



Review

The use of consumption data to assess exposure to biotechnology-derived foods and the feasibility of identifying effects on human health through post-market monitoring

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Abstract

The pre-market safety assessment of foods derived through biotechnology provides a scientific basis for concluding reasonable certainty of no harm and ensuring safety. At a minimum, the outcome of such an assessment provides sufficient information to estimate the likelihood of adverse effects on consumers, generally precluding the need for post-market monitoring. Post-market monitoring (PMM) may be appropriate under certain conditions where a better estimate of dietary exposure and/or nutritional consequence of a biotechnology-derived food is required, when a potential safety issue, such as allergenicity, cannot be adequately addressed through pre-market studies, or to corroborate dietary intakes of a nutritionally improved food with beneficial effects on human health. Monitoring programs must be hypothesis-driven, and are dependent upon the availability of accurate consumption data. Exposure assessment methods include both deterministic and probabilistic estimates of intakes using food supply data, individual dietary surveys, household surveys, or total diet studies. In the development of a monitoring approach, resource allocation should be dependent upon both the desired level of conservatism and the endpoint of interest. However, the cost of monitoring varies substantially, and the potential to determine causation may be limited.

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1. Introduction

The introduction of biotechnology-derived foods into global commerce through advances in scientific technologies has resulted in a greater scrutiny of the regulatory measures in place to ensure the continued safety of the food supply. Although the safety of foods derived through biotechnology is evaluated against the standard of safety applied to all foods in general prior to acceptance into the market, there remains a degree of uncertainty amongst some consumers and regulators regarding potential long-term effects on human health not otherwise predicted in the pre-market assessment of these foods. The standard of food safety does not and should not distinguish biotechnology-derived foods as different from any other food as this erroneously implies that pre-market safety assessment procedures inadequately address the scientific uncertainties associated with biotechnology-derived foods. In the context of safety, the pre-market assessment is designed to identify any potentially adverse or intended beneficial effects of a food or food component. Post-market monitoring (PMM) of biotechnology-derived foods is often construed as a means of ensuring safety through the causal identification of adverse health effects associated with the consumption of these foods, when, in fact, it is not. However, PMM may be appropriate when better estimates of dietary exposure or nutritional consequences are desired, or when a safety issue, such as potential allergenicity, has been indicated through the pre-market assessment of the food. It should be noted that PMM should not be intended as a substitute for any component of the pre-market assessment. While PMM is technically feasible, the factors governing implementation are complex. In order to be successful and worthwhile endeavors, monitoring programs should be guided by clear hypotheses, and are dependent upon the availability of accurate food composition and consumption data.

1.1. Pre-market safety assessment

The pre-market assessment of biotechnology-derived foods is a thorough, science-based approach that ensures the safety of the food to the consuming public. While implied that a food should not present an undue risk to the consumer, it is recognized that zero-risk does not exist, as all foods contain inherent chemical components that are toxic at certain levels of exposure (FAO/WHO, 2000). The existing standard of food safety has been defined as one of reasonable certainty of no harm, and it is against this standard that the safety of biotechnology-derived foods, and all foods, in general, is considered. There is general agreement (FAO/WHO, 2000) that the standard of safety applied to foods derived through biotechnology should be equivalent to that applied to foods derived through traditional

means. However, in reality, biotechnology-derived foods are scrutinized against a somewhat higher standard of safety. Compared with foods derived through traditional practices, biotechnology-derived foods have been subjected to detailed compositional analysis, and many have been assessed in toxicological and nutritional studies (Cromwell et al., 2002; Nair et al., 2002; Aulrich et al., 2001; Betz et al., 2000; Bohme et al., 2001; Martens, 2000; Edwards et al., 2000; Rogan et al., 2000; Sidhu et al., 2000; Kaniewski and Thomas, 1999; Taylor et al., 1999; Brake and Vlachos, 1998; Astwood et al., 1996; Hammond et al., 1996). While greater scrutiny has likely been appropriate in order to attain consumer acceptance and trust, experience gained from those biotechnology-derived foods accepted to date on the market indicates no major compositional changes in the food as consumed, nor resultant introduction or expression of toxic factors that were hitherto unknown.

The pre-market assessment of a biotechnology-derived food is generally a step-wise approach with specific safety determinant parameters that vary case-by-case, dependent on the food and intended use, and the nature of any modification to the food as consumed. A key component of this assessment involves consideration of any genetic change to the genome of the biotechnology-derived food. DNA introduced into biotechnology-derived foods is equivalent to other existing DNA in foods, and is considered to be as safe as any other DNA ingested with food (Jonas et al., 2001). It must be demonstrated, however, that the genetic change results in predictable and expected expression, and that any DNA insertion or genetic modification does not result in the expression of pathogenic, toxic, or allergenic products. There is general agreement (FAO/WHO, 2000; OECD, 1993, 2001) that the concept of substantial equivalence provides an appropriate starting point for the safety evaluation of foods derived through biotechnology, providing a basis to identify differences between the biotechnology-derived food and some suitable comparator. In the absence of major compositional changes in the biotechnology-derived food, moving forward in an assessment strategy focuses on the safety of the identified difference(s). Studies may include in vitro and in vivo evaluation of toxicological effects, potential allergenicity, and nutritional value following recommended standard methods (FAO/WHO, 2000; NRC, 2000; LSRO, 1998; Munro et al., 1996; FDA, 1992; WHO, 1987). However, it is important to note that some so-called “second-generation” biotechnology-derived foods may intentionally have specific characteristics or an enhanced composition of major inherent constituents. Consequently, those biotechnology-derived foods with major compositional changes will require additional consideration of these changes in the context of existing and expected dietary exposure, and toxicological and nutritional impacts.

In the pre-market safety assessment of any new food, biotechnology-derived or otherwise, it must be established that under the conditions of intended use, there would be no increased safety concern compared to that of existing foods. Safety can only be evaluated if one has knowledge of conditions of use and exposure. Furthermore, these parameters must be known if any PMM strategy is envisioned. For many biotechnology-derived foods with enhanced nutrients or foodstuffs intended for use as isolated products of gene expression, a range of safe intakes may be established from the literature. If safe intakes cannot be established with reasonable certainty, then appropriate toxicity studies must be conducted to ensure there are no safety concerns under the intended conditions of use. Methods of estimating dietary exposure of biotechnology-derived foods are discussed in the sections that follow, but suffice it to state that the use of food intake databases to estimate the intake of food additives and ingredients under the expected conditions of use provide reasonable, albeit often overestimated, consumption values in total and defined population categories. Numerous food intake databases exist which can be used to perform these calculations. The resultant exposure estimates are evaluated in comparison to data from standard toxicological and nutritional studies to ensure the safety of these food components (FAO/WHO, 2000; NRC, 2000; LSRO, 1998; Munro et al., 1996; FDA, 1992; WHO, 1987).

Apart from unique instances indicating a need for confirmation of pre-market dietary intake estimates or exposure in defined sub-populations, PMM is not standard practice in supporting the safety or regulatory approval of a food product. The need for consideration of PMM of biotechnology-derived foods with respect to adverse consequences to human health is apparently compelled by an unfounded perception of excess uncertainty regarding the presence of unintentional or otherwise unknown toxins or allergens in these foods. Ironically, the notion of required PMM for adverse effects from a biotechnology-derived food that meets the accepted standard of food safety contradicts the intent of any pre-market safety assessment and undermines confidence in any conclusion of safety derived from that assessment (Chesson, 2001). In light of the knowledge of the safety of those biotechnology-derived foods currently on the market, the call for PMM requires definition and prudence to be a worthwhile endeavor that complements the pre-market assessment and does not result in mixed messages to the public.

1.2. Post-market monitoring

The pre-market safety assessment of foods derived through biotechnology is designed to identify areas of safety or nutritional concern prior to the introduction of these foods for general consumption. Therefore, PMM

programs may be appropriate when specific hypotheses requiring directed investigation have been identified as a result of the pre-market assessment, and the data generated from pre-market studies are unable to address the particular hypothesis in question. Ill-defined use of PMM is unwarranted, and could be considered misguided, as it implies that PMM is an appropriate means of hazard identification, as opposed to a control option for risk management, and therefore undermines the reliability of traditional approaches for determining food safety.

Notwithstanding the rigorous pre-market safety assessment required by the European Novel Food Regulations (EC, 1997a), PMM of genetically modified foods and feeds, and products derived from genetically modified food ingredients, has been proposed on a case-by-case basis within the European Union (EU) (EC, 2001). The EU (EC, 1997b) and the Joint FAO/WHO Expert Consultation on foods derived from biotechnology (FAO/WHO, 2000) have also advocated the use of monitoring programs in a nutritional context to assess the impact of the introduction of a novel food on dietary consumption patterns, and to evaluate the potential effects these changes may have on the nutritional and health status of specific populations.

By definition, the proposed EU directives for the monitoring of genetically modified foods and feeds require the implementation of both passive and active measures, with specific initiatives targeted on a case-by-case basis as a result of the risk assessment process. Borzelleca (1995) defines active surveillance (monitoring) as, "...a carefully conceived and structured plan for obtaining information from consumers. It is initiated by the manufacturer who contacts consumers directly..." and passive surveillance (monitoring) as "...the collection of voluntary responses by consumers without input from the producer, distributor, or regulator". Passive monitoring may be useful in cases where immediate idiosyncratic adverse effects, such as allergenicity, are of concern. However, the hypotheses that can be answered via passive surveillance, and therefore their utility without further follow-up, are limited. Active monitoring may be appropriate when confirmation of pre-market consumption projections is required, when effects identified through passive surveillance require targeted investigation, or when the long-term monitoring of chronic health effects is of potential interest. In the latter case, it is arguable that PMM no longer constitutes monitoring per se but falls instead into the realm of epidemiological study and therefore, appropriate epidemiological techniques should be applied. However, the usefulness of any PMM program will be limited if precise estimates of exposure to a particular product are not known. The collection of adequate consumption data is therefore a crucial element in this process.

Post-market monitoring is not standard practice in supporting the safety of a food product; however, in some instances, the regulatory approval of certain food additives has been contingent upon the conduct of appropriate monitoring programs. It is notable that in these cases, studies were conducted in the absence of regulatory guidelines on the design or conduct of PMM of foods. For example, in the United States, the US Food and Drug Administration (FDA) made the approval of the sweetener aspartame (Butchko et al., 1994) and the fat substitute olestra (Allgood et al., 2001; Slough et al., 2001; Thornquist et al., 2000) conditional on studies including PMM. Similarly, the European Union Scientific Committee on Food (SCF) required PMM to accompany the marketing of “yellow fat spreads with added phytosterol esters” under regulatory mandate in the EU (SCF, 2002).

Obligatory PMM following the market introduction of yellow fat spreads containing phytosterols was implemented by the manufacturer as a Post Launch Monitoring (PLM) study in the EU (SCF, 2002) to collect data on consumption and potential health effects. Both active and passive monitoring were utilized to confirm whether actual product use by consumers was consistent with predicted and recommended uses, and to determine whether health side effects, not otherwise anticipated from pre-market studies, occurred following the marketing of phytosterol-containing spreads. Active monitoring of consumer purchasing patterns and dietary intake in multiple countries indicated that the products were being purchased and consumed by the intended target population; however, intakes were lower than pre-market estimates. A passive monitoring program constituting data from approximately 84,000 consumer-initiated reports to manufacturer call centers provided no evidence of product-related adverse effects, confirming the pre-market assessment of the safety of these products.

Regulatory initiatives analogous to the recent EU directives have not yet been proposed in North America; however, the US Food and Drug Administration (FDA) has made the approval of certain food additives conditional on the conduct of appropriate post-market surveillance programs. In order to confirm pre-market exposure projections, the post-market surveillance of aspartame consisted of the collection of consumption data from 1984 to 1992 through annual menu census surveys of over 5000 individuals. The results of these surveys indicated that consumption levels for aspartame were well below the acceptable daily intake (ADI). Anecdotal medical complaints passively collected in response to the introduction of aspartame were also forwarded to the Centers for Disease Control and Prevention (CDC) for detailed evaluation. The results of this evaluation provided direction for focused clinical studies (Butchko and Stargel, 2001).

The post-market surveillance program for olestra was also designed to incorporate both active and passive components. Passive data collection was initiated by the manufacturer to capture the spontaneous reporting of adverse health effects by consumers. These reports were then followed up by expert medical review and directed clinical studies where necessary (Slough et al., 2001). As well, an active component, the Olestra Post-marketing Surveillance Study (OPMSS), was used to confirm the accuracy of pre-market assumptions regarding levels of olestra consumption and its effects on serum micro-nutrient status, particularly on carotenoids and fat-soluble vitamins (Thornquist et al., 2000).

These examples highlight the relevant aspects of a viable PMM program. Post-market monitoring for these substances included active and passive components designed to address specific hypotheses, with program priorities identified relative to the particular case-by-case needs of each situation. Due to the resource intensive nature of PMM, definite goals for such a program should be established a priori, particularly when attempting to determine whether PMM is necessary and/or appropriate. However, PMM should not be exclusively associated with the surveillance of foods derived through biotechnology. It is not evident that inherent differences exist between foods derived via traditional means and biotechnology-derived foods that would necessitate the use of PMM specifically in one context or the other. Post-market monitoring would be equally applicable to both traditional and novel foods or food components, as illustrated by the above examples related to food additive consumption. Therefore, it may be useful to define PMM as a tool for assessing the continuing safety of any food component in the diet. This avoids propagating the notion that pre-market safety assessment procedures inadequately address the scientific uncertainties associated with foods derived through biotechnology.

2. Demonstration of causality

One intended outcome of a PMM strategy for a food with some purported effect on human health may be the demonstration of causality. Critical to the outcome of a PMM program intended to distinguish a cause-effect relationship between the consumption of food and a specific health effect on the consumer would be consideration of a valid hypothesis supported by measurable parameters. In the absence of defined hypotheses, data mining to investigate health-related effects would likely identify random correlations not limited to the consumption of foods derived through biotechnology.

While the safety of foods derived from biotechnology is established in the pre-market assessment and efficacy may be demonstrated in pre- or post-market clinical

studies, the ability to discern unpredicted adverse or intended beneficial effects on human health is challenging given the myriad of confounding variables encountered under real-world conditions. Correlations that have not been adjusted for confounding factors may be spurious and not causally related to dietary exposure to a food derived through biotechnology. Certain confounding or contributing risk factors should be anticipated prior to implementing a PMM program and minimized through proper statistical design and analyses. Furthermore, the ability of any data collected in a PMM program to demonstrate causality may be limited by the characteristics of the population included. In a PMM program, establishing a causal relationship between reported effects on human health and exposure to a particular food cannot rely on the notion of definitive proof, but rather on weight of evidence to establish a scientific basis of association. Prior to the inference of causation from any observed association between a factor and an effect, one must consider important criteria, initially set forth by Bradford-Hill (1965). These criteria include among others, the strength, consistency, plausibility and coherence of the observed association. It is not expected that all criteria described by Bradford-Hill (1965) be met in order to conclude causality; however, supportive evidence within a number of these criteria contributes to the overall strength of a cause-effect relationship.

3. A need for post-market monitoring?

3.1. Potential for allergenicity

The potential allergenicity of foods derived through biotechnology has been recognized as relevant for particular consideration since some of these modifications may result in the expression of novel proteins (Taylor and Hefle, 2002). The presence of proteins per se does not merit attention as a concern regarding the safety of biotechnology-derived foods. However, the current definition of food allergens (i.e. proteins eliciting an IgE-mediated hypersensitivity response in sensitive individuals following consumption) dictates that an assessment for allergenic potential is in order when the biotechnology-derived food or food ingredient contains a novel protein that would otherwise not be present in the diet. A pre-market decision tree strategy for assessing the allergenicity of foods derived through biotechnology has been recommended by the Food and Agriculture Organization of the United Nations and the World Health Organization (FAO/WHO, 2000, 2001), and has proceeded to step 8 of the Codex Alimentarius Commission's assessment of the safety of foods derived through biotechnology (Codex, 2002). The lack of a single definitive assay predictive of the allergenic poten-

tial of a food protein limits this strategy as a positive predictor of allergenicity. However, an absence of positive results in the overall outcome of the decision tree provides reasonable assurance that the likelihood of allergenicity is low.

Post-market monitoring may be considered an appropriate means of ensuring the safety of a biotechnology-derived food in those instances where the level of uncertainty, as indicated by the pre-market assessment, exceeds some level deemed acceptable by a regulatory authority. The reality of this scenario occurring is remote given that it is unlikely any food with any significant degree of uncertainty would be accepted into the market. In addition, PMM may be considered in those cases where the intended use of a biotechnology-derived food may result in an increased exposure to a protein already consumed in the diet, i.e. the amount/extent of exposure is increased, or where there may be a change in the population of consumers, i.e. exposure within or across population subgroups is increased. Under whichever circumstance implemented, surveillance for the incidence of allergic response to a food represents a passive monitoring program for spontaneous adverse events occurring under conditions of acute exposure.

A PMM program to assess the potential allergenicity of a food derived through biotechnology is simplified by the hypothesis of whether the food is allergenic; however, the program must contend with elements related to exposure assessment (e.g. accurate estimates of consumption, traceability, etc.) in order to provide surveillance data of any usefulness. In addition, such a program must be aware of further challenges that exist due to limitations in the extent of current understanding regarding food allergens. While it is reported that greater than 90% of all food allergies worldwide are caused by proteins associated with the consumption of cow's milk, crustaceans, eggs, fish, peanuts, soybeans, tree nuts, and wheat, or ingredients derived from these foods, the properties of a protein that make it allergenic, as well as the biological variables governing one's susceptibility to developing an allergy, remain to be determined (Taylor and Hefle, 2002). Allergic reactions to food clearly represent a special case of food safety because there is a dearth of reliable data available regarding the extent of exposure to a protein (e.g. amount and duration) required to induce sensitization to a food allergen. Furthermore, once an individual is sensitized it is unclear what level of subsequent exposure to the offending food could elicit an allergic response (Taylor et al., 2002). Food allergies represent a unique challenge in ensuring the safety of any food introduced into the population, biotechnology-derived or otherwise. Implementation of a PMM program for allergenicity strictly to complement pre-market assessment data, or with the intent of reducing scientific uncertainty,

should be tempered by the knowledge that allergic reactions to food represent individualistic responses in that the majority of the population can consume the offending food without adverse reaction. Caution must be exercised in the surveillance approach taken and efforts should be made to distinguish those populations that may be at particular risk, as defined by the specific conditions under which PMM is undertaken. Guidance towards susceptible populations of individuals should be available from the multiple assessment tests conducted in the pre-market evaluation.

3.2. Chronic health effects

The association between diet and health is well recognized. Notwithstanding this fact, it is difficult to establish a causal relationship between a particular dietary component and a specific health endpoint, even when an extensive amount of research has been conducted. For example, more than 50 years of evidence has been required to support the currently accepted relationship between dietary modification and the risk of coronary heart disease (Schaefer, 2002).

The use of a PMM program to identify chronic adverse health effects not otherwise indicated by the pre-market safety assessment would be highly impractical and costly, if not scientifically questionable. This would require the prospective long-term monitoring of a specific population in the absence of a hypothetical outcome, or alternatively, the retrospective identification of potential exposure to a particular biotechnology-derived food in a group of individuals known to have a specific disease or health condition. The former situation implies that PMM can be implemented without the generation of specific hypotheses, and therefore undermines the conclusion of “reasonable certainty of no harm” accorded by the pre-market assessment, while the latter requires precise historical estimates of exposure in both the affected group and in a reasonable control population. It is questionable whether either case constitutes true surveillance and from a regulatory perspective both scenarios are reactive in nature. Regardless, without proper design and the identification of appropriate hypotheses, confounding factors would almost certainly plague any observational investigation, as it is difficult to control for these factors even in well-defined dietary surveys with targeted outcomes. In long-term studies with vague endpoints, statistical power would be difficult to obtain, and consumer uncertainties associated with foods derived through biotechnology would certainly be aggravated. Apart from the special case of allergenicity, which could be considered an acute adverse event, the potential for adverse effects based on the chronic consumption of biotechnology-derived foods would be no different than those associated with the chronic consumption of other novel foods, and by

definition should be minimal, as the approval of a food is dependent on its pre-market assessment of safety.

To the contrary, a food with a potentially beneficial effect on human health, as indicated in pre-market assessment studies, may require confirmation of its purported benefits through PMM, or conclusive demonstration of a positive diet-health relationship. With the advent of second-generation biotechnology-derived foods designed to provide specific nutritional benefits, or enhanced functional characteristics, the use of PMM to detect physiologically relevant beneficial health effects may be more appropriate and more readily applicable than the situation depicted for adverse effects. In this case, PMM would constitute a traditional targeted epidemiological study specifically designed to monitor the long-term benefits of a particular biotechnology-derived food. Difficulties associated with implementing this type of investigation would be similar to the difficulties associated with any long-term dietary study, particularly in terms of compliance, mitigating or confounding factors, contributing risk factors and the inherent heterogeneity of any study population in terms of predisposition to effects (van den Brandt et al., 2002). Continual changes in both food availability and individual dietary habits also make it difficult to establish a direct causal relationship between any observed health benefits and the long-term consumption of foods derived through biotechnology.

3.3. Confirming pre-market exposure estimates

A key step in the pre-market safety assessment process is the generation of dietary intake estimates and their comparison to published guidelines, such as acceptable daily intakes for food additives, tolerable upper intake levels for nutrients, or provisional tolerable weekly intakes for contaminants. A tiered approach to exposure assessment is generally advocated, whereby broad screening tools are used to determine the need for more highly refined consumption estimates (Kroes et al., 2002). The pre-market exposure assessment may provide an initial screening of consumption, as it is often based on several conservative or “worst-case” assumptions that result in overestimates of intake. For example, it is often assumed that all food products within an intended food category contain the ingredient or food component at the maximum specified level of use. In the case of aspartame, increasingly conservative consumption estimates were based on the general replacement of all sucrose, carbohydrate, and traditional sugar-sweetened foods with aspartame-containing foods (Butchko et al., 1994). In addition, the 90th to 97.5th percentile users-only intakes are often used as the basis for evaluation. In short-term dietary surveys this may significantly overestimate the consumption of infrequently used food products. When no

toxicologically significant exposure is indicated as a result of this type of preliminary assessment, further refinement may not be warranted.

In certain situations, PMM may provide valuable confirmation of pre-market consumption projections. For instance, the pre-market exposure assessment may not capture real-world exposure scenarios, or a more accurate estimate of intake may be desired for comparison with upper limits of safety. As well, pre-market exposure estimates may not adequately characterize consumption by specific population groups. These include critical subsets of the population that may be at greater risk due to genetic susceptibility, perturbations in metabolism due to chronic medical conditions, or certain age-groups (Kroes et al., 2002). In these situations, post-market assessment may provide an additional measure of safety through the validation of pre-market assumptions regarding anticipated intake levels and additional sampling to determine patterns of exposure in specific subgroups of the population, particularly those individuals at potentially greater risk.

3.4. Identifying changes in dietary intake patterns or behaviors

With the advent of biotechnology-derived foods with enhanced nutritional characteristics or improved functionality, consumers may self-select for a particular nutritional or physiological benefit. Consequently, actual levels of exposure and any subsequent impact on dietary consumption patterns, and therefore nutritional status, may not be evident until after the market introduction of the biotechnology-derived food product. Potential alterations in the micro- or macronutrient profile of a biotechnology-derived food could significantly affect dietary intakes, causing nutrient deficits or alternatively, causing intakes to approach or exceed the upper level (FAO/WHO, 2000). Similarly, nutritional status may be affected if the biotechnology-derived food product alters consumption patterns via the displacement of other core foods or food components (EC, 1997b). In specific cases, these considerations may necessitate the use of PMM.

The results of the pre-market exposure assessment are critical to identifying the potential short-term impact of the consumption of a novel food or verifying that acceptable safety limits are not exceeded. To assess the long-term impact of the introduction of a biotechnology-derived food on consumption patterns and nutritional status, repeated sampling of specific population subgroups would be required. This could also be useful from a marketing standpoint, to assess the market penetration of a product, identify changing consumer preferences, or verify the intakes of a targeted demographic group. However, the presence of confounding factors makes the long-term monitoring of consumption

patterns difficult and minimizes any observed associations between diet and health, as those individuals who make a nutritionally significant or healthy food-choice also are likely to have significantly different dietary patterns from individuals who do not make similar choices.

4. Methodology for estimating exposure

The implementation of a PMM strategy designed to identify potential adverse or positive effects on human health is dependent upon the availability of accurate consumption data. Exposure assessment methods that have traditionally been used to quantify the intakes of food additives, flavorings and contaminants, micro- and macronutrients, and whole foods, could theoretically be applied to the PMM of biotechnology-derived foods to obtain appropriate consumption estimates and confirm pre-market predictions.

Exposure to a particular substance can be quantified if the food chemical concentration and consumption of a particular food are known or can be estimated with a certain degree of reliability. There are two elements to this process. Adequate data must be available to assess the fate of the product or commodity within the food supply. Secondly, a monitoring program that provides requisite information on the consumption of relevant foods must be established. The hypotheses of the monitoring program dictate the level of accuracy required in the generation of intake estimates via an exposure assessment, which in turn are dependent upon the precision of the supporting data. Therefore, the contribution of exposure assessment to the overall PMM process is directly related to the quality of information underlying the evaluation. This emphasizes the need for setting study objectives a priori, to ensure that adequate and appropriate data are collected for subsequent analyses, and that potential future uses of the data are anticipated. In the event that existing data are used to estimate the intake of novel foods or food components, such as biotechnology-derived foods or foods containing biotechnology-derived ingredients, this also highlights the need for standardized methods of data collection in terms of both food consumption and food composition, to increase the international comparability of results.

In order to quantify the concentration of a biotechnology-derived food or ingredient therefrom at the level of the processed food material or brand level, measures for ensuring the traceability of the commodity or food ingredient must be readily available to document the movement of this material through the feed and food chain (Stave, 2002). If particular food products containing biotechnology-derived ingredients could not be identified with a high level of accuracy

throughout all levels of food production, processing, and distribution, the potential detection of latent health effects from biotechnology-derived foods would not be possible. For some, there is a tendency to consider PMM not on a case-by-case basis, but as the complete representative monitoring of adverse health effects from exposure to biotechnology-derived foods. For this scenario to generate useful data, a central repository for the biotech content of specific foods or primary agricultural commodities would need to be available, and current food composition databases would need to be expanded to incorporate market-specific information. As well, if the aim of a PMM program were to monitor potential long-term effects on human health, temporal information on food composition would need to be included in these databases. Current, historical, and future levels of biotechnology-derived food components in the food supply would need to be accurately measured, in order to accurately assess acute and chronic health effects. Clearly, this would be a time intensive and costly effort.

In order to determine food consumption by specific population groups, several different methods may be applied. Average per capita estimates of food consumption can be determined from food balance sheets or household purchase data, which provide annual estimates of food availability at a national level. However, food availability data generally provide crude overestimates and do not allow accurate measurement of consumption by specific individuals or population groups. Individual dietary surveys, including weighed dietary records, dietary recalls, food frequency questionnaires, or dietary histories, provide more accurate information at the individual level. This includes an approximation of the intake distribution from which estimates for the mean intake and percentiles of high-level consumption can be generated for the total surveyed population and specific user-groups. Assuming that more than one day of intake data are available for at least a subset of the sample, habitual intake estimates can be derived from these short-term measures (NRC, 1986; Nusser et al., 1996). If chronic health endpoints form the basis for the PMM program, the integration of habitual intake values from repeated sampling may be required to provide an estimate of lifetime cumulative exposure.

The accuracy of the exposure assessment for foods derived through biotechnology or ingredients therefrom is dependent upon the model used and the validity of the underlying parameters (Kuiper et al., 2001). In order to assess the intake of specific food components, mathematical methods for integrating food composition and consumption data include, in ascending order of refinement, point estimates, simple distributions, and probabilistic modeling or Monte Carlo analysis. Point estimates combine a single estimate of food chemical concentration with a corresponding fixed, generally

“worst-case”, estimate of food consumption. Alternatively, simple distributions combine the distribution of exposures with a fixed value for chemical concentration. Lastly, probabilistic analyses include a measure of the variabilities associated with both food consumption and food composition data. By utilizing data from these respective distributions, estimates of the probability of various exposure outcomes can be calculated through iterative mathematical modeling. Probabilistic modeling is especially relevant when considering the introduction of second-generation biotechnology-derived foods, where several different products may be intended for a similar nutritional benefit or physiological health effect. Monte Carlo assessment could determine the probability of aggregate exposure to several different biotechnology-derived food sources with the same functional characteristics, and therefore compare intended food uses with consequent exposure in particular target groups, susceptible sub-groups, or the population in general. Recently, with the advent of more sophisticated analytical techniques, biomarker-based methodologies for quantifying exposure to food chemicals are garnering considerable interest, but few have yet been validated (Kroes et al., 2002).

In the development of a monitoring approach, resource allocation should be dependent upon the desired level of precision, the practical applicability of the method, and the nutritional or safety endpoint of interest. When considering the long-term health effects of foods derived through biotechnology, habitual or lifetime intake estimates may be necessary. However, the overestimation of either food consumption, or the biotechnology-derived content of relevant foods, in a long-term epidemiologic study would consequently lead to the overestimation of exposure. Therefore, the risks or benefits associated with the consumption of the biotechnology-derived food would subsequently be underestimated. If accurate exposure assessments are needed, probabilistic modeling provides a valuable refinement to the coarse evaluation obtained via deterministic approaches. However, the cost and resources needed to implement these methods vary substantially, and the potential to determine causation may be limited. The PMM method used to estimate consumption should be evaluated a priori on a case-by-case basis to determine the most appropriate means for establishing a specific relationship between the nutritional enhancement or characteristic trait of the food derived through biotechnology and its potential effects on human health.

5. Conclusions

The use of PMM to establish a causal relationship between the consumption of biotechnology-derived foods and potential adverse or beneficial effects on

human health is difficult and would be resource-intensive in terms of both time and cost. When evaluating the feasibility of PMM, several points bear consideration. Current pre-market safety assessment principles apply to all foods in general, biotechnology-derived or otherwise. To attain regulatory acceptance, however, foods derived through biotechnology tend to be subject to greater scrutiny and a higher standard of safety than that applied to foods derived through traditional means. A requirement for routine PMM of biotechnology-derived foods is not necessary. Where PMM is advocated, it should be applied similarly to all food products, based on a well-defined strategy for determining case-by-case whether monitoring is necessary and/or appropriate. Monitoring should be dependent, not on the technology used to develop the food, but on scientifically driven hypotheses relative to endpoints that potentially compromise human safety or benefit human health. Post-market monitoring could be useful in certain instances where a better estimate of dietary exposure and/or nutritional consequence of a biotechnology-derived food is required, when a potential safety issue, such as allergenicity, cannot be adequately addressed through pre-market studies, or to corroborate dietary intakes of a nutritionally enhanced food with beneficial or adverse effects on human health.

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