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TRENDS IN FOOD SCIENCE &TECHNOLOGY

1. General introduction: the role of science in identifying common ground in the debate on genetic modification of foods

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1.1. Introduction

The purpose of this special issue is to provide an independent analysis of the scientific basis for assessing the benefits and risks of transgenically modified food crops and animals, specifically in relation to their current and future impacts on human health and nutrition worldwide. The transgenic modification of foods is among the major scientific achievements of the last 100 years. It is an advance that has great potential for beneficial and harmful effects; as such, it is appropriate to examine the scientific basis for present and potential uses of the technology and to identify knowledge gaps related to current and future aims and the technologies that enable them.

Achieving the aims of transgenic modification technology requires ongoing dialogue among society and technologists and scientists engaged in the development and application of the technology. A series of key discoveries over the past century in the sciences of genetics, molecular biology and related fields, from Mendel's description in the late 19th century of the principles of genetic inheritance, to Watson and Crick's discovery in the 1950s of the double helix structure of DNA and the recent elucidation of the human genome, have formed the basis for a biological revolution. Scientists responsible for this revolution, which has made the transgenic modification of foods possible, and those who are most interested in its potential applications have been inconsistent in participating in and/or responding to dialogue between science and society. The results of successful dialogue are exemplified by the early implementation of recombinant DNA technology in medicine, leading to such benefits as the production and acceptance of human insulin and other highly bioactive substances. Failures are evident in the serious lack of present consensus on appropriate uses of technology for the transgenic modification of food and fibre crops to improve and/or safeguard human and animal health and the environment. Ideally the dialogue between scientists and society-at-large should reflect mutual concern to improve the human condition and minimise inequalities; dialogue should consider the values of diverse groups and result in the most achievable advantageous balances between science directed at applied missions and science conducted solely for the purpose of generating new knowledge.

This special issue is intended to help redress past failures in dialogue and build on past successes. Its focus is on human health and, more specifically, on the improvement of human nutrition by transgenic modifications of plant and animal food sources. It is intended for lay and professional audiences informed about or involved in scientific and technological fields. Its principal focus is the technological dimension of transgenic modification relevant to human health and nutrition. Environmental, socioeconomic, and cultural concerns

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are also included, although not as extensively, and bioethical and political considerations are given much less attention. The special issue takes no position on appropriate policies that societies should adopt as a consequence of the scientific knowledge that is reviewed, and it consistently strives to assess scientific reliability, recognising that quantifiable boundaries of (un)certainty are a defining characteristic of scientifically derived data. Unfortunately, (un)certainty in the inferences drawn from the reduction of data to information often cannot be quantified to the same extent. However, the robustness of underlying data does help assess the reliability of the inferences drawn from them. Thus uncertainties expressed as probabilities are underscored not to argue for or against specific positions but to facilitate informative debate.

This special issue is motivated by two global forces — mounting population pressures and rising quality-of-life expectations — and the assumption that solutions and responses to the problems and challenges these two forces present have technological dimensions.

1.1.1. Population trends

The world's population reached 6 billion at the start of the 21st century and is expanding at a rate of approximately 800 million per decade. Despite anticipated reductions in growth during this century, the world's population in 2050 is expected to have increased by 132–182%, that is to between 7.9 and 10.9 billion. Six countries account for half of the current annual population growth: Bangladesh, China, Indonesia, India, Pakistan, and Nigeria. Using the least optimistic projections, populations in the 48 countries that represent the globe's less economically developed regions are projected to increase from 4.9 billion to 8.2 billion by 2050 (an increase of 167%). Under such a scenario, it is projected that 75% of the world's population will reside in the world's less economically developed countries by mid-century. It also is of concern that projected growth rates are accelerated in countries classified as 'least developed'. Their population is expected to increase by 274%, from 658 million to 1.8 billion, in the same period (UN Population Division).[1] Many expect that these population pressures will exacerbate food insecurity and micronutrient deficiencies, unless issues of food availability and accessibility are addressed in an anticipatory manner.

1.1.2. Rising quality of life expectations

Rising quality of life expectations represent the second force that motivates this special issue. The relevance of rising expectations is evident in three influential reports. One was published recently by the World Bank (2001), the second is the *UN Millennium Declaration* adopted by the Millennium Summit of the United Nations in September of 2000,[2] and the third is a recent WHO report by the Commission on Macroeconomics and Health (2002). Each report looks beyond survival to significant poverty reduction and improved quality-of-life standards. The latter report takes this a step further with the following assertion:

> "Improving the health and longevity of the poor is an end in itself, a fundamental goal of economic development. But it is also a means to achieving the other development goals relating to poverty reduction. The linkages of health to poverty reduction and to long-term economic growth are powerful, much stronger than is generally understood."

For the purposes of this discussion, it is possible to go yet further by pointing out that health is not achievable unless adequate amounts of wholesome and safe foods are available and accessible during all life stages. This principle is as fundamental as is any other firmly rooted axiom in science.

Thus, although humanitarian concerns often provide the principal arguments for assuring 'food-for-all' across geographic regions and socioeconomic classes, the biologic imperatives for achieving nutrient and food security that are linked to health and economic development are sufficiently strong to promote those goals.

1.1.3. Assumptions

This special issue's focus on the transgenic modification of plants and animals explicitly assumes that such technology has the potential to achieve positive, dramatic, and useful results. The robustness of this assumption is tested throughout this special issue. Generally, arguments promoting the utility of transgenic technologies are based on the increased versatility and speed by which such modifications can be produced, relative to traditional breeding techniques (Custers, 2001), and on the view that the technology offers only partial potential solutions. The focus on transgenic modification is not intended to imply that solutions and responses to current or future problems and challenges should be solely or even partially technological in nature. The only assertion made is that the technological dimension merits consideration along with others, for

[1] UN Population Division, & Department of Economic and Social Affairs (2001) *World Population Prospects — The 2000 Revision,* New York, Population Division, United Nations, available [November 2002] at http://www.un.org/esa/population/.

[2] UN General Assembly. (2000) *United Nations Millennium Declaration*. New York, United Nations, available [November 2002] at http://www.un.org/millennium/declaration/ares552e.pdf.

example economic policies, such as those that govern global trade and agricultural subsidies.[3]

Most importantly, full accessibility to diverse, nutritionally adequate, wholesome diets remains the goal, not the implementation of technological advances for their own sake.

Less explicit, but equally important, are two other assumptions, which are less rigorously explored in this special issue.

The first is that the capabilities for exploiting technological possibilities enabled by current scientific advances must be available to the developing world. This assumption is based on the view that without these capabilities the iterative process alluded to briefly in the opening paragraphs' consideration of the importance of dialogue among science and other members of society will be hampered severely.

The second is that transgenic modifications of plants and animals hold known and unknown risks, as do all technologies, old and new. Implicit in this second assumption is that absolute safety is not an achievable standard. Thus, within the context of specific topics, this special issue explores how available scientific knowledge can assist more comprehensive reviews of the standard of 'reasonable certainty of no harm' and how science can contribute to the public's trust in such processes.

In the light of these assumptions the special issue assumes, as have other attempts to explore this topic[4] that identifying the following is essential:

- the 'magnitude' of benefits and risks;
- who is likeliest to benefit from the application of specific technologies;
- to whom risks are likeliest to accrue — ascertained to the degree possible; and
- the time frame for anticipated benefits and risks.

Thus, in the context of specific topics, the special issue explores how science can help inform answers to these questions.

1.2. The present position

1.2.1. Benefits and risks associated with the products and process of genetic modification

The documented contributions of genetic modifications of animals and food crops to human nutrition come from traditional breeding techniques. Successes have come from applications that have resulted in increased and more efficient production. There are no examples whereby the modification of the composition of specific plant and animal foods through genetic techniques (traditional or modern) has resulted in documented improvements in human nutritional status at a population level. Transgenically modified plant foods currently in the food system were designed, for the most part, to achieve herbicide tolerance or resistance to pests. Other than fish, the development of transgenic animals intended for human consumption remains principally in the research and development phase.

There is evidence that genetic modifications achieved through either traditional or transgenic techniques may result in harm. The two most frequently cited examples of risks that may result from genetic modifications achieved through traditional techniques are the elevation of psoralen concentrations in celery that was bred to be insect resistant (Beir, 1999) and the increased concentrations of solanine in potatoes that resulted from selective breeding (Van Gelder, Vinke, & Scheffer, 1988). The most often cited example of a modification achieved through transgenic techniques is the expression of a Brazil nut gene in soybean, to increase the methionine content of soy (Nordlee, Taylor, Townsend, Thomas, & Bush, 1996). The allergencity of the product halted its further development and commercialisation.

The current lack of clearly demonstrated benefits to consumers of transgenic modifications, and conflicting views about the likelihood of unintended adverse effects may influence the public's views on the acceptability and long-term safety of genetically modified (GM)[5] foods (GMFs).

Indeed most concerns in the current debate about GMFs appear to focus on actual and/or perceived knowledge gaps related to (i) the safety of unintended changes in food composition arising from genetic modifications (Kuiper, Kleter, Noteborn, & Kok, 2001), (ii) the safety of the inserted DNA itself (e.g. consequences of inserting animal or viral DNA into plants; Gasson, & Burke, 2001) and (iii) the potential for transferring gene(s) from one organism to another (e.g. conferring antibiotic resistance to microorganisms in the human gut).[6] Other concerns stem from uncertainties related to

[3] International Institute for Sustainable Development (2001). Summary of the International Conference on Sustainable Food Security for All by 2020, *Sustainable Developments, 58,* 1–9, Manitoba, Canada, International Institute for Sustainable Development, available {November 2002] at http://www.iisd.ca/linkages/download/pdf/sd/sdvol50num3.pdf.

[4] EU-US Biotechnology Forum (2000) *The EU-US Consultative Forum, Final Report,* available [November 2002] at http://europa.eu.int/comm/external_relations/us/biotech/report.pdf.

[5] In this chapter the term genetically modified is used to encompass traditional plant breeding and transgenic changes, whereas transgenic modification refers to the insertion of genetic material into an organism by recombinant DNA techniques.

[6] FAO/WHO (2000) Safety Aspects of Genetically Modified Foods of Plant Origin: Report of a Joint FAO/WHO Expert Consultation on Foods derived from Biotechnology (29 May–2 June 2000), Geneva, Switzerland, World Health Organization, available [November 2002] at http://www.who.int/fsf/GMfood/FAO-WHO_Consultation_report_2000.pdf.

the safety of the process itself for the environment (e.g. reduction in biodiversity) and/or from various religious, ethical or other personal beliefs or preferences.

1.2.2. Anticipated benefits and risks: health and environmental

It is projected that GM plants and animals will provide benefits and risks in two broad, non-mutually exclusive areas: health and the environment. Health benefits are expected to fall into one of four categories—(i) enhancement of food security (enough to eat; Pinstrup-Andersen, 2001), (ii) enhancement of nutrient security (adequate nutritional content; Royal Society of London *et al.*, 2002), (iii) more targeted health benefits, such as passive immunisation (Thanavala, Pang, Lyons, Mason, & Arntzen, 1995) and (iv) the reduction of diet related, adult onset, chronic diseases through the manipulation of specific food components (e.g. fat composition; Palombo, DeMichele, Liu, Bistrian, & Huang, 2000). Environmental benefits are expected to fall into three categories—reduced pesticide use and improved land and water use. The reduced use of pesticides and the health protection such reductions represent are among the salient examples of overlap between health and environmental benefits.

Health risks associated with the approaches that are reviewed generally fall into four categories—allergies, toxicities, nutrient imbalances, and decreasing diet diversity. Allergic reactions generally refer to clinically evident, adverse immunological responses to specific antigens. Toxicity refers to the ability of a substance to cause non-immunological adverse effects to the consumer. Nutrient imbalances refer to the possibility that the quantities of two or more nutrients might interfere adversely with nutrient absorption or post-absorptive utilisation (Institute of Medicine, Food and Nutrition Board, 2001). Concerns about diet diversity arise from the possibility that the biofortification of staple crops might displace multiple foods that traditionally served as good sources of the 'fortificant' and, thus, potentially other food constituents important to health. Diverse diets that include animal foods and a predominance of plant foods are the basis of most recommended food-based dietary guidelines (Tucker, 2001). Unfortunately, the plant constituents responsible for positive health outcomes are understood incompletely. The potential inadvertent omission of putative beneficial plant constituents because of decreasing diet diversity is of concern.

Environmental risks focus most frequently on decreases in biodiversity; however, potential health risks related to the possible allergies associated with the inhalation of pollen or dust that includes GM, allergy causing material has received scant attention (Royal Society, 2002). Decreases in biodiversity may result from enhanced competitiveness brought about by transgenic modifications or from agricultural policies and economic pressures that favour the production of GMFs at the expense of unmodified alternatives.

Categories of risk and benefit in the context of sustainable development are discussed in Chapter 9.

1.3. Assessing recognised and unintended benefits and risks

Given assurances about the safety of intended modifications that are made by proponents of GMFs, many of the public's concerns focus on the possibility of unintended consequences and the risks these represent. It appears that the same scientific advances that lead to 'potential unprecedented benefits' also increase the assurance level sought by the public when they are considering the efficacy of putative benefits, lower the probabilities of harm the public appears willing to accept, and enhance the perceived personal control that is desired in order to reject or accept known and unknown risks. This is most apparent in the different levels of evidence demanded for products developed through transgenic modification and traditional breeding techniques (EU-US Biotechnology Forum).[7] Although this situation may appear unique to considerations of transgenic *versus* traditional breeding products, it is consistent with changes in the public's expectations of the broader food and nutrition sector that have been unfolding over the last 80 years. Major public nutritional concerns have shifted in that period, from a sole focus on nutritional deficiencies, to concerns about diseases associated with nutrient excesses, to the present expectations that the food supply should protect from disease, promote a state of well-being that transcends the absence of clinical disease and, increasingly, that such expectations should be met with minimal or no risk. In the USA, the private sector responded to this shift by adding health and structure/function claims to food and nutrient/supplement labels (Nesheim, 1999; Bretcher, Bender, Wilkening, McCabe, & Anderson, 2000) to gain marketing advantages for their products. This represents a marked shift from traditional marketing claims limited to improved taste and low cost. Furthermore, progressive improvements in the quality and quantity of the food supply have been identified as major contributors to improving health and to the enabling of major economic achievements (Link & Phelan, 2002). Thus, expectations that the technological achievements that make GMFs possible should be coupled to enhanced assurances about health risks are not surprising.

This view also is underscored by a longer-term historical perspective. One of the earliest examples of science and policy failing to 'get it right' is the British Admiralty's attempt to prevent scurvy among its sailors.

[7] EU–US Biotechnology Forum (2000) *The EU-US Consultative Forum, Final Report,* available [November 2002] at http://europa.eu.int/comm/external_relations/us/biotech/report.pdf.

The Admiralty noted correctly, in the 18th century, that the Mediterranean lemon helped to prevent scurvy. However, it chose to substitute the Mediterranean lemon with the West Indian lime (McNeil, 1977). Unfortunately, the West Indian lime has a much lower vitamin C content than the Mediterranean lemon despite their similar appearance and taste; thus scurvy continued to affect British sailors.

Another example is the improvement of agricultural practices in the late 19th and early 20th centuries, which led to increased availability of animal products. Significant nutritional benefits resulted from the change; however, the new diet also led to increased saturated fat consumption. Shifts in agricultural policies and practices, therefore, inadvertently helped catapult cardiovascular disease to become a major cause of mortality and morbidity in western countries (Stallones, 1980).

The most recent example is margarine. The good intentions that led to its recommendation as a way of reducing saturated fat intakes failed to anticipate the adverse effects of trans fatty acids (Katan, 2000).

Reflecting briefly on these examples illustrates that the following question is not without merit:-

'Why shouldn't the 'same' science that 'promises' previously unattainable benefits also substantially upgrade assurances about anticipated benefits and unintended risks, in order to avoid these types of mistakes?'

1.3.1. Relevant technology and biology

However, is it 'reasonable' to expect that science 'anticipate' unintended effects? This question speaks directly to growing expectations that scientific endeavours should provide technical information within objectively determined 'limits of uncertainty' and 'anticipate' problems and solutions, rather than being limited to 'after the fact' assessments. The question also highlights the need for more comprehensive compositional analyses of primary and secondary plant metabolites and for more comprehensive assessments of the functional consequences of the consumption of GM whole foods. Available technologies and biological knowledge can help address such expectations.

Growing capabilities in proteomics and metabolomics permit increasingly comprehensive assessments of compositional changes. The principal problems these advances confront lie not in the compositional analyses themselves, but in assessing the significance of the results of those analyses (Kuiper *et al.*, 2001). For example, the range and causes of normally occurring compositional fluctuations in primary and secondary plant metabolites are incompletely understood. Without a more complete understanding of both, more comprehensive analytical information may not be useable.

Nonetheless, as reviewed below, present knowledge strongly supports the likelihood that unanticipated compositional changes will result from both transgenic modifications and traditional breeding. However, this says nothing about the functional health consequences of such changes. The potential for allergenicity is the best-documented consequence, but there is little scientific work that points to other specific problems with any of the GMFs currently approved for human consumption (Taylor & Hefle, 2001). However, this observation is tempered by the dangers of confusing the absence of information with the absence of effects**,** as exemplified by historical experiences with trans fatty acids and saturated fats. With this caveat in mind and considering the high likelihood that compositional differences will be multiple rather than single, testing the safety of whole foods becomes central to assessing the functional consequences of unanticipated compositional changes.

Generally tests of 'safety/toxicity' rely on the description of dose–response relationships, which are impossible to achieve in studies of whole foods based on traditional techniques.[8]

Such models, however, reflect past technological possibilities and limitations. Microarray technology is an example of an advance that may support new approaches for assessing the functional consequences of feeding whole foods (Noordewier & Warren, 2001; Phelps, Palumbo, & Beliaev, 2002).

The feeding of whole foods coupled to systematic, multigenerational assessments of differential gene expression, in specific tissues, at diverse periods of development, in multiple mammalian species is one approach suggested by this technology; specific differences in gene expression between experimental and control groups could be screened and followed up with more specific functional assessments. This is theoretically feasible and offers a highly comprehensive approach to screening simultaneously for 'anticipated' and 'unanticipated' benefits and harm. Such approaches are neither easy nor inexpensive. However, it is easy to foresee the development of guidelines, such as those discussed by the EU-US Biotechnology Forum[9] below, to determine the type and comprehensiveness of information required to assess 'reasonable certainty of no harm' and to substantiate the efficacy of putative benefits. Proteomics and metabalomics offer complementary opportunities.

[8] FAO/WHO (2000) Safety Aspects of Genetically Modified Foods of Plant Origin: Report of a Joint FAO/WHO Expert Consultation on Foods derived from Biotechnology (29 May–2 June 2000), Geneva, Switzerland, World Health Organization, available [November 2002] at http://www.who.int/fsf/GMfood/FAO-WHO_Consultation_report_2000.pdf.

[9] EU-US Biotechnology Forum (2000) *The EU–US Consultative Forum, Final Report,* available [November 2002] at http://europa.eu.int/comm/external_relations/us/biotech/report.pdf.

1.3.2. Concerns about unintended effects

Given that technology is not necessarily a barrier, are concerns regarding unintended significant functional consequences misplaced?

The functional characterisation of protein networks, the flexibility of protein synthesis, through alternative splicing, and the multifunctionality of the proteome, transcriptome, and metabolome suggest that the modification of genomic sequences, through the introduction of one or more complete copies and/or fragments of genes into a target organism, is likely to have effects beyond those that are intended.

A very useful overview was published recently in *Nature* that supports the need to rethink the potential consequences of a flexible genome. Greenspan (2001) stresses that the single-gene-single-function paradigm has been so strong that the demonstration of pleiotropy has often been 'sufficient to dismiss the importance of a gene.' Increasingly however, the concept of isolated, single-gene-single-function, sequential linear pathways often is found to fail rigorous experimental scrutiny. This has led to a new appreciation that an organism's hereditary/regulatory machinery appears to act through complex, interactive distributed networks. This alternative suggests that genomic robustness is not the result of redundancy (i.e., two or more independent genes capable of bringing about the same outcome) but of degeneracy (i.e. an interconnectivity among multiple specific genes that imparts an ability to attain the same or very similar outputs via multiple strategies). Such interconnectivity is consistent with the nature of protein networks, which appear to follow a 'highly heterogeneous, scale-free topology' rather than a 'uniform exponential topology in which proteins on average possess the same number of links' (Jeong, Mason, Barabasi, & Oltvai, 2001). Such characteristics suggest that random genetic changes are unlikely to have serious consequences to the genetically altered organism. Confidence in the view that pleiotropic effects of random genetic modifications will not be harmful to altered organisms is enhanced if most metabolic networks are interconnected in this way. However, the interconnectivity of metabolic networks also suggests that if a 'key' node in the network is altered, outcomes may not be preserved. Recent work in yeast by Jeong and colleagues demonstrates that the likelihood that the removal of a protein proves lethal to an organism correlates with the number of interactions of the protein. However, this does not preclude the possibility that changes of less interconnected proteins could be significant. The severity of the effects of changes involving less interconnected proteins may result in alternate strategies that, while they successfully preserve outcomes key to the altered organisms survival, may be detrimental to those who consume it.

Considering that plant genomes are estimated to contain 20 000–60 000 genes, that approximately 15–25% encode proteins that play enzymatic roles in the production of hundreds of thousands of low molecular weight plant compounds, that only a few compounds represent 'so-called' primary metabolites (i.e. metabolites common to most plants), and that metabolic networks are interactive in nature, it can be appreciated why, at least in principle, pleotropic effects merit continued consideration (Pichersky & Gang, 2000).

To appreciate the possible impacts of unintended consequences, it is reasonable, to seek examples of unintended consequences of a highly specific, successful alteration. The best example to examine may be the intended and unintended consequences of folate fortification. Even though folate fortification has not been achieved by transgenic means (Scott, Rebeille, & Fletcher, 2000), it can be used as a case study of the potential consequences of highly targeted changes that come into widespread use and involve no ancillary alterations of primary or secondary metabolites.

As background—folate fortification is required of processed grains in the USA. The levels required could be achieved (at least in theory) by transgenic means. The goal of fortification is the prevention of neural tube defects (Murphy *et al.*, 2000), which are among the most common human congenital abnormalities. Neural tube defects are estimated to occur in 1 in 1000 live births; the major types of these defects are anencephaly and spina bifida.

Current data indicate that folate fortification has succeeded in its intended effect; that is, it has reduced the incidence of neural tube defects (Murphy *et al.*, 2000). However, the mechanism remains incompletely understood; thus, it is not possible to determine, conclusively, whether the decrease in neural tube defects is the result of preventing the birth defects or the supplementation effectively reduces the viability of affected infants early in development, thus preventing their birth (Hook & Czeizel, 1997).

A small but significant increase in the rate of spontaneous abortions is associated with increased folate intakes, as shown in Fig. 1.1 (Hook & Czeizel, 1997). The data can be interpreted in at least two ways. Higher folate levels may decrease fetal viability. Alternatively high folate intakes may prolong survival of affected fetuses to stages that allow their loss to become evident

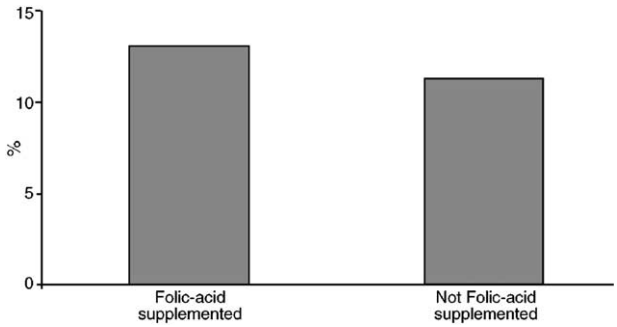

Fig. 1.1. Change in spontaneous abortion associated with folate supplementation. Adapted from Hook & Czeziel, 1997.

to the mother. It is estimated that 20–50% of all pregnancies are lost unknowingly to women because of the early stage at which many spontaneous abortions occur.

Individuals who carry polymorphisms associated with risk for folate-responsive neural tube defects appear to be at increased risk for spontaneous abortion (Nelen, Blom, Steegers, den Heijer, & Eskes, 2000; Unfried *et al*., 2002). Studies of naturally occurring and genetically engineered animal models that carry mutations in genes seemingly unimportant to folate metabolism show that fetal viability is reduced by the defect and that maternal folate supplementation can rescue affected fetuses (Greene & Copp, 2002). If such rescues occur in humans who are supplemented with folate, what other consequences may accompany widespread folate supplementation?

Provocative and controversial data from southern Spain strongly hint that current manipulations of the food supply may influence the genotype of population(s) over a very short period (Munoz-Moran, Dieguez-Lucena, Fernandez-Arcas, Peran-Mesa, & Reyes-Engel, 1998). Fig. 1.2 illustrates the shift in the frequency of an alanine to valine mutation in the methylenetetrahydrofolate reductase (MTHFR) gene, which encodes a protein that plays a key role in normal folate metabolism. This VV genotype is linked to a decreased activity in the MTHFR enzyme and is associated with increases in plasma homocysteine and birth defects. Supplementation with folate is associated with both a reduction in homocysteine levels and decreased birth defects.

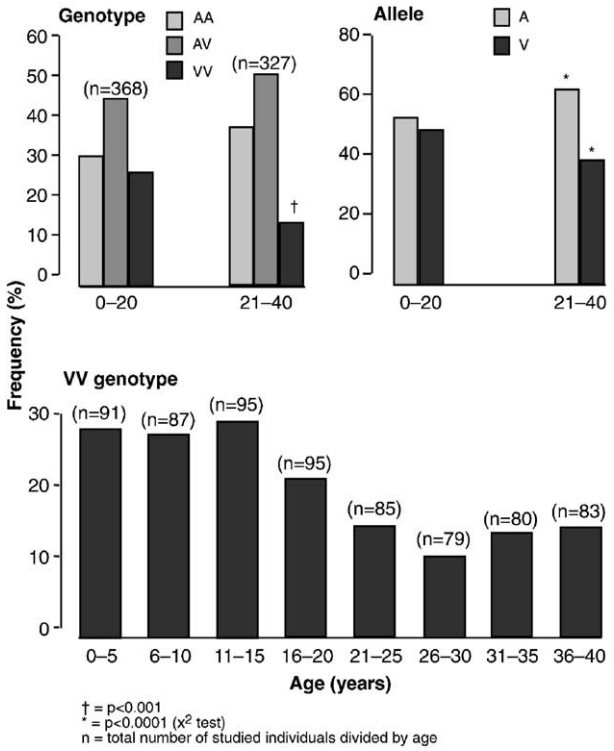

Fig. 1.2. Frequency of MTHFR 677C→T mutation (alanine to valine) in southern Spain. From Muñoz-Moran, E., Dieguez-Lucena, J.L., Fernandez-Arcas, N., Peran-Mesa, S., & Reyes-Engel, A. (1998). Reprinted with permission from Elsevier Science (*The Lancet*, 1997, Vol. 350, Pages 513–515).

The increasing frequency of the VV genotype in the population studied coincides with the timing of increased folate supplementation of pregnant women in that population and most probably represents the rescue of fetuses that would have been aborted spontaneously without the added folate in maternal diets. If this genotypic shift is confirmed, it will support the possibility that marked changes in the nutrient content of commonly consumed foodstuffs can alter the genotypes of populations. If dietary changes are effective in inducing MTHFR allele selection that is detectable at a population level, over such a short period, perhaps other selections are possible and ongoing as a consequence of today's rapidly changing food supply. Furthermore, understanding the role of nutrition in early and subsequent development may become more important, as the ability to change the composition of the food supply increases.

These are not trivial considerations. They raise the important point that food is unlike most other commodities that are purchased. Owing to advances in biology, it is recognised more than ever that phenotypes can be acutely and perhaps permanently manipulated by the food supply. Historically, acute effects have not been difficult to identify, and they are increasingly better understood. The phenotypic consequences of classical nutrient deficiencies are known, as are some acute toxicities arising from nutrient excess. Longer-term phenotypic consequences of significant shifts in food composition or supply are not well understood. Nonetheless, human epidemiological data and various types of animal experiments demonstrate that epigenetic changes with long-term or possible permanent health consequences are also likely, in response to nutritional stimuli (Waterland & Garza, 1999, 2002). If allelic prevalence in populations can shift as quickly as suggested by the Spanish data or permanent epigenetic changes can be imprinted in early development, through nutritional means, current policies could result in dependencies that may or may not be to the collective or individual advantage.

1.4. Scientific dimensions of other issues of current interest

Food labelling, tracing foods through the food system, and post-market surveillance are examples of other issues of current interest that raise significant technological challenges. The nature and magnitude of these challenges hinge on the relevance of unanticipated compositional changes to GMFs and to their functional relevance to consumers. All three examples present challenges related to setting appropriate detection limits of GM material and the use or development of technologies for their determination. Identifying appropriate detection limits for labelling and tracing foods is most dependent on the nature of likely functional con-

sequences, the extent of exposure, and dose-effect relationships. The challenges presented by potential allergens, for example, in which case trace amounts may be life threatening, are different to those presented by substances that do not present risks below established thresholds. A more complete consideration of these issues is found in Chapter 8.

1.5. Determining what and how much information is needed

Considerations such as these raise the need for guidelines to determine the magnitude of effort that is appropriate to assure 'reasonable certainty of no harm,' tracing foods through the production, processing, marketing, and distribution system, etc. Several groups that have examined various facets of GMFs have included such guidelines in their discussions and recommendations. Guidelines recommended by the EU–US Biotechnology Forum appointed by Presidents Prodi and Clinton provide a recent example.[10]

- **Taking action proportionate to the nature of the potential risk**

Assessing potential risk is at the core of risk assessment. The hazard or hazards that are of concern must be identified, the hazard must be characterised in the most quantitative terms possible, the underlying mechanisms of action must be understood and the exposure must be assessed. The goal of these evaluations is to have a robust assessment of the probability and severity of adverse effects and of the likely exposure to the offending agent of populations who are at particular risk and the general population.

- **Applying consistent precautionary limits in assessing all food products**

This guideline addresses the need for consistency in risk analyses of all food products, recognising, for example, the differences and commonalities among the risks presented by GMFs, traditional breeding, and the chemical and microbial contamination of foods through other mechanisms.

- **Applying more stringent limits on risks that are not easily reversible**

This is relevant to how quickly remedial actions can be taken and how quickly adequate responses can be anticipated, when products in widespread use are found to present a significant risk. Of particular concern to this discussion is the self-replicating nature of genomic transformations.

- **Examining the extent to which precaution advances or detracts from relevant societal goals**

The political nature of policies and decisions that directly or indirectly affect the food supply and the political dimensions of risk assessment, management and communication are recognised. The consumer's perceived degree of personal control appears to play a major role in the nature, likelihood, and severity of risks individuals are willing to accept. Alcohol and tobacco are examples of products that present substantial, recognised risks and yet, significant numbers of individuals are willing to accept these, in the light of perceived personal gains.

- **Consideration of the costs that caution imposes**

Finally, an obvious fact of economic life is that there is no 'free lunch.' People encounter and willingly accept risks constantly in their daily lives. Minimising diverse risks comes at different costs. Effective understanding of the determinants of costs people are willing to tolerate and those that they are not must account for the complex interactions of multiple variables that are embedded in these guidelines.

Guidelines such as these reflect the conclusion that a 'one size fits all' approach for assessing risks and benefits of GMFs is neither sustainable nor advisable. The alternative to the flexibility inherent in such guidelines is either doing 'everything' or 'nothing,' a choice that is inherently counterproductive regardless of views about the appropriateness or inappropriateness of GMFs.

Such guidelines are useful only if they are developed sufficiently well to allow the clear delineation of information that is needed for their effective application. Understanding what information is required, determining the limits of uncertainty that are appropriate to its derivation, and developing objective processes for the discovery of knowledge are all key areas that need the participation of science. However, it is equally clear that good science will not be enough; each guideline also embeds dimensions that are broader than those normally encompassed by the scientific process.

1.6. Outline of special issue

Chapters 2–4 review topics pertaining to GM crops and human nutrition and food quality, improving agricultural practices, and industrial products and processes; Chapters 5–7 review GM fish, livestock, poultry, and microorganisms. Each of Chapters 2–7 reviews current knowledge on the expected or potential con-

[10] EU–US Biotechnology Forum (2000) *The EU–US Consultative Forum, Final Report,* available [November 2002] at http://europa.eu.int/comm/external_relations/us/biotech/report.pdf.

tribution of GM technology, outcomes and impacts of the use of GM organisms (GMOs), standards of use, methods for evaluation of outcomes and impacts, and knowledge gaps. Chapter 8 reviews the scientific basis for risk assessment of GMOs. Economic and social issues pertaining to the use and control of GMOs are reviewed in Chapter 9, and public attitudes toward GMFs are discussed in Chapter 10. This outline is intended to serve the process of dialogue alluded to above and thus inform ongoing discussions related to the application of technological innovations that make GMFs possible.

1.7. References

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