than 10 million tonnes of biotechnology-derived soybean meal is imported into the European Union per year for use in monogastric and ruminant livestock diets. Thus, as biotechnology-derived crops have become an increasingly important source of feedstuffs for farm animals, it is important to review the safety of meat, milk, and eggs derived from animals fed these crops.

Table 1. Biotechnology-derived crops as a percentage of respective global plantings for 2005 (James 2005)

Crop	Percentage of global crop areas
Soybeans	60
Corn	24
Cotton	11
Canola	5

Evaluation of the safety of animal feedstuffs obtained from biotechnology-derived crops is the responsibility of governmental regulatory agencies, a complete listing of which is provided by the Organization for Economic Cooperation and Development (OECD 2006). In addition, companies that sponsor biotechnology-derived crops have developed voluntary product stewardship programs. Combined data generated for regulatory reviews and stewardship initiatives are substantial and invaluable for assessing the empirical safety of these crops and the resulting foods produced by animals fed these crops.

Numerous biotechnology-derived crops now have completed the regulatory process in several countries including the United States, Canada, Argentina, Japan, the European Union, Australia, New Zealand, India, Russia, China, and South Africa. Currently, more than 60 biotechnology-derived crops modified mainly for agronomic traits have completed regulatory consultations in the United States, and the majority of these varieties are available commercially.

The objectives for this paper are to provide an overview of regulatory assessments of biotechnology-derived crops and to summarize the empirical data generated for assessing the safety

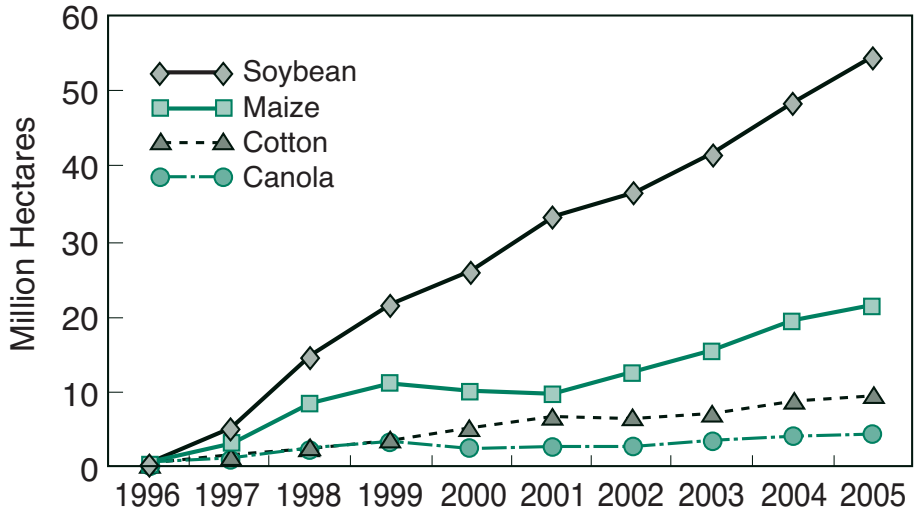

Figure 1. Global area of transgenic crops used regularly as feedstuffs for livestock, 1996 to 2005 (James 2005).

of meat, milk, and eggs derived from animals fed biotechnology-derived crops that express agronomic input traits.

Overview of Regulatory Assessments for Biotechnology-derived Crops Modified for Agronomic Input Traits

National regulatory agencies are charged with the oversight for assessing the safety and wholesomeness of animal feedstuffs derived from biotechnology-derived crops. Although differences exist in the individual philosophies and political approaches with which individual countries developed their regulatory systems for biotechnology-derived or novel crops, the scientific approaches to evaluating the potential environmental and health risks of these crops are very similar.

Safety assessments conducted by regulatory agencies use scientific, risk-based methods to evaluate the novel trait(s) and, ultimately, the new crop. A comparative assessment process identifies similarities as well as intended and unintended differences between novel and conventional crops and their food and feed products. Intended effects are the desired change(s) in the new crop that are the result of genetic modification(s). Unintended effects include all other differences between the new crop and its conventional counterpart and encompass predicted and unexpected changes. The focus of the subsequent safety assessment is on differences between the novel crop and appropriate comparators.

Because risk factors are unique for given crops and for introduced traits, the specific analyses and comparisons are determined on a case-by-case basis. The World Health Organization (WHO 2004), the United Nations Food and Agricultural Organization/World Health Organization (UNFAO/WHO 2000), and the European Food Safety Authority (2004), which produced a *Guidance Document of the Scientific Panel on Genetically Modified Organisms for the Risk Assessment of Genetically Modified Plants and Derived Food and Feed*, have outlined the questions to be addressed in the risk assessments. The authors refer readers to MacKenzie (2000) for a comprehensive, in-depth international comparison of regulatory frameworks for food and feedstuffs derived from modern biotechnology.

Comparative Safety Assessment Process

An underlying tenet for scientific assessments of the safety and nutritional assessment of biotechnology-derived crops is based on the question, "Is the biotechnology-derived crop as safe as conventional counterpart crops?" In regulatory terms and from the public perspective, conventional crops are considered safe by virtue of an apparent history of safe use. Thus, the comparative assessment process, often referred to as the concept of *substantial equivalence* (OECD 1993), is important for identifying similarities and intended and unintended differences between conventional and biotechnology-derived crops to determine whether the novel crop is as safe as the conventionally bred crop. When novel and conventional crops do not differ in their safety and nutritive value they are considered "substantially equivalent." In the United States, regulatory agencies prefer the designation "not materially different" to express that no meaningful differences were identified in plant composition of nutrients, antinutrients, and/or natural plant toxicants.

The comparative safety assessment process has gained broad acceptance and endorsement from many regulatory agencies and scientific advisory organizations worldwide, including the Codex Alimentarius Commission of the United Nations FAO/WHO (2000), and has been reviewed by a number of workers including Kuiper and colleagues (2001) and Cockburn (2002). This concept has subsequently been strengthened by the production of consensus documents developed by the OECD (OECD 2001a, b; 2002a, b, c; 2003). In addition, results from animal feeding studies with biotechnology-derived and conventional crops provide further assurance of the safety and nutritive evaluation of biotechnology-derived crops, as was concluded during regulatory assessments for these crops (for reviews focused on animal feedstuffs see Clark and Ipharraguerre 2001; Flachowsky, Chesson, and Aulrich 2005).

Assessing Agronomic and Phenotypic Characteristics

An initial phase of regulatory assessments by plant breeders is a comparison of agronomic and plant phenotypic characteristics for the new crop with an appropriate counterpart. Cockburn (2002) provides an example of such a comparison for corn that includes the following parameters: leaf orientation, plant height, silking date, ear size, height, tip fill, tassel size and color, dropped ears, early plant vigor, leaf color, root strength, reaction to pesticides, late-season appearance, susceptibility to pathogens, and yield. These characteristics are sensitive indicators of changes in plant physiology and metabolism, and when differences occur, they are robust indicators of a lack of equivalence.

Assessing Compositional Comparability

Another phase of the comparative assessment is a compositional analysis conducted to determine if biologically meaningful differences occur between biotechnology-derived and conventional crops. These analyses provide information on macronutrients, micronutrients, antinutritive factors, and naturally occurring toxins known to be important for the specific crop species evaluated as a feedstuff.

Macronutrients consist of carbohydrate components (e.g., total digestible fiber, neutral-detergent fiber, acid-detergent fiber, and starch), crude protein, fatty acids, crude fat, amino acids, and ash. The micronutrients that are assessed commonly are key minerals and vitamins. Examples of antinutritive factors and naturally occurring toxins are trypsin inhibitors and gossypol, which are present naturally in soybean and cottonseed products, respectively.

For most conventional feed crops, the OECD has identified the key nutrients, antinutritive factors, and natural plant toxicants that are important for human and animal nutrition and safety (OECD 2001a, b; 2002a, b, c).

It is important to note that for the same crop there are significant differences in the composition of conventionally bred varieties (see ILSI 2004a); therefore, the compositional analysis of biotechnology-derived crops must be assessed against conventional crops with similar genetic background and compared in the context of natural variability found across conventional varieties as reported in the scientific literature and recognized databases (ILSI 2004a). For example, to confirm compositional equivalence, Ridley and colleagues (2002) evaluated more than 50 compositional parameters from various plant components in a variety of biotechnology-derived maize, a control variety, and 15 commercial, nonbiotechnology-derived varieties grown at several geographical locations for two cropping seasons in both replicated and nonreplicated trials.

Assessing Nutritional Equivalence

Compositional analyses for biotechnology-derived crops with agronomic traits such as herbicide tolerance and/or insect resistance typically are sufficient to verify food and feed safety for unintended effects.

Although the safety of meat, milk, and eggs derived from animals fed biotechnology-derived crops with improved nutritional characteristics will not be discussed in this paper because their introduction into commercial agriculture is not yet widespread, readers should note that the issue of their safety and nutritional assessment has been addressed in a publication by the International Life Sciences Institute (ILSI 2004b).

Ultimately, the objective for regulatory agencies is to determine the safety and nutritional impact of differences that may exist between biotechnology-derived and conventional crops. Crops that differ in composition or nutritive value can be commercialized when they present no undue risk; crops that present undue risk are unacceptable for commercialization as food or feed crops.

Assessing the Safety of Novel Constituents

Toxicity testing is used to determine the safety of novel compounds in biotechnology-derived crops. These studies are initiated on a case-by-case basis and are conducted according to internationally accepted protocols. Results of acute oral toxicity studies for the novel proteins expressed in commercially available biotechnology-derived plants indicate no detrimental effects for laboratory animals (Agbios 2004a). For example, no effects were observed at testing concentrations for the CP4 5-enolpyruvylshikimate-3-phosphate synthase and crystalline CryIIIA protein that exceeded estimated human daily intake by 1,000 times and 1,000,000 times, respectively (Agbios 2004a).

Results of Feeding Studies in Farm Animals

Feeding studies with target species have been conducted as part of stewardship initiatives, and there is growing evidence to suggest that once compositional equivalence of biotechnology-derived crops has been established, nutritional equivalence has been demonstrated. These trials included work with chickens, pigs, sheep, dairy cows, beef cattle, rabbits, buffalo, and fish, and compared the use of conventional and biotechnology-derived varieties of soybean, corn grain, fodder beet, sugar beet, sugar beet pulp, and cotton seed modified for herbicide tolerance and insect protection. Relevant studies are cited by the OECD (2003) and have been reviewed recently (Clark and Ipharraguerre 2001; Faust and Glenn 2002; Flachowsky, Chesson, and Aulrich 2005). Endpoint measurements in these studies included feed intake, nutrient digestion, animal performance, and animal health.

Recent multigenerational studies comparing diets with nonbiotechnology-derived and biotechnology-derived insect resistant (Bt 176) corn with quail and laying hens for 10 and 4 generations, respectively, have been reported by Flachowsky, Halle, and Aulrich (2005) and Halle, Aulrich, and Flachowsky (2006). The authors reported that the biotechnology-derived corn did not influence health and performance of poultry significantly nor did it affect the quality of meat and eggs of animals compared with the nonbiotechnology-derived isogenic counterpart.

Results from these trials have confirmed the nutritional equivalence and safety of biotechnology-derived and conventional counterparts, and, as such, provide valuable information for public dialogue on the use of biotechnology-derived food ingredients for the production of staple foods from animals. Results from these trials corroborate the safety and nutritional equivalence for biotechnology-derived varieties as concluded initially by regulatory assessments. Furthermore, these results indicate that for compositionally equivalent biotechnology-derived crops, routine-feeding studies with target species generally add little to safety and nutritional assessments (Flachowsky, Chesson, and Aulrich 2005; OECD 2003).

The Fate of Consumed Proteins and DNA

Digestion of Proteins and DNA in Livestock

Although foodstuffs consist of a complex mixture of many ingredients, this paper will focus on DNA and protein digestion by livestock, because these represent the novel constituents in biotechnology-derived crops. Aulrich, Pahlow, and Flachowsky (2004) and Chiter, Forbes, and Blair (2000) have shown that even before ingestion, conservation of forages through ensiling and certain feed-processing methods can cause considerable fragmentation of plant DNA. Even though animal feedstuffs may contain intact DNA, the quantity of this component in most food crops is less than 0.02% on a dry matter basis (Beever and Kemp 2000).

In addition, farm animals and humans are exposed to other sources of DNA in the gut, including shed epithelial cells, white blood cells, bacteria, viruses, and protozoa. Consequently, exogenous DNA (i.e., DNA from outside the organism) is present constantly within the gastrointestinal tract of farm animals and humans. The DNA intro-

duced into biotechnology-derived crops is not different from other sources of DNA in the diet. Further, there is a long history of apparent safety associated with the consumption of DNA by farm animals and humans. Based on this history, the FAO, the WHO, and the U.S. Food and Drug Administration have stated that the consumption of DNA from all sources—including introduced DNA in biotechnology-derived crops—presents no health or safety concerns (OECD 2003; UNFAO/WHO 1991; USFDA 1992).

Within the digestive tract, DNA and proteins are broken down rapidly by digestive enzymes into small fragments: DNA into fragments and nucleotides; proteins into polypeptides, peptides, and amino acids (see reviews by Beever and Kemp 2000; Faust and Glenn 2002; Jonas et al. 2001). For dietary DNA, McAllan (1982) estimated that more than 85% of the plant DNA consumed by ruminants is degraded to nucleotides or smaller constituents before incorporation into rumen microbes or before entering the duodenum. The majority of nucleotides produced from DNA digestion in small intestinal contents, therefore, are derived from microbial DNA. He further reported that most of the ingested DNA was degraded to mononucleotides within 4 hours. Individual nucleotides or short sequences of nucleotides are not known to transfer genetic information. Under normal conditions in both ruminants and monogastrics, digestible proteins are broken down in the digestive tract and absorbed as free amino acids (mostly) and di- and tripeptides (Stevens 2000).

Certain researchers, however, have reported the capability to detect minute amounts of intact ingested proteins and DNA in blood samples from humans and animals. Tsume and colleagues (1996) reported that when ovalbumin was administered orally to humans, 0.007–0.008% of the intact ingested protein was detected in circulation. Schubbert and colleagues (1997) reported that when mice were dosed with purified M13 phage DNA, fragments accounting for approximately 0.1% of the original DNA were detected in white blood cells 2 to 8 hours after dosing.

These latter findings have intrigued researchers and encouraged several regulatory agencies, especially in the European Community, to commission additional studies to understand better the fate of consumed transgenic proteins, transgenic DNA, and endogenous plant DNA (Deaville and Maddison 2005; Einspanier 2001; Phipps, Deaville, and Maddison 2003). Although these studies are expected to advance scientific understanding, it is important to recognize that no detrimental effects have been identified for humans or farm animals from the consumption of currently available biotechnology-derived crops. In fact, these crops had no measurable or observable effects when fed to mice and quail throughout multiple generations; further, no detrimental effects were reported in reproductive parameters, such as testicular development, that are highly sensitive to toxic agents (Brake and Evenson 2004; Brake, Thaler, and Evenson 2004; Flachowsky, Halle, and Aulrich 2005).

Nevertheless, a number of safety concerns were raised including the potential for transgenic DNA (tDNA) and/or the protein encoded by the transgene to transfer to meat, milk, and eggs derived from animals fed diets containing biotechnology-derived crops. As a result, the search for tDNA fragments and the novel proteins in the digestive tract of livestock and their presence in foods such as meat, milk, and eggs gathered momentum.

Studies to Detect Transgenic Proteins in Meat, Milk, and Eggs from Animals Fed Biotechnology-derived Crops

It is expected that transgenic proteins and other dietary proteins largely are broken down during digestion into peptides and amino acids; rapid breakdown may be expected to minimize the opportunity for absorption of intact molecules. Stability of transgenic proteins during digestion is evaluated during the regulatory process for biotechnology-derived crops, and results indicate that they are broken down rapidly in the gastrointestinal tract (Agbios 2004b).

The results of studies with dairy cattle, growing calves, broiler chickens, and swine have not detected the presence of transgenic protein in products and tissues from farm animals fed currently available biotechnology-derived crops (Ash, Novak, and Scheideler 2003; Chowdhury et al. 2003; Jennings et al. 2003a, b; Yonemochi et al. 2002, 2003).

Studies to Detect Transgenic and Naturally Occurring DNA in Food Samples from Animals Fed Biotechnology-derived Crops

Studies have been undertaken to determine whether fragments of tDNA could be detected in animal tissues and food products such as meat, milk, and eggs. Dairy cows, growing cattle, pigs, broiler chickens, and laying hens were fed diets containing biotechnology-derived crops (Deaville and Maddison 2005; Einspanier et al. 2001; Faust 2000; Jennings et al. 2003a, b; Klotz and Einspanier 1998; Klotz, Mayer, and Einspanier 2002; Phipps, Deaville, and Maddison 2003; Reuter and Aulrich 2003; Weber and Richert 2001; Yonemochi et al. 2002, 2003). In these studies, highly sensitive polymerase chain reaction (PCR) and Southern blot methodologies were used to assess samples for the presence of tDNA from the respective varieties. No fragments of tDNA from the single copy transgenes were detected in samples of meat, milk, eggs, skin, duodenal tissue, leukocytes, lymphocytes, blood, and organ tissue obtained from animals fed currently available biotechnology-derived crops. These studies have been reviewed by Clark and Ipharraguerre (2001), the OECD (2003), and Flachowsky, Chesson, and Aulrich (2005).

Likewise, several researchers have been unable to detect fragments from naturally occurring plant-based (single-copy, endogenous) genes in food samples from farm animals (Jennings

et al. 2003a, b; Weber and Richert 2001). Other researchers, however, have reported finding fragments of naturally occurring multicopy plant genes in certain animal tissues and fluids (Einspanier et al. 2001; Klotz and Einspanier 1998; Klotz, Mayer, and Einspanier 2002; Nemeth et al. 2004; Deaville and Maddison 2005).

Although these results at first appear contradictory, the explanation may be that DNA from multicopy genes is far more abundant than that of the single-copy genes such as the transgenes in the current biotechnology-derived varieties. Consequently, the uptake of tDNA would be a much rarer event and, therefore, more difficult to detect. Thus, the detection of DNA in meat, milk, and eggs is likely to be a function of its abundance and also analytical sensitivity. This view is supported by a very recent, detailed study by Deaville and Maddison (2005) working with poultry. They reported that although 23% of all animal samples contained fragments of the multicopy rubisco gene, tDNA from the single copy transgene—although detected in the early part of the gastrointestinal tract—was not detected in any animal tissues. The PCR analytical technique used in the majority of studies was able to detect tDNA fragments of about 200 base pairs.

One paper by Agodi and colleagues (2006), however, in which greatly enhanced analytical sensitivity was used, has now been published and reports that very small fragments of the transgenes *cry1a(b)* and *cp4epsps* have been found in conventional and organic milk samples in Italy. The sizes of the tDNA fragments were 106 and 146 base pairs (bp) for *cry1a(b)* and *cp4epsps*. These fragments must be put into the context of the size of the intact transgene and its minimal functional unit, which for *cry1a(b)* and *cp4epsps* were 3,500 and 1,800 bp, respectively. Thus, although the Agodi study has detected very small fragments of transgenes in milk, their size is so small that they would not have any genetic integrity or functionality, and there is still no scientific evidence to suggest that meat, milk, and eggs derived from animal receiving biotechnology-derived crops are anything other than as safe as those derived from animals fed conventional crops. Furthermore, no differences in rumen microbial populations were detected when cattle were fed *Bacillus thuringiensis (Bt)* corn and its conventional control hybrid (Einspanier et al. 2004).

These findings are supported further by studies documenting that tDNA is rendered nonfunctional by processes in the mammalian digestive tract (Einspanier et al. 2004; Heritage 2002; Martin-Orue et al. 2002). Thus, it is extremely improbable for mammalian cells to incorporate fully functioning genes present in consumed plant tissues. To verify this conclusion, mice were fed for eight generations with large amounts of a unique transgenic DNA construct. No transmission, incorporation, or functional expression of this construct was observed when cells from these mice were studied; however, this same construct was capable of functional expression when injected using gene therapy techniques (Hohlweg and Doerfler 2001; for review see Doerfler 2000). These findings support the observations of Beever and Kemp (2000) that no plant gene (or gene fragment) has ever been detected in the genome of animals or humans. Furthermore, it is unlikely that microflora present in the gut will incorporate fully functional genes present in biotechnology-derived crops as evidenced in original work by Chambers and colleagues (2002).

Conclusions

Despite the scientific intrigue of this debate, the critical issue is whether the possible presence of plant DNA fragments in animal tissues is a safety risk; evidence indicates that this possibility presents no risk. Relevant studies and their findings are listed here:

- Farm animals and humans have a long history of safety associated with the consumption of DNA; consequently, the consumption of DNA from all sources—including introduced DNA in biotechnology-derived crops—presents no health or safety concerns (UNFAO/WHO 1991; USFDA 1992).
- When gene fragments from ingested DNA have been detected in animal tissues/fluids, these fragments are not biologically functional; further, their presence has never been associated with any deleterious effects for animals or with any disruptions of normal animal gene function (as reviewed by Beever and Kemp 2000).
- No plant gene (or gene fragment) has ever been detected in the genome of animals or humans, despite a long history of daily consumption of endogenous plant DNA.
- There is no scientific evidence to suggest that meat, milk, and eggs derived from animals receiving biotechnology-derived crops is anything other than as safe as those derived from animals fed conventional crops.

Recommendations

1. Continue using a case-by-case safety assessment approach to ensure that the regulatory specifications are appropriate for addressing identified risks for individual biotechnology-derived plant products.
2. Assess risks, as opposed to hazards, for individual biotechnology-derived crops using science-based approaches. The regulatory process must maintain a fine balance between making reasonable risk assessments and imposing excessive regulatory burdens that ultimately will stifle future technology development.
3. Provide adequate funding to regulatory groups to ensure that public health is safeguarded and that scientific reviews of regulatory assessment data are timely.
4. Provide resources to increase significantly public outreach and dialogue about biotechnology-derived crops, their benefits and risks, and mechanisms designed to evaluate consumer safety, such as the regulatory process and stewardship initiatives.

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