IFT Expert Report on Biotechnology and Foods

Preface

The use of modern biotechnology (recombinant DNA technology) to produce foods and food ingredients is a subject of heightened interest among consumers and public policy makers, and within the scientific community. As a result, the news media have extensively covered the subject, seemingly with each development. Eager to contribute to a meaningful dialogue on scientific issues and consumer concerns about rDNA biotechnology, the Institute of Food Technologists (IFT), the 29,000-member nonprofit society for food science and technology, implemented a new initiative. IFT's leaders provided the impetus and strategies, including establishment of a Task Force, for the initiative. The Biotechnology Task Force identified the overall goal of providing science-based information about this modern tool to multiple audiences, e.g., its members, journalists, and the general public. The Task Force identified issues within three main topics—safety, labeling, and benefits and concerns—and decided that each would be addressed within a comprehensive, scientific report.

IFT convened a panel of experts, comprising IFT members and other prominent biotechnology authorities, to prepare report sections on each of the three main topics. Each panel contributed to an *Introduction* section. Thus, this scientific report consists of four parts: *Introduction*, *Safety*, *Labeling*, and *Benefits and Concerns*. Members of the panels of experts are identified within each report section. IFT's Office of Science, Communications, and Government Relations coordinated the development of the report.

The report focuses on rDNA biotechnology-derived foods, food ingredients, and animal feed of plant origin, and on the use of rDNA biotechnology-derived microorganisms such as yeasts and enzymes in food production. Milk from cows that have received rDNA biotechnology-derived hormones is discussed; transgenic animals resulting from the application of rDNA biotechnology techniques to animal production are not addressed.

The *Introduction* presents background information to help readers understand rDNA biotechnology-derived foods and federal regulation and oversight of rDNA biotechnology. The *Safety* section discusses issues relevant to evaluation of rDNA biotechnology-derived foods, including the concept of substantial equivalence, introduced genetic material and gene products, unintended effects, allergenicity, and products without conventional counterparts. The international scientific consensus regarding the safety of rDNA biotechnology-derived foods is also discussed. The *Labeling* section provides an overview of the relevant United States food labeling requirements, including constitutional limitations on the government's authority to regulate food labeling and specific case studies relevant to labeling rDNA biotechnology-derived foods. The *Labeling* section also discusses U.S. and international labeling policies for rDNA biotechnology-derived foods and the impact of labeling distinctions on food distribution systems. Consumer perceptions of various label statements are also discussed. The *Benefits and Concerns* section considers in detail numerous specific benefits regarding plant attributes; food quantity, quality, and safety; food technology and bioprocessing; animals; the environment; economics; diet, nutrition, and health; and medical benefits. Concerns addressed include economic and access-related concerns, research incentives, environmental concerns, monitoring, allergenicity, antibiotic resistance transfer, and naturally occurring toxicants.

The report sections were published in three issues of *Food Technology*. The first page of each report section identifies the *Food Technology* publication volume, month, and page numbers.

IFT extends its deep gratitude to each of the panelists. These experts traveled to full-day meetings in Chicago and devoted many other hours to drafting their respective sections of the report, participating in multiple conference calls to discuss drafts, and reviewing the other report sections. IFT appreciates their invaluable dedication to furthering the understanding of rDNA biotechnology—a tool that is vital to enhancing the world's food supply.

Founded in 1939, the Institute of Food Technologists is a nonprofit scientific society with 29,000 members working in food science, technology, and related professions in the food industry, academia, and government. As the society for food science and technology, IFT brings sound science to the public discussion of food issues.

Contents

IFT Expert Report on Biotechnology and Foods

Introduction

The use of modern biotechnology to produce foods and food ingredients is a subject of significant public interest today, at the consumer, public policy, and scientific levels. The popular press and media have reported a wide range of views on these foods and food ingredients.

To promote a meaningful public discussion of these foods and food ingredients, IFT has commissioned three expert panels to review the available scientific literature on three different, but related aspects, of these foods and food ingredients: human food safety, benefits and concerns, and labeling. The panels' report will also discuss some of the public policy implications of the underlying science.

In keeping with the widespread usage in the popular press and media, the report uses the terms "rDNA biotechnology" and "rDNA biotechnology-derived foods" to describe the application of recombinant DNA, or rDNA, technology to the genetic alteration of plants and microorganisms, and foods made therefrom. This technology, commonly known as genetic modification or gene splicing, allows for the effective and efficient transfer of genetic material from one organism to another. Instead of cross-breeding plants for many generations or introducing mutations to introduce a desired trait—processes that are imprecise and that sometimes introduce unwanted changes—scientists can identify and insert one or more genes responsible for a particular trait into a plant or microorganism with greater precision and speed, although the current technology produces gene insertions at random locations. These transferred genes, or transgenes, do not have to come from a related species in order to be functional, and can be moved virtually at will among different living organisms.

This report focuses on rDNA biotechnology-derived foods, food ingredients, and animal feed of plant origin, and on the use of rDNA biotechnology-derived microorganisms such as yeasts and enzymes in food production. While milk from cows that have received rDNA biotechnology-derived hormones is discussed, transgenic animals resulting from the application of rDNA biotechnology techniques to animal reproduction are beyond the scope of this report. Health and medical benefits associated with rDNA biotechnology-derived plants are discussed briefly.

This first section presents background information to assist the reader in understanding rDNA biotechnology-derived foods. It will first discuss biotechnology in the broad sense and how rDNA biotechnology-derived foods are the latest step in a 10,000-year sequence of human intervention in the genetic improvement of food, then it will discuss federal regulation and oversight of rDNA biotechnology.

Overview of Biotechnology

Biotechnology in the broad sense is, in fact, not a discrete technology. It refers to a group of useful enabling techniques, including but not limited to genetic modification, that have wide application in research and commerce. Over the past several decades, such techniques have become so integrated into the practice of plant breeding and microbiology and so commingled with conventional techniques as to blur distinctions between "old" and "new." A useful working definition of biotechnology used by several United States government agencies is the application of biological systems and organisms to the production of useful goods and services. These encompass advances in biology, genetics, and biochemistry to tech-

This section is reprinted from *Food Technology*, vol. 54, no. 8, August 2000.

nical and industrial processes as different as drug development, fish farming, forestry, crop development, fermentation, and oil spill clean-up (OTA, 1984).

Turning to food biotechnology, the history of the development of modern genetics and molecular biology, which underpins much of this technology, has been discussed and reviewed by a number of authors. Two accounts accessible to interested non-specialists are those by Grace (1997), and Watson and Tooze (1981). Historically, the key role played by deoxyribonucleic acid (DNA) in determining the mechanism of inheritance in all living organisms was first established by Avery et al. (1944), who, using S and R type pneumococci, showed that DNA from one strain of bacteria can be taken up by a different strain, hereditarily altering that second strain. This pivotal demonstration was the first description of transformation, a mechanism of gene transfer that involves the uptake and integration of isolated DNA by an organism. It is a phenomenon that is central to an understanding of rDNA biotechnology, and may even be said to mark the beginning of the concept of the new biotechnology.

Geneticists had earlier recognized that the chromosomes, linear structures composed of DNA and protein, were the vehicles of inheritance in the sense that they carried genes determining inherited characteristics. Genes were conceived of as beads on a string. Genes that encode similar functions in different organisms are called orthologs (also loosely called homologs), and genes that have the same structure in different organisms are said to have synteny (also loosely called homology). Many organisms are diploid, that is, they have two sets of chromosomes, one inherited from each parent. The pairs of chromosomes are present, in a constant and characteristic number, in all the cells of an organism.

When the cells divide, the chromosomes also divide equally, by a process called mitosis. When a diploid organism prepares for sexual reproduction by forming gametes, a reduction division, called meiosis, reduces the number of chromosomes so that each egg or sperm cell has exactly half the diploid number. At meiosis, there is a random assortment of maternally and paternally derived chromosomes, which is further complicated by exchanges between paired homologous chromosomes due to "crossing over" that takes place between chromosomes. Thus, in a sense, the genetic constitution of each gamete resembles a hand of cards dealt from a well-shuffled deck. In nature, gametes (germ cells) generally unite randomly at fertilization to restore the diploid condition. Plant breeders use this variation by selecting the best plants that result from these combinations and stabilizing them by inbreeding or propagating them vegetatively. Thus, sexual reproduction produces "recombinant" organisms, in the sense that the organisms possess DNA rearranged and combined from two separate organisms.

The task of plant and animal breeders is to select individuals that retain in a heritable way the desirable features of the parent lines. The segregation of genes with easily detected effects, such as round versus wrinkled seeds, was observed by Mendel, who first described the discrete nature of inheritance in peas.

Twentieth-century plant breeding, even before the advent of modern rDNA biotechnology methods, sought ways to take advantage of useful genes and gradually has found a wider and wider range of plant species and genera on which to draw. Breeders have long used interspecies hybridization, transferring genes between different, but related, species. Subsequently, plant geneticists found ways to perform even wider crosses between members of different genera using tissue culture techniques. Crops resulting from such wide crosses are commonly grown and marketed in the U.S. and elsewhere. They include familiar and widely used varieties of tomato, potato, corn, oat, sugar beet, bread and durum wheat, rice, and pumpkin.

Although DNA was known to play a key role in inheritance, it was not until Watson and Crick (1953) described the structure of the double-stranded DNA molecule that scientists understood how the exact replication of the DNA occurred at each cell division and how the sequence of nucleotides in the DNA molecule determined the sequence of nucleotides in messenger ribonucleic acid (mRNA) and in turn, through a triplet code, the sequence of amino acids in a protein.

When the DNA sequence of a gene is expressed, it is transcribed to form a single-stranded mRNA molecule, which is translated to make a protein. It is now known that the instructions for programming the development of a fertilized egg cell, or zygote, into an adult organism composed of millions of cells carrying identical sets of genes are encoded in the nucleotide sequence of the DNA. This is in the form of a code based on the four nucleotides, adenine, thymine, cytosine, and guanine, which form a series of three-letter words, or codons, that specify the amino acid sequences of the many thousands of proteins that carry out the cellular functions.

Biochemists have established that the basic metabolic events in all organisms have far more in common than was previously suspected. They found that not only is DNA the universal code used by all living things, but that the central functions of all organisms are nearly identical. DNA and ribonucleic acid (RNA) replication, protein synthesis, photosynthesis, energy metabolism, and a host of other functions were found to have much in common throughout living systems. Molecular biologists soon learned to determine the sequences of genes that encoded these properties.

As more and more genes were sequenced and compared, scientists found that the products of the genes that encode similar traits in very diverse organisms are often very similar in protein sequence. It also became apparent that most genes do not have characteristics specific to the organism in which they are found. In fact, it is impossible to determine the organism from which a gene arises by inspection of the gene sequence alone, although codon usage does vary among major groups of organisms. Put another way, there is no way to identify "fish genes," "tomato genes," or "broccoli genes." The uniqueness of organisms instead lies not only in the DNA sequences of their genes, but also the organization of the genes which are present, and at what time and to what extent they are expressed.

Enormous quantities of DNA have now been sequenced for a wide range of organisms. The genomes (the totality of genetic material) of several bacteria and small organisms have already been fully sequenced, and the genome sequences of higher organisms such as plants, insects, animals, and humans will soon be available. In fact, about 40 genomes are expected to have been sequenced by the end of 2000 (Lander and Weinberg, 2000). Even sequencing of the human genome is now more than 90% complete. One key observation is that, in the

Expert Report

CONTINUED

course of determining DNA sequences, identical genes are regularly found in organisms that are only remotely related. This observation has provided evidence that genetic transfer has occurred in nature to produce natural rDNA-containing organisms.

A discovery important to modern rDNA biotechnology techniques (Linn and Arber, 1968) was the recognition that a series of so-called "restriction enzymes," thought to protect cells from invading viral DNA, could be used to cut the DNA at precise sites defined by the sequence of four, five, or six nucleotides at the site where the cut would be made. By using DNA ligases—enzymes that fuse together two pieces of DNA—the pieces of DNA formed by cutting DNA with restriction enzymes could be joined together into a single piece of DNA. The fragments or pieces of DNA could also come from two different organisms. Pieces of DNA from different organisms are often called "heterologous DNA" and when heterologous fragments of DNA are joined together by a ligating enzyme, the fragment of DNA is said to be a "recombinant" molecule; i.e., it recombines DNA from two heterologous sources. The word "recombinant" is used analogously to describe the recombination of DNA of the parental chromosomes that takes place during meiotic cell division.

This ability to splice together pieces of heterologous DNA means that it is possible to clone fragments of DNA by splicing them into a bacterial plasmid, a circular self-replicating DNA molecule that multiplies inside the bacterial cell when it is introduced into the bacteria by a process called transformation. If the heterologous DNA was spliced into a site on the plasmid where the DNA would have an opportunity to be transcribed to mRNA, and then translated to form a functional and active protein, its action in the cell can be detected so that the function of the cloned fragment can be identified. By this means, it is possible to produce very large numbers of copies of a known DNA fragment that can then be used to transform other organisms, such as plants and animals.

Two methods of plant transformation are in use at the present time. One method, known as the ballistic or free DNA method, uses a gun to shoot microscopic particles of gold or tungsten into cultured plant cells. The particles are first coated with the DNA carrying the gene of interest, isolated from the bacteria in which it has been cloned. Then, these particles are accelerated by releasing a charge of helium under high pressure. A small proportion of the particles penetrate not only the plant cell wall but the nuclear membrane as well. The DNA carried by these particles can be taken up and integrated into plant chromosomes.

Although the entire nucleotide sequence of the segment of DNA to be introduced is usually known with the free DNA method, the site where the DNA is integrated cannot be predicted. While the sequence of the starting DNA can be determined with precision, free DNA delivery frequently leads to integration of multiple copies or portions of the gene of interest. Selectable markers, i.e., genes whose expression can be detected soon after the cells have been treated with DNA, are used to recover the very small fraction of cells that are transformed. For example, if the markers confer resistance to a toxic agent, such as an antibiotic or a herbicide added to the culture medium, then only those cells which carry and express the non-host DNA are able to grow.

Another method, more widely used today, employs the bacterial plant pathogen *Agrobacterium tumefaciens*. In nature, this bacterium infects wounds in broad-leafed plants and induces the formation of tumors or galls. The mechanism of tumor induction using the *Agrobacterium* method involves the movement of a part of the DNA of a large plasmid carried by the bacterium into some of the host cells. In some of the cells, a host cell chromosome takes up a part of the plasmid DNA, whereupon the plasmid DNA directs the cell to undergo repeated divisions that result in tumor formation. This integrated tumor-inducing DNA also directs the synthesis of an uncommon group of amino acid derivatives (opines) that only the bacterium can use as a source of carbon and nitrogen for further growth. The tumor-inducing DNA can be made nonpathogenic by removing the elements responsible for releasing the controls of cell division and for opine formation. The nonpathogenic DNA (T-DNA), which no longer induces tumor formation, can then be used to carry a different organism's gene into a host-cell chromosome. As with the free DNA method, cells carrying T-DNA can be detected by incorporating selectable markers such as antibiotic or herbicide resistance. In this way, only cells carrying the resistance markers can grow on culture media in which the antibiotic or herbicide is incorporated; all untransformed cells are killed.

The use of *A. tumefaciens* greatly increases the precision of DNA insertion. *Agrobacterium* uses specific DNA-signaling sequences (T-DNA borders) to determine the start and stop points of DNA transfer to plant cells. Although there can still be substantial variation in the transferred DNA, the endpoints of DNA transfer are usually localized to a small region, within 10–100 bases. Moreover, the number of copies of inserted genes can usually be limited to one or a few. Recent improvements in transformation procedures have permitted researchers to largely switch from the free DNA techniques to *Agrobacterium*. In any case, the precision of rDNA biotechnology permits accurate determination of the location and number of copies of the inserted DNA, even if the location of DNA insertion cannot be controlled.

Scientific knowledge of the structure of the plant genome has grown as a result of research on the "laboratory plant" *Arabidopsis thaliana*, a small plant in the cabbage family that has only five chromosomes and grows from seed to seed in about seven weeks. Sequencing the entire genome of this plant is now almost complete. Because of the great similarities among plants in general, *Arabidopsis* can be used as a crop plant analog, and DNA sequences from *Arabidopsis* of known function can be used to identify their homologs in economic crops. DNA markers can be used to identify chromosome regions that carry blocks of genes of individually small effect, quantitative trait loci or QTLs, which contribute to characteristics such as yield, maturity, baking quality, flavor, and aroma, making possible much more sophisticated selection procedures for plant breeding (McCouch, 1998).

The opportunity to select and multiply a gene of interest and then introduce it into a crop plant was of great interest to most plant breeders because it heralded the era of directed genetic change.

It was now possible to introduce a new gene into an accepted and adapted variety in a single step. This reduced the long and tedious process of winnowing out the many forms that are inferior to the adapted varieties that are characteristic products of most conventional breeding programs which introduce new characters from wild unadapted material. In practice, rDNA biotechnology-derived forms can be better thought of as new forms of germplasm to be incorporated into breeding programs, thereby extending the range of characteristics available to a breeder. The breeder must still test the results to ensure that the step of introducing the non-host gene, or transgene, causes no other changes that would be detrimental to the farmer, the consumer, or the environment. As discussed in the *Safety* section of the report, these tests include detailed analyses of the composition of the product harvested from the rDNA biotechnology-derived form.

The first rDNA biotechnology-derived food plant marketed in the U.S. was the *FlavrSavr*™ tomato, introduced in 1994. Produced using T-DNA, this tomato carried an antisense gene for the enzyme polygalacturonase (PG), an enzyme formed as the fruit ripens and which is responsible, in large part, for fruit softening. The gene encoding PG was isolated, inverted in the cloning vector (producing an antisense form), and then introduced into cells that also carry the gene in the normal orientation. In the inverted DNA, the mRNA is transcribed from the wrong DNA strand to form an antisense message. As a result, much less of the enzyme is produced. It was expected that the fruits of the tomato would have an extended shelf life, since they would not soften as rapidly as normal fruit. In fact, the *FlavrSavr* tomato was not a commercial success as a retail product because of uncompetitive agronomic characteristics; however, a processing variety engineered with a related construct proved to be useful to processors, since the ripe fruit has a higher solids content, resulting in economic and quality advantages.

Following the introduction of the rDNA biotechnology-derived tomato in 1994, other rDNA biotechnology-derived crops that contained modified agronomic traits soon followed. These plants included squash that are resistant to some strains of zucchini yellows and watermelon mosaic viruses in 1994, insect-resistant potato and cotton in 1995 and corn in 1996, and herbicide-tolerant soybean and canola in 1996. Although the consumer's awareness is largely limited to these products, there are many others under development that are expected to appeal more directly to consumers. These include fruits, root and leaf vegetables, and grains with enhanced nutritional and health-promoting properties.

Recombinant DNA Biotechnology-Derived Foods

Recombinant DNA biotechnology-derived foods are part of the continuing sequence of genetic improvement of the food supply. Although it is sometimes portrayed as fundamentally new, the newness of rDNA biotechnology is best considered from a historical perspective.

The plants and animals that modern agriculture produces today to feed the world's people are the result of more than 10,000 years of genetic modification and refinement. For example, there is the agricultural green revolution, which has contributed to increased human longevity and improved quality of life in developing countries. The green revolution is viewed by many knowledgeable scientists as the latest major achievement in a long quest begun by ancient agriculturists who first cultivated and domesticated wild plants for food and fiber.

Genetic modification of plants began approximately 10,000 years ago when man first used what is referred to as selective breeding. This technique simply involved saving seeds from the most vigorous plants in an environment for replanting at a later time. Over a period of many years, this selection resulted in higher-yielding varieties of the crop. It is this type of selection that, for example, turned the wild precursor of modern maize, teosinte, into an important human food and animal feed crop in America. The same processes in the Near East—the Fertile Crescent—resulted in einkorn and emmer wheat, barley, lentil, pea, chickpea, and bitter vetch (Lev-Yadun et al., 2000). Likewise, the progenitor of the modern tomato bears almost no resemblance to its modern relatives, which are the result of centuries of selection and DNA recombination at the organism level.

Selective breeding relies principally on sexually transmitted genetic diversity in a starting population. By picking the best or most vigorous plants, breeders over time enrich the genetic makeup of a plant for attributes such as higher yields, increased resistance to pests, and greater compatibility with production schemes. It should be noted that this process in itself runs counter to natural selection. Breeding involves selection for optimal growth for human purposes or other characteristics in an agricultural setting and in many cases is inconsistent with nature and the ability of the organism to survive under evolutionary pressure. Therefore, human intervention has involved what can be called a primitive type of genetic engineering from the outset.

An excellent example of breeding versus natural selection can be gleaned from the history of cultivated wheat. The seeds of wild wheat relatives are dispersed by the shattering of brittle seed heads. In the earliest stages of domestication, 10,000 years ago, forms that do not shatter were selected, which enabled gatherers to collect the ripe seeds rather than pick them up from the ground. Such a mutation in nature would prevent seed dispersal and lead to rapid extinction of those plants in the wild.

As the available unused genetic diversity of the species diminishes, the potential for improvement also decreases. Since crop improvement relies on genetic diversity, i.e., new sources of genes and expression of existing genes, continued improvement has required and will continue to require even greater diversity. This need for diversity led to the next developments in plant breeding when farmers discovered that crosses between certain closely related species would produce fertile offspring. Cross-breeding (also known as interspecies or intergeneric breeding), either fortuitous or intentional, permitted recombination and selection among genes at a whole new level to provide new sources of genetic diversity and desirable traits.

Interspecies or cross-breeding offers two possible outcomes. First, new species that contain all of the genes from multiple parents can be created. Thus, triticale, a fertile wheat-rye hybrid, became a reality. The first wheat-rye hybrid plants, reported in 1876, were completely sterile, but fifteen years later fertile sectors were reported on a spike that resulted from spontaneous chromosome

Expert Report

CONTINUED

doubling (Gregory, 1987). Second, another alternative involves recombination, where a single genome is maintained in the offspring, but that genome now consists of randomly chosen copies of genes from either of the parent species. This latter type of breeding in a sense is the precursor to modern rDNA biotechnology; however, it is highly imprecise. Large segments of chromosomes containing thousands of individual genes have been introduced from one species into another in this way. This type of technology is employed today by breeders of many crops, including tomato (discussed below), soybean, canola, and cotton, which are all products of extensive genetic modification and selection.

The products of naturally occurring interspecies crosses have been employed for thousands of years, and many of the foods eaten today are derived from such crosses. A good example is cultivated hexaploid wheat, which has three different genomes, each derived from a wild ancestral species. For thousands of years, this technology has relied upon the ability of a genetic cross to produce fertile offspring. Thus, it is considered "natural." Many interspecific hybrids are infertile; for example, the original wheat-rye hybrids were sterile, and seeds could only be produced after spontaneous chromosome doubling had taken place. Thus, while interspecific crosses opened up a vast new genetic resource to plant breeders, the need for fertile progeny limited the usefulness of this diversity.

Sometimes, a cross of two species can produce a viable embryo, which develops for a period of time, then degenerates and dies. However, by using the technique known as embryo rescue, the embryo can be recovered shortly after fertilization and placed in an in-vitro tissue culture system. In this artificial setting, the embryo can develop into a mature, fertile plant. Tissue culture can thus expand access to genetic diversity by saving crosses that would not survive outside a laboratory.

Some attention has been paid to the use of ionizing radiation and chemicals to induce mutations and expand the range of variation available to breeders, but very few successful new forms of crop plants have been obtained in this way. The same is true of somaclonal variation arising in tissue culture. However, spontaneous mutations have been important in the development of some cultivated plants.

All of these conventional techniques for crop improvement share the disadvantage that they are, by nature, imprecise and unpredictable and only occasionally useful. Spontaneous and induced mutation can lead to one desirable change and many undesirable collateral changes in an organism's DNA makeup, which must be selected out. Breeders cannot and do not attempt to define in molecular terms the changes that they make within a genome. Rather, they employ standard selection procedures to screen for new plants with novel alterations and incorporate these plants into their breeding programs. In spite of the undefined nature of these changes, many years of experience have affirmed the safety and usefulness of genetically improved varieties. Plant breeders, farmers, food manufacturers, and consumers all have routine, frequent, and extensive exposure to these genetically improved varieties.

An excellent example of how breeders use all of the above techniques is the tomato. The tomato, *Lycopersicon esculentum* var. *cerasiforme*, originates from central Mexico. The original species bears little resemblance to current varieties, which are the result of much genetic manipulation. The growth habits of the plant, resistance to viruses, diseases, and nematodes, as well as fruit taste and appearance are a consequence of mutation, hybridization, and selection. For example, resistances to several diseases, tobacco mosaic virus, and nematodes were introduced from the distantly related species, *Lycopersicon peruvianum* and *Lycopersicon chilense*. Crosses between these two species and *L. esculentum* required embryo rescue. Each new resistance represents the introduction of a large chromosome segment from the distant relative into *L. esculentum*. The typical introduced non-host DNA segment contains between 100 and 1,000 genes.

A specific example illustrates the imprecision of traditional breeding. Introduction of resistance to the fungal disease *Fusarium* crown rot involved a cross between an irradiated *L. esculentum* variety and *L. peruvianum* (Rowe and Farley, 1981). From this cross, a resistant plant was selected and used in subsequent breeding. This resistance gene, along with its complement of other genes, is present in many commercial varieties of tomato today. As the tomato is a member of the nightshade family and many of its wild relatives contain high levels of toxicants in the interspecific crosses with *L. esculentum*, breeders have selected for varieties with minimal toxicant content. While there is no requirement for toxicant screening in traditional tomato breeding programs, it is widely practiced. Moreover, toxicant screening is an integral part of assessing the safety of new rDNA biotechnology-derived varieties.

It is against this experience base that rDNA biotechnology must be examined and compared. Recombinant DNA techniques involve the introduction of one or a few defined genes into a plant. While these introduced genes are often from other, non-host sources, the introduction of non-host DNA is not novel. In fact, remnants of an ancient *Agrobacterium* transformation have been identified in *Nicotiana* species (Furner et al, 1986). It is important to note that it is the very same *Agrobacterium* that is now used widely by researchers to introduce genes into plants.

Similarly, microorganisms have been used in food technology for thousands of years. As early as 6000 B.C., Sumerians and Babylonians used yeast to brew beer. Although the ancients knew nothing about microorganisms and could not knowingly culture them, they nevertheless systematically selected those with desirable fermentation characteristics to improve their food. In modern times, the increasingly powerful science of genetics has been systematically applied to produce many valuable variants of yeast and bacteria.

Recombinant DNA techniques have provided both an important new set of tools and access to a broader range of markets. They enable researchers seeking specific plant characteristics to precisely identify, characterize, enhance, and transfer the appropriate individual genes rather than uncontrolled and randomly assorted groups of genes, hoping the desired ones were included. Researchers can now readily move selected and well-characterized genetic material from virtually any source in nature, greatly increasing the diversity of useful genes available for crop and microbe

improvement. The long, continuous search for improved plants and the benefits of useful microorganisms is now increasingly based on the use of rDNA biotechnology techniques.

Microorganisms are used in the production of foods, beverages, industrial detergents, antibiotics, organic solvents, vitamins, amino acids, polysaccharides, steroids, and vaccines. Practical applications of pre-rDNA biotechnology include a variety of organisms used in pest control (including many that are themselves often considered to be pests, in other settings, e.g., preparations of the bacterium *Bacillus thuringiensis* sold at most garden supply stores). Biological agents are also used as growth promoters for plants. Preparations containing the bacterium *Rhizobium*, which fixes atmospheric nitrogen, converting it into nitrogen-containing ions that are essential plant nutrients, have been sold in the U.S. since the late 19th century. As early as the mid-1980s, these pre-rDNA biotechnology products, together, had a value in excess of $100 billion annually (Anonymous, 1985). Since the introduction of rDNA biotechnology, many of these microorganisms have been improved, such as those used to produce the enzyme chymosin necessary for cheese production.

Some critics of rDNA biotechnology have taken the view that it represents a fundamental change from traditional techniques for the genetic modification of plants and microorganisms. In a 1989 report, the National Research Council considered and rejected this argument:

> However, no conceptual distinction exists between genetic modification of plants and microorganisms by classical methods or by molecular techniques that modify DNA and transfer genes. . . . The same physical and biological laws govern the response of organisms modified by modern molecular and cellular methods and those produced by classical methods.

The NRC went on to characterize rDNA biotechnology as part of a sequence of scientific advances that has extended over a 10,000-year period (NRC, 1989).

A 1991 joint Food and Agriculture Organization/World Health Organization consultation, addressing the question of the safety of rDNA biotechnology-derived foods, came to similar conclusions (FAO/WHO, 1991):

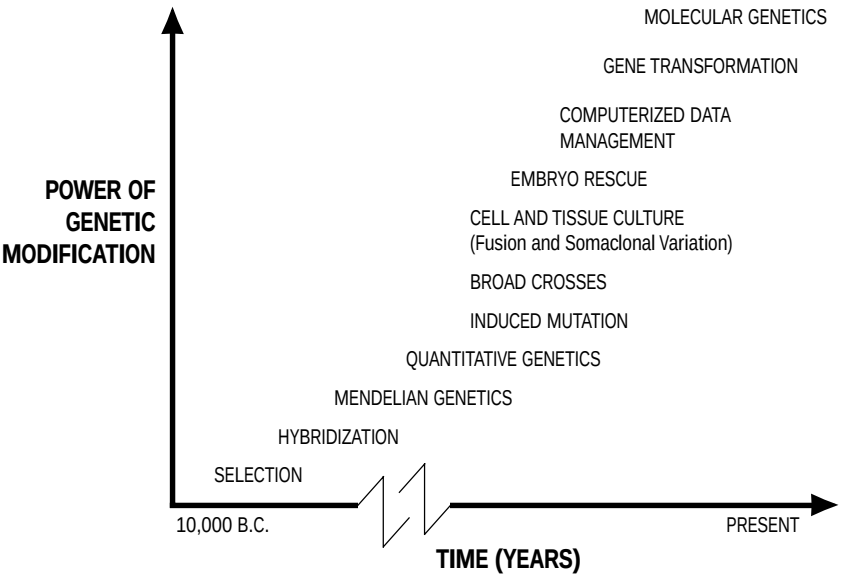
> Biotechnology has a long history of use in food production and processing. It represents a continuum embracing both traditional breeding techniques and the latest techniques based on molecular biology. The newer biotechnological techniques, in particular, open up very great possibilities of rapidly improving the quantity and quality of food available. The use of these techniques does not result in food which is inherently less safe than that produced by conventional ones.

A timeline that shows the increasing power of genetic modification over the past 12,000 years appears in Fig. 1.

Even though food derived from biotechnology in the broad sense is hardly new, some critics nevertheless have been concerned that rDNA biotechnology may result in different and dangerous organisms. Considering that there are tens of thousands of the host organism's own genes, the introduction by precise techniques of one or a few additional, well-characterized genes does not create an organism that is more likely to be changed in gross physical properties or wholesomeness than an organism derived through a traditional breeding program. Indeed, because of the greater precision in selecting the desired trait, an adverse result is unlikely. A corn plant with a newly inserted bacterial gene that confers increased resistance to the European corn borer (a commercially important insect predator) is still a corn plant. Likewise, a microorganism long used for food production is not altered in any fundamental way by the insertion of additional copies of a gene-encoded rate-limiting enzyme. Aided by the recent voluminous data from the DNA sequencing of various genomes and other basic research on plants, such questions have been widely discussed and reported by an array of national and international scientific groups. Their conclusions are discussed in the *Safety* section of the report.

Consider whether genetic recombination, itself, is of concern. It has already been established that people have long engaged in the systematic improvement of domesticated microbes, plants, and animals. But the impact and importance of these changes are much smaller than what occurs continuously in nature. Innumerable recombinations between related and unrelated organisms have occurred by several mechanisms. Sexual reproduction randomly combines genes from two parents in the offspring, which then has a unique set of genes to pass along to the next generation. In the gut, decomposing tissue, and infected wounds, bacteria take up naked mammalian DNA, albeit inefficiently, when they encounter disintegrating cells, and some of this DNA may be in-

Fig. 1—Increase in power of genetic modification over time. Adapted from NRC (1989)



corporated into the bacterial genome, but there is no established evidence that this happens (Davis, 1986). Over the past million years and longer, mammalian-bacterial genetic hybrids have appeared, been tested by competition within bacterial populations and by environmental stresses, and conserved or discarded by natural selection. Similar genetic recombination and hybridization also has been widespread among fungi, viruses, and plants.

Evolutionary biology provides data relevant to the issue of the uniqueness of chimeric genes (genes containing modified or substituted control signals joined to portions of the native genetic information) created by rDNA biotechnology. Does the transfer into a squash of a viral gene to confer viral resistance affect its "squashness" or transfer "viralness" to the new hybrid? The sequencing of various genomes during the past decade has revealed that nature has been remarkably conservative about maintaining and using effective molecules as they evolved. Similar protein sequences and biochemical pathways are found in different species, across genera, and even across phylogenetic kingdoms. The *Escherichia coli* genome, for example, contains gene sequences that are closely related to those in a wide spectrum of organisms, ranging from other bacteria to plants, insects, amphibia, birds, and humans.

Another issue, conversion of a nonpathogen into a pathogen through limited genetic recombination, is best considered within the context of the nature of pathogenicity. This process is both complex and multifactorial. Pathogenicity usually is not a trait produced by a single gene; however, the transfer of a single gene to an organism that has all the other necessary genes can make it pathogenic. Pathogenicity requires the coordinated activity of a set of genes that affect essential properties.

A pathogen must possess three general characteristics, each of which involves multiple genes. First, pathogens must survive and be able to multiply or produce toxin in or upon host tissues or food sources. This necessitates an appropriate oxygen tension, pH, temperature, water activity, and nutritional milieu. Pathogens must be able to adhere to specific surfaces on or in the host. Second, the pathogen must be able to resist or avoid the host's defense mechanisms for the period of time necessary to multiply to sufficient levels to cause disease. Third, the pathogen must be able to survive outside of the host and must be disseminated to new host organisms. The organism must be meticulously adapted to this pathogenic lifestyle. On the other hand, a mutation that interferes with a gene essential to any one of the three characteristics of a pathogen can eliminate pathogenicity. It is worth noting that severe pathogenicity is even more dependent upon favorable conditions and is, therefore, much rarer in nature than mild pathogenicity.

The probability of creating and commercializing an organism inadvertently capable of producing a medical or agricultural problem is therefore quite small. The expert panels are of the view that this probability is lower with rDNA biotechnology than with the more random, less targeted, and less predictable traditional methods of genetic modification. In rDNA biotechnology-derived organisms, typically one, two, or three genes are being inserted. The genes, gene products, and their functions are known. This information guides scientists in determining which possible risks are relevant and need to be explored. In comparison, with traditional breeding, a large number of genes with unknown functions are involved, making it much more difficult to sort through the progeny and focus on the relevant risks involved.

Adverse outcomes accompanying genetic change have always been possible but are routinely intercepted during the usual, extensive testing that takes place in growth chambers, greenhouses, and the field. Whatever the technique used to craft a variety, it goes through extensive testing before being used commercially, particularly if the developer chooses to enter it into formal seed registration programs. In practice, the testing is even more extensive in the case of an rDNA biotechnology-derived variety. Therefore, the expert panels are of the view that rDNA biotechnology has the potential to reduce still further the chance that any such mishap will occur. The field and chemical testing that accompany it—even more thorough than in traditional genetic modification—make such an unfavorable outcome even more unlikely. As noted earlier, genetic changes that make a plant more useful to humans usually have made the plant less "fit" and less able to survive in the wild.

Federal Regulation of rDNA Biotechnology

Regulatory oversight over rDNA biotechnology spans three major federal agencies: the Food and Drug Administration (FDA), the Environmental Protection Agency (EPA), and the U.S. Department of Agriculture (USDA). Jurisdiction over the varied rDNA biotechnology products is determined by their use, as has been the case for products made by traditional means. More than one agency may be involved in regulating different aspects of an rDNA biotechnology-derived product. As the regulatory mandate varies, so does the nature of the agencies' risk assessment and management protocols.

The "Coordinated Framework for Regulation of Biotechnology," prepared by the White House's Office of Science and Technology Policy (OSTP) and published in the *Federal Register* of June 26, 1986 (51 FR 23302), is the current comprehensive federal policy for ensuring the safety of rDNA biotechnology research and products. It established the principles and procedures for coordination and jurisdiction among federal agencies for the oversight of rDNA biotechnology. Subsequently, the OSTP prepared and published in the *Federal Register* of February 24, 1992 (57 FR 6753) "Exercise of Federal Oversight within Scope of Statutory Authority: Planned Introductions of Biotechnology Products into the Environment." This notice described a risk-based, scientific approach to the oversight of planned introductions of rDNA biotechnology-derived products into the environment, focusing on the characteristics of the product and the environment into which it is being introduced, not the process by which the product is created.

The ultimate goal of the OSTP policy is to ensure the overall safety to humans and the environment of, in relevant part, foods, food ingredients, and feeds produced using rDNA biotechnology. In an April 2000 report, the National Research Council stated: "In general, the current U.S. coordinated framework has been operating effectively for over a

decade" (NRC, 2000).

Although the approach outlined in the 1986 and 1992 OSTP regulatory policy guidelines states that federal policies should be risk-based—i.e., should focus on the risk-related characteristics of products, rather than on the process used—that principle has not been followed by regulatory agencies. The fundamental approach by the federal government to the review and regulation of rDNA biotechnology-derived products has largely been through a process-based trigger to oversight. As discussed below, crops and microbes produced using rDNA biotechnology have been consistently subjected to higher requirements and standards than those applied to similar products produced using traditional techniques (Miller, 1997, 2000). At this time, there is less experience with rDNA biotechnology-derived products, but that experience base is increasing substantially.

Food and Drug Administration

FDA regulates different aspects of rDNA biotechnology under the authority of the Federal Food, Drug, and Cosmetic Act (FFDCA) and the Public Health Service Act (PHSA). FDA has a mandate to ensure the safety of all food (except for meat and poultry products) sold in the U.S., as well as the safety and efficacy of pharmaceutical products. To date, FDA has conducted almost fifty reviews of rDNA biotechnology-derived plant products used for human food or animal feed.

• Human Food and Animal Feed. Except for meat and poultry products regulated by USDA, FDA is responsible for ensuring the safety and proper labeling of food products for human consumption. FDA also regulates the safety and labeling of animal feed, taking into account both the safety to human consumers of animal-derived food products and the safety to the animal being fed. FDA's statutory authority is provided by the FFDCA. FDA's framework for the regulation of food labeling is discussed in the *Labeling* section of the report; the framework for the regulation of food safety is discussed below.

FDA has very broad authority to regulate the introduction of new food crops, whether conventionally grown, produced through hybridization or cross-breeding, or produced using rDNA biotechnology. Every firm or individual that produces whole foods or food ingredients is legally required to ensure the safety of foods and food ingredients introduced into commerce. FDA has a number of enforcement tools that can be used to ensure the safety of food. Specifically, the FFDCA prohibits the adulteration of any food item that moves in interstate commerce (21 USC §342). Of particular importance, foods are deemed adulterated if they contain certain poisonous and deleterious substances (21 USC §342(a)(1)). With certain exceptions that are not relevant to this discussion, the FFDCA defines a "food additive" as any substance, not "generally recognized as safe" (GRAS) by qualified experts for its intended use, that becomes a component or otherwise affects the characteristics of food (21 USC §321(s)). Food additives must be the subject of a petition to FDA, followed by FDA premarket approval; their manufacturers have the burden of establishing, through scientific testing, the safety of the substances (21 USC §348). In comparison, a food manufacturer that believes its food ingredient is GRAS may market the ingredient without seeking FDA's concurrence, subject to the risk that FDA will disagree and take legal action to remove the ingredient from the marketplace.

In the U.S., whole foods such as fruits, vegetables, and grains are not regulated as "food additives" and are not required to undergo premarket approval; nor are they commonly subjected to extensive safety testing. Thus, new varieties of crop plants produced by traditional breeding methods are not subject to FDA premarket review. Nevertheless, authority exists to ensure that such foods do not present a reasonable possibility that consumers might be injured by consuming them. With respect to all foods, FDA can initiate legal action to remove a food from the market if it is judged to present a health risk. While there is no evidence that such authority has ever needed to be exercised with respect to traditional breeding practices, plant breeders and food processors have several times intercepted toxic food plants before they reached the market. An example, mentioned in the *Safety* section of the report, is the Lenape potato.

On May 29, 1992, FDA published a policy statement (57 FR 22983) on foods and animal feed derived from new plant varieties developed by conventional and new breeding techniques, including rDNA biotechnology techniques. FDA stated:

> This policy statement is a clarification of FDA's interpretation of the Federal Food, Drug, and Cosmetic Act (the act) with respect to technologies to produce foods, and reflects FDA's current judgement based on new plant varieties now under development in agricultural research. This action is being taken to ensure that relevant scientific, safety, and regulatory issues are resolved prior to the introduction of such products into the marketplace.

FDA set forth its authority to control food products derived by rDNA biotechnology techniques and listed the safety issues that need to be addressed in assessing the safety of whole foods that contain or use rDNA biotechnology-derived plants and microorganisms. One key point is that under certain conditions, foods and food ingredients derived from rDNA biotechnology-derived plants or microorganisms may be subject to the provisions of existing requirements governing food additives and GRAS substances. FDA noted that in the case of foods derived from new plant varieties, it is the transferred genetic material and intended expression product(s) that could be subject to food additive requirements if these materials are not GRAS. FDA stated that if the intended expression product is a protein, carbohydrate, or other substance that differs substantially from substances currently present in food, then that substance might not be GRAS and may be a food additive requiring premarket approval. Another important point is that if an rDNA biotechnology-derived plant or microorganism is used to produce a GRAS substance or an approved food additive, the resulting material would continue to be regulated in a similar fashion to the way in which it has historically been regulated.

FDA's 1992 policy on new plant varieties applies irrespective of whether the plant arose from rDNA biotechnology or "conventional" genetic modification methods. FDA does not routinely subject foods from new plant varieties to a premarket approval process or to extensive scientific safety tests. FDA's policy does, however, define certain safety-related characteristics of new foods—such as transfer of an allergen or increased levels of a natural toxicant—that trigger additional scrutiny. FDA's policy in-

Expert Report

CONTINUED

cludes a flow chart (Fig. 2) for guidance that asks a series of questions directed to scientific issues of safety and nutrition of the foods derived from the new plant variety. The assessment focuses on the following risk-based considerations:

- Toxicants known to be characteristic of the host and donor species.
- The potential that food allergens will be transferred from one food source to another.
- The concentration and bioavailability of important nutrients for which a food crop is ordinarily consumed.
- The safety and nutritional value of newly introduced proteins.
- The identity, composition, and nutritional value of modified carbohydrates, fats, or oils.

Fundamentally, FDA's current (1992) policy is that existing requirements mandate the same safety standards for foods, food ingredients, and feeds, regardless of the techniques used in their production and manufacture. Nevertheless, FDA has maintained a "voluntary consultation procedure," in which producers of rDNA biotechnology-derived foods are asked to consult with the agency before marketing their products, and without exception they have done so (HHS, 2000). To date, almost 50 new rDNA biotechnology-derived foods have been evaluated successfully in FDA's voluntary consultation process. These evaluations are summarized in Table 1. Each entry represents a separate consultation, and each consultation may represent more than one line of the traits indicated. Products are grouped by the year in which their consultations were completed. The trait introduced into the variety plus the origin and identity of the introduced gene responsible for the trait are given (FDA, 2000).

FDA's official policy may change significantly, as the Clinton Administration announced in May 2000 that FDA will publish a proposed rule that would require producers to notify FDA 120 days before marketing an rDNA biotechnology-derived food and provide the agency with data that affirm the new food's safety. In practice, assuming that new regulatory requirements are proposed and finalized, FDA's current voluntary consultation procedure would become mandatory.

• Pharmaceuticals and Human Vaccines. FDA regulates rDNA biotechnology-derived pharmaceutical products for human and animal use under the FFDCA and the PHSA. FDA also regulates rDNA biotechnology-derived vaccines for human use under the PHSA, while USDA regulates vaccines for animal use. Under both the FFDCA and the PHSA, new products must be the subject of premarket approval, based on laboratory and clinical testing to show the safety and effectiveness of the products for their intended uses (21 USC §§355 and 360b; 42 USC §262).

U.S. Department of Agriculture

Two USDA agencies are relevant to the regulation of foods and other products derived using rDNA biotechnology.

• Foods. The Food Safety and Inspection Service (FSIS) is responsible for regulating the safety and labeling of meat and poultry products for human consumption. FSIS consults with FDA regarding the safety of food ingredients. Because transgenic animals are beyond the scope of this report, USDA's regulation of meat and poultry products will not be discussed further.

The Animal and Plant Health Inspection Service (APHIS) is the agency within the USDA charged with protecting American agriculture against pests and diseases. Under the Plant Quarantine Act (PQA, 7 USC §151) and the Federal Plant Pest Act (FPPA, 7 USC §150), APHIS can regulate the importation and interstate movement of plants and plant products that may result in the entry into the U.S. of injurious plant diseases or insect pests.

The field-testing and the commercial sale of agricultural rDNA biotechnology-derived crops are regulated by APHIS through a permit and notification system. USDA's regulations (7 CFR Part 340) cover the introduction of organisms and products altered or produced through genetic engineering which are plant pests or for which there is reason to believe are plant pests. "Plant pests" include agents that can directly or indirectly injure or cause disease or damage in or to any plant. A "regulated article" includes any organism or any product, which has been altered or produced through rDNA biotechnology, which is a plant pest, or for which there is reason to believe is a plant pest. The permit and notification system does not apply to plants that are modified through traditional breeding methods. Thus, USDA's regulatory protocol is process based.

The introduction of a regulated article is prohibited unless a permit under 7 CFR Part 340 authorizes the introduction. The regulation is intended to prevent the introduction, dissemination and establishment of plant pests in the U.S. APHIS will grant a permit only if it determines that the plant poses no significant risk to other plants in the environment and is as safe to use as more traditional varieties. APHIS can authorize nonregulated status for an article through a petition for a "determination of nonregulated status." Nonregulated status allows a plant to be treated like any other plant, i.e., allows for the plant to be widely grown and commercialized.

• Animal Vaccines. APHIS regulates animal vaccines under the Virus-Serum-Toxin Act (21 USC §§151–159). In general, animal vaccines are subject to premarket approval, based on testing to show their safety and effectiveness.

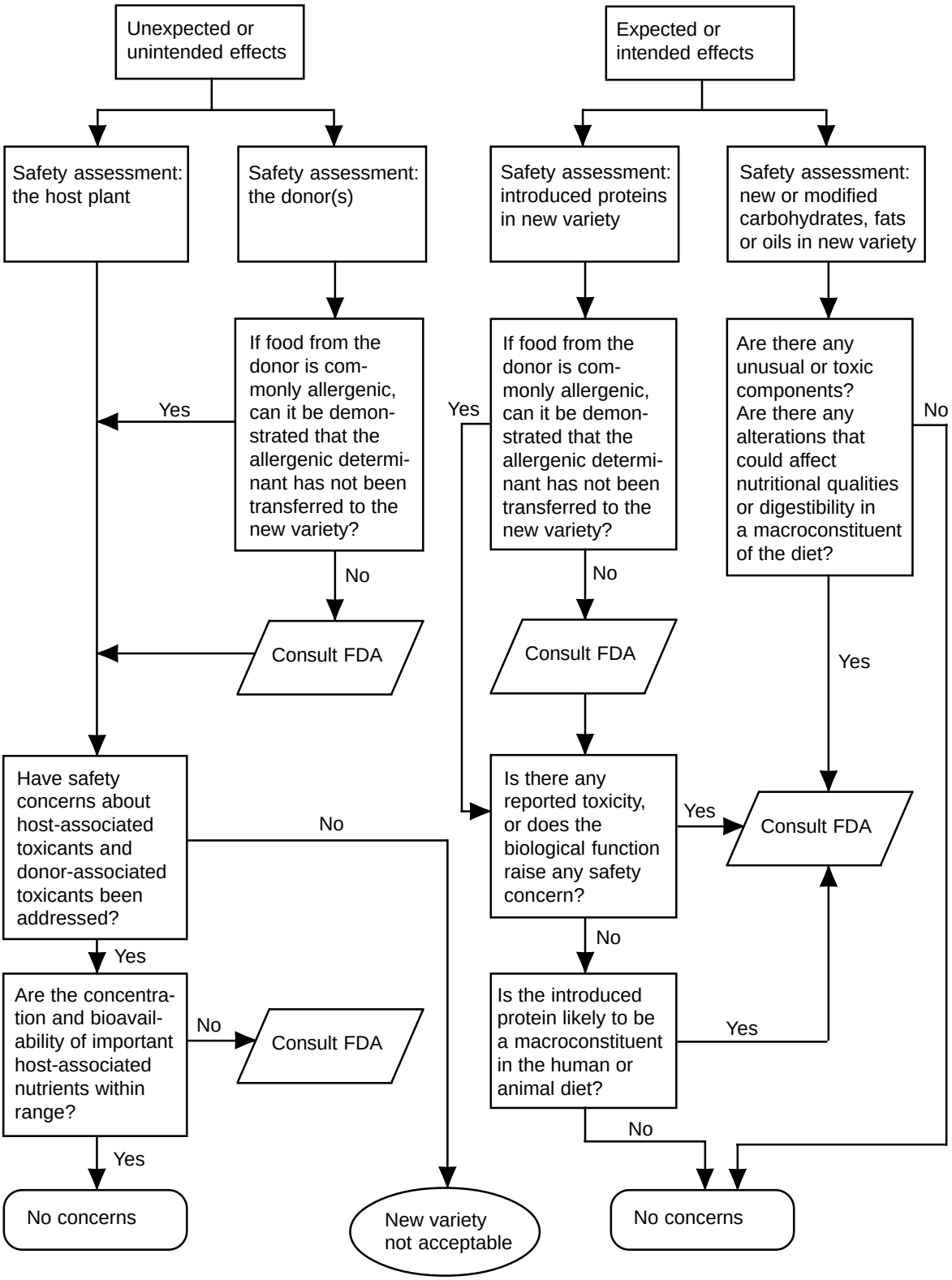
Environmental Protection Agency

EPA's stated mission is to protect human health and to safeguard the natural environment—air, water, and land—upon which life depends. EPA's responsibilities under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA, 7 USC §§136–136r) for registering pesticides, setting environmental tolerances for pesticides, and establishing exemptions for pesticide residues in and on crops are relevant to rDNA biotechnology-derived foods. A pesticide is any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest.

The Food Quality Protection Act (FQPA) of 1996 amended FIFRA and the FFDCA by establishing a single, health-based standard for assessing the risks of pesticide residues in food or feed. The standard measures the aggregate risk from dietary exposure and other non-occupational sources of exposure. EPA must now focus explicitly on exposures and risks to infants and children, assuming when appropriate, an additional safety factor to account for uncertainty in data.

If EPA determines that there is a "rea-

Fig. 2—Safety assessment of new varieties: summary. From FDA (1992)



sonable certainty that no harm" to the public will result from aggregate exposure to a particular pesticide residue, then that residue level will be deemed "safe."

In the case of pesticides produced by plants developed using rDNA biotechnology, EPA's November 23, 1994 (59 FR 60519), proposed rule takes the view that its regulatory process is focused on the pesticide and not on the plant; plants are subject to regulation only if they produce plant pesticidal proteins as a result of modification with rDNA techniques. Although EPA has not finalized that proposed rule, EPA has been implementing its essential elements since 1995 (NRC, 2000). EPA's evalua-

Table 1 Foods derived from new plant varieties derived through rDNA technology: final consultations under FDA's 1992 policy. From FDA (2000)

Year/Firm	New variety	Trait gene and source
2000		
Aventis	Male-sterile corn	The barnase gene from *Bacillus amyloliquefaciens*.
1999		
Agritope Inc.	Modified fruit-ripening cantaloupe	S-adenosylmethionine hydrolase gene from *Escherichia coli* bacteriophage T3.
BASF AG	Phytaseed canola	The phytase gene from *Aspergillus niger* var van Tieghem.
Rhone-Poulenc Ag Co.	Bromoxynil-tolerant canola	The nitrilase gene from *Klebsiella pneumoniae* subsp. *ozaenae.*
1998		
AgrEvo, Inc.	Glufosinate-tolerant soybean	Phosphinothricin acetyltransferase gene from *Streptomyces viridochromogenes*.
	Glufosinate-tolerant sugar beet	Phosphinothricin acetyltransferase gene from *S. viridochromogenes*.
	Insect-protected and glufosinate-tolerant corn	The *cry9C* gene from *Bacillus thuringiensis* (Bt) subsp. *tolworthi* and the bar gene from *Streptomyces hygroscopicus*.
	Male-sterile or fertility-restorer and glufosinate-tolerant canola	The male-sterile canola contains the barnase gene, and the fertility-restorer canola contains the barstar gene from *B. amyloliquefaciens*. Both lines have the phosphinothricin acetyltransferase gene from *S. viridochromogenes*.
Calgene Co.	Bromoxynil-tolerant/insect-protected cotton	Nitrilase gene from *Klebsiella pneumoniae* and the *crylA(c)* gene from *B. thuringiensis* subsp. *kurstaki*.
	Insect-protected tomato	The *crylA(c)* gene from *B. thuringiensis* subsp. *kurstaki*.
Monsanto Co.	Glyphosate-tolerant corn	A modified enolpyruvylshikimate-3-phosphate synthase gene from corn.
	Insect- and virus-protected potato	The *cryIIIA* gene from *B. thuringiensis* sp. *tenebrionis* and the Potato Leafroll Virus replicase gene.
	Insect- and virus-protected potato	The *cryIIIA* gene from *B. thuringiensis* sp. *tenebrionis* and the Potato Virus Y coat protein gene.
Monsanto Co./Novartis	Glyphosate-tolerant sugar beet	The enolpyruvylshikimate-3-phosphate synthase gene from *Agrobacterium* sp. strain CP4, and a truncated glyphosate oxidoreductase gene from *Ochrobactrum anthropi*.
Pioneer Hi-Bred	Male-sterile corn	The DNA adenine methylase gene from *E. coli.*
University of Saskatchewan	Sulfonylurea-tolerant flax	Acetolactate synthase gene from *Arabidopsis*.
1997		
AgrEvo, Inc.	Glufosinate-tolerant canola	Phosphinothricin acetyltransferase gene from *S. viridochromogenes.*
Bejo Zaden BV	Male-sterile radicchio rosso	The barnase gene from *B. amyloliquefaciens.*
Dekalb Genetics Corp.	Insect-protected corn	The *crylA(c)* gene from *B. thuringiensis*.
DuPont	High-oleic-acid soybean	Sense suppression of the GmFad2-1 gene which encodes a delta-12 desaturase enzyme.
Seminis Vegetable Seeds	Virus-resistant squash	Coat protein genes of Cucumber Mosaic Virus, Zucchini Yellow Mosaic Virus, and Watermelon Mosaic Virus 2.
University of Hawaii/ Cornell University	Virus-resistant papaya	Coat protein gene of the Papaya Ringspot Virus.

tion of products of rDNA biotechnology is distinct from the procedures used to assess the safety of the products of more conventional technology. In April 2000, the NRC issued a report after evaluating the science and regulation of rDNA biotechnology-derived pest-protected plants. The NRC panel accepted without critical evaluation the EPA's regulatory approach. In contrast, eleven major scientific societies representing more than 80,000 biologists and food professionals published a report warning that the EPA policy would discourage the development of new pest-resistant crops and prolong and increase the use of synthetic chemical pesticides; increase the regulatory burden for developers of pest-resistant crops; limit the use of biotechnology to larger developers who can pay the inflated regulatory costs; and handicap the U.S. in competition for international markets.

Continued on next page

Table 1 ***continued***

Year/Firm	New variety	Trait gene and source
1996		
Agritope Inc.	Modified fruit-ripening tomato	S-adenosylmethionine hydrolase gene from *E. coli* bacteriophage T3.
Dekalb Genetics Corp.	Glufosinate-tolerant corn	Phosphinothricin acetyl transferase gene from *S. hygroscopicus.*
DuPont	Sufonylurea-tolerant cotton	Acetolactate synthase gene from tobacco, *Nicotiana tabacum* cv. *Xanthi.*
Monsanto Co.	Insect-protected potato	The *cryIIIA* gene from *B. thuringiensis.*
	Insect-protected corn	The *cryIA(b)* gene from *B. thuringiensis* subsp. *kurstaki.*
	Insect-protected corn	The *cryIA(b)* gene from *B. thuringiensis* subsp. *kurstaki.*
	Glyphosate-tolerant/insect-protected corn	The enolpyruvylshikimate-3-phosphate synthase gene from *Agrobacterium* sp. strain CP4 and the glyphosate oxidoreductase gene from *O. anthropi* in the glyphosate tolerant lines. The *cryIA(b)* gene from *B. thuringiensis* subsp. *kurstaki* in lines that are also insect protected.
Northrup King Co.	Insect-protected corn	The *cryIA(b)* gene from *B. thuringiensis* subsp. *kurstaki.*
Plant Genetic Systems NV	Male-sterile and fertility-restorer oilseed rape	The male-sterile oilseed rape contains the barnase gene from *B. amyloliquefaciens*; the fertility restorer lines express the barstar gene from *B. amyloliquefaciens.*
	Male-sterile corn	The barnase gene from *B. amyloliquefaciens.*
1995		
AgrEvo Inc.	Glufosinate-tolerant canola	Phosphinothricin acetyltransferase gene from *S. viridochromogenes.*
	Glufosinate-tolerant corn	Phosphinothricin acetyltransferase gene from *S. viridochromogenes.*
Calgene Inc.	Laurate canola	The 12:0 acyl carrier protein thioesterase gene from California bay, *Umbellularia californica.*
Ciba-Geigy Corp.	Insect-protected corn	The *cry1A(b)* gene from *B. thuringiensis* subsp. *kurstaki.*
Monsanto Co.	Glyphosate-tolerant cotton	Enolpyruvylshikimate-3-phosphate synthase gene from *Agrobacterium* sp. strain CP4.
	Glyphosate-tolerant canola	Enolpyruvylshikimate-3-phosphate synthase gene from *Agrobacterium* sp. strain CP4.
	Insect-protected cotton	The *cryIA(c)* gene from *B. thuringiensis* subsp. *kurstaki.*
1994		
Asgrow Seed Co.	Virus-resistant squash	Coat protein genes of Watermelon Mosaic Virus 2 and Zucchini Yellow Mosaic Virus.
Calgene Inc.	*FlavrSavr*™ tomato	Antisense polygalacturonase gene from tomato.
	Bromoxynil-tolerant cotton	A nitrilase gene isolated from *Klebsiella ozaenae.*
DNA Plant Technology Corp.	Improved-ripening tomato	A fragment of the aminocyclopropane carboxylic acid synthase gene from tomato.
Monsanto Co.	Glyphosate-tolerant soybean	Enolpyruvylshikimate-3-phosphate synthase gene from *Agrobacterium* sp. strain CP4.
	Improved-ripening tomato	Aminocyclopropane carboxylic acid deaminase gene from *Pseudomonas chloraphis* strain 6G5.
	Insect-protected potato	The *cryIIIA* gene from *B. thuringiensis* sp. *tenebrionis.*
Zeneca Plant Science	Delayed-softening tomato	A fragment of the polygalacturonase gene from tomato.

Expert Report

CONTINUED

Summary

In this section, the general concept of biotechnology has been introduced and the scope of the overall report has been defined. Further, extensive background information has been provided to assist the reader in understanding rDNA biotechnology-derived foods. Biotechnology has been discussed in considerable detail, and the point has been made that, in the view of many knowledgeable scientists, rDNA biotechnology-derived foods are the latest major step in a 10,000-year process of genetic improvement of food. Finally, this section has discussed federal regulation and oversight of rDNA biotechnology.

This section has provided the foundation for the three sections that follow. The sections are based on a review of the scientific literature on three different but related aspects of rDNA biotechnology-derived foods—human food safety, benefits and concerns, and labeling—and the public policy implications of the underlying science. In developing this state-of-the-science report, it is IFT's intent to promote a meaningful public discussion of the subject that is based on sound science.

REFERENCES

Anonymous. 1985. Health impact of biotechnology: Report of a WHO Working Group. Swiss Biotechnol. 2: 7-16.

Avery, O.T., MacLeod, C.M., and McCarty, M. 1944. Studies on the chemical nature of the substance inducing transformation of Pneumococcal types. J.Exp.Med. 79: 137-158.

Davis, B.D. 1986. Evolution, epidemiology, and recombinant DNA. In "Storm Over Biology," pp. 271-273. Prometheus Books, Buffalo.

FAO/WHO. 1991. Strategies for assessing the safety of foods produced by biotechnology. Report of a Joint FAO/WHO Consultation. Food and Agriculture Org./ World Health Org.. World Health Org., Geneva.

FDA. 2000. "Foods Derived from New Plant Varieties Derived through Recombinant DNA Technology." Food and Drug Administration, Center for Food Safety and Applied Nutrition, Washington, D.C. (http://vm.cfsan.fda.gov/~lrd/biocon.html).

Furner, I., Huffman, G., Amasino, R., Garfinkel, D., Gordon, M., and Nester, E. 1986. An *Agrobacterium* transformation in the evolution of the genus *Nicotiana*. Nature 319: 422-427.

Grace, E.S. 1997. "Biotechnology Unzipped: Promises and Realities." Joseph Henry Press, Washington, DC.

Gregory, R.S. 1987. Triticale breeding. In "Wheat Breeding: Its Scientific Basis," ed. F.G.H. Lupton, pp. 269-286. Chapman & Hall, London.

HHS. 2000. FDA to strengthen pre-market review of bioengineered foods. Press release, U.S. Dept. of Health and Human Services, Washington, D.C., May 3.

Lander, E.S. and Weinberg, R.A. 2000. Genomics: Journey to the center of biology. Science, March 10, p. 287.

Lev-Yadun, S., Gopher, A., and Abbo, S. 2000. The cradle of agriculture. Science 288: 1602-1603.

Linn, S. and Arber, W. 1968. Host specificity of DNA produced by *Escherichia coli*. X. *In vitro* restriction of phage Fd replicative form. Proc. Natl. Acad. Sci. 59: 1300-1306.

McCouch, S. 1998. Toward a plant genomics initiative: Thoughts on the value of cross-species and cross-genera comparisons in the grasses. Proc. Natl. Acad. of Sciences. 95: 1983-85.

Miller, H.I. 1997. Chpt. 3 in "Policy Controversy in Biotechnology: an Insider's View." R.G. Landes Co. and Academic Press, Austin, Tex.

Miller, H.I. 2000. Anti-biotech sentiment has its own risks. Financial Times, March 22, p. 10.

NRC. 1989. "Field Testing Genetically Modified Organisms: Framework for Decisions." Natl. Res. Council. National Academy Press, Washington, D.C.

NRC. 2000. "Genetically Modified Pest-Protected Plants: Science and Regulation." Natl. Res. Council. National Academy Press, Washington, D.C.

OTA. 1984. Commercial biotechnology: An international analysis. OTA-BA-218, p. 3. U.S. Congress, Office of Technology Assessment. U.S. Govt. Printing Office, Washington, D.C.

Rowe, R.C. and Farley, J.D. 1981. Strategies for controlling *Fusarium* crown and root rot in greenhouse tomatoes. Plant Disease Repts. 65: 107-108.

Watson, J.D. and Crick, F.H.C. 1953. Molecular structure of nucleic acid. A structure for deoxyribose nucleic acid. Nature 171: 737-738.

Watson, J.D. and Tooze, J. 1981. "The DNA Story: A Documentary History of Gene Cloning." W.H.Freeman, San Francisco. ●

Key documents referenced in the report and other biotechnology resources

Food and Drug Administration (FDA) Center for Food Safety and Applied Nutrition

- Biotechnology main page: vm.cfsan.fda.gov/~lrd/biotechm.html
- 1992 policy statement: vm.cfsan.fda.gov/~acrobat/fr920529.pdf
- Guidance on current consultation procedures: vm.cfsan.fda.gov/~lrd/consulpr.html

U.S. Department of Agriculture (USDA)

- Agency regulation of biotechnology: www.aphis.usda.gov/biotechnology/index.html
- Biotechnology resources from the National Agricultural Library (NAL): www.nal.usda.gov/bic
- NAL Internet resources and links: www.nal.usda.gov/bic/www.html

National Research Council (NRC)

- 2000 report on genetically modified pest-protected plants: books.nap.edu/catalog/9795.html
- 2000 report on transgenic plants and world agriculture: bob.nap.edu/html/transgenic/notice.html
- 1989 report on field testing of GMOs: www.nap.edu/books/0309040760/html

Food and Agriculture Organization of the United Nations (FAO)

- Statement on biotechnology: www.fao.org/biotech/state.htm
- Biotechnology resources: www.fao.org/waicent/faoinfo/agricult/guides/subject/b.htm
- 1996 joint FAO/WHO consultation, Biotechnology and Food Safety: www.fao.org/waicent/faoinfo/economic/esn/biotech/tabconts.htm

World Health Organization (WHO)

- Genetically modified food main page, including information about Codex Alimentarius activities: www.who.int/fsf/gmfood/index.htm
- 2000 joint FAO/WHO consultation, Safety Aspects of Genetically Modified Foods of Plant Origin: www.who.int/fsf/gmfood/fao-who_consultation_report_2000.pdf
- 1990 FAO/WHO joint consultation, Strategies for Assessing the Safety of Foods Produced by Biotechnology: www.who.int/faf/gmfood/bio1991repo.pdf

Organization for Economic Co-operation and Development (OECD)

- Biotechnology and food safety main page: www.oecd.org/subject/biotech
- 1993 report on safety evaluation of biotech foods: www.oecd.org/dsti/sti/s_t/biotech/prod/modern.htm
- Biotechnology publications main page: www.oecd.org//ehs/icgb/biopubs.htm

Institute of Food Technologists (IFT)

- Main page: www.ift.org
- Backgrounder on Genetically Modified Organisms: www.ift.org/resource/pdf_files/gmoback.pdf

American Dietetic Association (ADA)

- Position statement on food biotechnology: www.eatright.org/abiotechnology.htm

Council for Agricultural Science and Technology (CAST)

- Biotechnology communications: www.cast-science.org/biotechnology/index.html

International Food Information Council (IFIC)

- Main page: www.ificinfo.health.org

IFT Expert Report on Biotechnology and Foods

Human Food Safety Evaluation of rDNA Biotechnology-Derived Foods

This section begins with a discussion of issues relevant to safety evaluation of recombinant DNA biotechnology-derived foods, including the concept of substantial equivalence, safety of introduced genetic material and gene product, unintended effects, allergenicity, and products without conventional counterparts. It is followed by the scientific consensus of international scientific groups regarding safety of rDNA biotechnology-derived foods.

Issues Relevant to Safety Evaluation

Food manufacturers are required by law to ensure the safety and quality of their products regardless of the source or identity of the ingredients. Traditional foods are viewed by the Food and Drug Administration as "safe" based on a long history of use. The consuming public also views traditional foods as safe. However, many traditional foods contain naturally occurring toxins that can present hazards to consumers under some circumstances of exposure. Fortunately, in most circumstances, these naturally occurring toxins are present in concentrations that are not hazardous to consumers ingesting typical quantities of the food prepared under typical conditions. Also, some traditional foods are allergenic to some consumers, even though they are safe for the vast majority of consumers.

New foods produced through conventional breeding or introduced into the marketplace from other parts of the world are not required to undergo any type of safety assessment. They are assumed to be safe because they are comparable to other varieties (if newly introduced through conventional breeding) or because they have been safely consumed in other parts of the world. In fact, these newly introduced foods may contain numerous unique components that are not individually or collectively assessed for safety.

In contrast, products derived through rDNA biotechnology are assessed for safety before their introduction into the food marketplace. Food manufacturers also must ensure the safety and quality of products that contain ingredients derived from rDNA biotechnology. In 1992, FDA provided a general outline for the safety assessment of rDNA biotechnology-derived food products based on risk analysis related to the characteristics of the products (FDA 1992). All of the existing foods produced using rDNA biotechnology have undergone a rigorous science-based safety assessment focusing on the characteristics of the products, especially the unique components. While this practice has been voluntary in the United States, FDA announced in May 2000 that it intends to propose a premarket notification system for rDNA biotechnology-derived foods that would make this unofficial policy into a regulatory requirement (HHS, 2000). Thus, in practice, the safety assessment of foods derived using rDNA biotechnology has been more stringent than for conventionally derived products.

Biotechnology Report: Safety

CONTINUED

Substantial Equivalence

In the safety assessment of rDNA biotechnology-derived foods, it is helpful to compare the new plant variety to its traditional counterpart because the counterpart has a history of safe use as a food. The concept of substantial equivalence effectively focuses the scientific assessment on potential differences that might present safety or nutritional concerns.

Substantial equivalence is not an absolute determinant of safety per se, since compositional changes in an rDNA biotechnology-derived food may have no impact on the safety of the food. However, substantial equivalence provides a process to establish that the composition of the plant has not been changed in such a way as to introduce any new hazards into the food, increase the concentration of inherent toxic constituents, or decrease the customary content of nutrients. For example, high-oleic-acid soybean oil from rDNA biotechnology-derived soybeans has an oleic acid concentration that falls outside the range typically found in soy oils. From a scientific perspective, this food is nevertheless considered safe, based on scientific knowledge about the safety of oleic acid, a common fatty acid in foods.

A determination of substantial equivalence considers the intentional and unintentional effects of genetic modification, and includes an evaluation of phenotypic and compositional characteristics. With respect to food safety, substantial equivalence involves the quantitative assessment of the concentration of inherent constituents in the modified food, compared to the often wide range typically found in its traditional counterpart, under similar food production conditions.

Most food sources (e.g., soybeans, corn) are exceedingly complex mixtures that vary widely in composition, so it is necessary to consider all of the factors that determine the normal range of variation (IFBC, 1990). Key constituents measured include nutrients, such as proteins, fats, carbohydrates, vitamins, and minerals, as well as inherent antinutritional factors, toxins, and allergens (Miraglia et al., 1998). The breadth of technology used to measure these constituents is evolving rapidly, with new methods available to assess the integrity of metabolic pathways and to measure secondary metabolites, functional proteins, and gene expression at the molecular level.

A recent report (FAO/WHO, 2000) of the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) considered the concept of substantial equivalence:

> A comparative approach focusing on the determination of similarities and differences between the genetically modified food and its conventional counterpart aids in the identification of potential safety and nutritional issues and is considered the most appropriate strategy for the safety and nutritional assessment of genetically modified foods.
>
> The Consultation was of the view that there were presently no alternative strategies that would provide a better assurance of safety for genetically modified foods than the appropriate use of the concept of substantial equivalence. Nevertheless, it was agreed that some aspects of the steps in safety assessment process could be refined to keep abreast of developments in genetic modification technology. The concept of substantial equivalence was developed as a practical approach to the safety assessment of genetically modified foods. It should be seen as a key step in the safety assessment process although it is not a safety assessment in itself; it does not characterize hazard, rather it is used to structure the safety assessment of a genetically modified food relative to a conventional counterpart. The Consultation concluded that the application of the concept of substantial equivalence contributes to a robust safety assessment framework. The Consultation was satisfied with the approach used to assess the safety of the genetically modified foods that have been approved for commercial use.

Similarly, in a May 2000 report, the Organization for Economic Cooperation and Development (OECD) examined the safety of novel foods and feeds. It concluded that:

> Safety assessment based on substantial equivalence is the most practical approach to address the safety of food and food components derived through modern biotechnology.

In its 1992 policy on foods derived from new plant varieties (FDA 1992), FDA employs the concept of substantial equivalence by focusing on the characteristics of the food product. Foremost, this policy on food products from new plant varieties is intended to be applied regardless of the derivation of the plant, i.e., through conventional breeding or rDNA biotechnology methods. FDA has identified certain characteristics of these foods that would dictate the need for further scrutiny to establish safety. These include a substance that is completely new to the food supply, an allergen expressed in an unusual or unexpected circumstance, changes in the concentrations of major dietary nutrients, and increased concentrations of antinutritional factors and toxins inherent to the food. Although the FDA policy does not specifically use the term substantial equivalence, the absence of the characteristics mentioned above would lead to the conclusion that a food from a new plant variety is substantially equivalent to its traditional counterpart.

Safety of Introduced Genetic Material and Gene Product

Under FDA's current (1992) policy, as a starting point, the characteristics of the product are assessed, including the nucleotide sequence of the DNA of the genetic material that is used for plant transformation. This procedure provides important information on the encoded protein(s), regulatory elements controlling expression, and the presence or absence of additional potential coding sequences within the DNA. Although all extraneous non-coding DNA may not be identified, it can be minimized to very small segments. This level of detail cannot ordinarily be determined for new plant varieties produced in conventional ways such as hybridization.

Thus, the FDA policy contemplates that the structure and function of proteins encoded by the gene(s) introduced into plants will be understood in considerable detail. This information is used to assess the level of any potential risk, both of the introduced protein and of other products that may be produced or altered by the presence of the introduced protein. An additional factor is the source of

the gene. The FDA policy contemplates that the following questions be addressed: Does the source organism have a history of safe use? and Does the source of the gene produce any endogenous toxins or allergens, that would need to be assessed in the genetically modified plant?

Any potential safety concerns associated with the source organism would serve to focus the safety assessment of the rDNA biotechnology-derived plant and the products derived from that plant. For example, if a gene were obtained from a source that produced a known allergen, the proteins encoded by the introduced DNA would have to be assessed to demonstrate that this DNA did not encode an allergen.

• Safety of Introduced Genetic Material. The initial step in a safety assessment is full characterization of the genetic construct being inserted. This step includes identifying the source of the genetic material to establish whether it originates from a pathogenic, toxin-producing, or allergenic source. Parameters measured include the size of the genetic construct that is inserted into the plant genome, the number of constructs inserted, the location of insertion, and the identification of genetic sequences within the construct that allow for its detection (marker sequences) and expression (promoter sequences) in the plant.

The genetic material transferred is composed of DNA. All food, rDNA biotechnology-derived or otherwise, contains DNA. Individuals consume large quantities of DNA when eating conventional foods (Beever and Kemp, 2000). The DNA introduced using rDNA biotechnology represents only a tiny fraction of the total DNA consumed when the food is eaten, and transfer of genes from rDNA biotechnology-derived plants to mammalian cells is extremely unlikely.

Since DNA occurs in all foods, it is not subject to a safety evaluation (IFBC, 1990; Miraglia et al., 1998). It is well-established that DNA is rapidly digested in the gastrointestinal tract, and there is no evidence of DNA transfer from foods to human intestinal cells or gut microorganisms (Donaldson and May, 1999). Any plant DNA that might be found in human tissues is likely to be a small, non-functional fragment resulting from centuries of consumption and does not imply that plant foods are unsafe. Moreover, the likelihood of transfer of rDNA segments from foods produced using rDNA biotechnology is far less than for DNA from conventional foods simply because the novel DNA is less than 1/250,000 of the overall amount consumed (FAO/WHO, 2000).

Earlier rDNA biotechnology-derived foods were based on the use of selectable marker genes that confer resistance to an antibiotic. A workshop convened by the WHO concluded that the presence of marker genes per se in food would not constitute a safety concern (WHO, 1993). FAO/WHO (2000) recently reconsidered the issue of antibiotic resistance marker genes and again found there is no evidence that the markers currently in use pose a health risk to humans or domestic animals. Still, genes that confer resistance to drugs with specific medical use or limited alternative therapies should not be used in widely disseminated rDNA biotechnology-derived foods.

Following extensive examination, FDA decided to permit the use of kanamycin-resistance genes in the development of rDNA biotechnology-derived tomatoes, oilseed rape, and cotton for food and feed use and permitted these crops in food and feed (FDA, 1994). FDA concluded that the DNA for kanamycin resistance was not different from other rDNA in its digestibility and does not pose a food safety concern.

The marker gene used to confer kanamycin resistance was the neomycin phosphotransferase, type II gene (NPTII). The NPTII protein is rapidly degraded, like other dietary proteins, when subjected to conditions which simulate mammalian digestion. This protein has also been tested in acute toxicology studies at levels more than one million times the level that would be consumed by people eating food from rDNA biotechnology-derived plants. Finally, the transformation of intestinal bacteria by kanamycin resistance from plants is negligible, with a calculated theoretical maximum of less than 1 in 100,000 compared to bacterial transfers of resistance (WHO, 1993). Thus, this protein poses no food safety concerns. FDA concluded that there is no inherent danger presented by the presence of the antibiotic resistance markers used in earlier rDNA biotechnology-derived foods. These marker genes, such as the NPTII gene, do not present a food or feed safety concern and are not considered to be either toxic or allergenic.

The risk that the use of antibiotic resistance genes could lead to a transfer of antibiotic resistance and reduced efficacy of antibiotics is extremely small, because it would require a series of events, each of which is highly unlikely. Moreover, if such a move did occur, antibiotic selection would be needed to make the newly resistant strain a common one (Salyers, 2000). These concerns are addressed in additional detail in the *Benefits and Concerns* section.

• Safety of Gene Product. FDA's 1992 policy also contemplates that, once the genetic construct has been fully characterized, an assessment of the safety of the gene product will be conducted. [The gene product is the protein, often an enzyme, that is produced by the newly introduced gene(s) and is present in the rDNA biotechnology-derived food or food ingredient, e.g., the protein expressed in Bt corn, encoded by genes from *Bacillus thuringiensis* (Bt), that confers pesticidal specificity for lepidopteran insects.] Safety evaluations typically include identification of the composition and structure of the gene product; a quantification of the amount of gene product expressed in the edible portion of the food; a search for similarity to known toxins and antinutritional factors, allergens, and other functional proteins; a determination of the thermal and digestive stability of the gene product; and the results of both in-vivo and in-vitro toxicological assays to demonstrate lack of apparent allergenicity or toxicity (Donaldson and May, 1999).

Unintended Effects

From a safety perspective, unintended effects of genetic modification have been speculated to manifest as the unintended expression of some unknown or unexpected toxic or antinutrient factor, or the otherwise unintended enhanced production of known toxic constituents (Royal Society, 1998).

However, based on the knowledge gained to date from the multitude of foods derived from rDNA biotechnology, there is no scientific evidence of the occurrence of such unintended effects. Given the more precise and predictable nature of genetic change accomplished through rDNA techniques as compared to the random genetic changes observed in conventional breeding, such unintended effects would be considered less likely in foods derived from rDNA biotechnology. Furthermore, these effects have been observed infrequently in the many thousands of crosses involving conventional crop breeding. In such cases, the source of the toxic constituent can typically be traced back to a related species used in conventional cross-breeding manipulations. For example, high glycoalkaloid concentrations were found in the conventionally bred Lenape potato, and the variety was subsequently withdrawn by the

Biotechnology Report: Safety

CONTINUED

U.S. Department of Agriculture (Zitnak and Johnston, 1970). These toxins are present in all potatoes, and new potato cultivars are routinely screened for glycoalkaloid content. The unusually high glycoalkaloid content in Lenape was attributed to the use of the wild, non-tuber-bearing *Solanum chacoense* in its parentage. Interestingly, Lenape is a parent of Atlantic, a current potato variety with a glycoalkaloid content typical of the range for edible potatoes.

Allergenicity

Food allergies involve abnormal immunological responses to substances in foods, usually naturally occurring proteins found in commonly allergenic foods such as peanuts, milk, and seafood. Allergic reactions can be manifested by symptoms ranging from mild cutaneous or gastrointestinal symptoms to life-threatening anaphylactic shock reactions. Virtually all food allergens are proteins, although only a small fraction of the proteins found in nature (and in foods) are allergenic. Since genetic modifications involve the introduction of new genes into the recipient plant and since these genes would produce new proteins in the improved variety, the potential allergenicity of the newly introduced protein should be a key component of the safety assessment process.

An assessment of the potential allergenicity of rDNA biotechnology-derived foods typically follows the decision-tree process outlined by the International Food Biotechnology Council (IFBC) and the Allergy and Immunology Institute of the International Life Sciences Institute (ILSI) (Metcalfe et al., 1996). This strategy focuses on specific scientific criteria, including the source of the gene(s), the sequence homology of the newly introduced protein(s) to known allergens, the immunochemical reactivity of the newly introduced protein(s) with immunoglobulin E (IgE) antibodies from the blood serum of individuals with known allergies to the source from which the genetic material was obtained, and the physicochemical properties, e.g., digestive stability, of the introduced protein.

At the recently concluded expert consultation (FAO/WHO, 2000), several other criteria, including the level of expression of the newly introduced protein(s) in the edible portions of the improved variety and the evaluation of the functional category for the introduced protein (some functional categories of proteins, e.g., high-methionine 2S albumins, are known to contain several allergens from different sources), were suggested for addition to the IFBC-ILSI allergenicity assessment strategy.

The first step of the allergenicity assessment (Fig. 1) involves the classification of the source of the genetic material as either commonly allergenic, less commonly allergenic, or of unknown allergenic potential. Eight foods or food groups, including milk, eggs, fish, crustacean shellfish, peanuts, soybeans, tree nuts, and wheat, are well accepted as commonly allergenic; these eight foods or food groups account for more than 90% of all food allergies in the world (FAO, 1995). More than 160 other foods have been described to cause allergic reactions (Hefle et al., 1996), and would be classified as less commonly allergenic. However, many of the genes that have been and will be used to produce rDNA biotechnology-derived foods are obtained from sources with no history of allergenicity as foods. Certainly, if the source contains well known environmental allergens, e.g., ragweed that contains common ragweed pollen allergens, then the allergenicity of newly introduced protein(s) from such sources must be carefully evaluated.

The approaches to allergenicity assessment vary according to the nature of the source of the transferred genetic material. If the genetic material is obtained from a known allergenic source, either commonly or less commonly allergenic, and the encoded protein is expressed in the edible portion of the rDNA biotechnology-derived food, then the protein must be considered to be an allergen unless proven otherwise.

In such situations, the next step in the allergenicity assessment is a determination of the immunoreactivity of the newly introduced protein with IgE antibodies from the sera of individuals allergic to the donor organism. The blood serum can be tested for reactivity with the purified protein or extracts of the genetically modified food using immunoassays (Yunginger and Adolphson, 1992; Taylor and Lehrer, 1996). If a sufficient number of test sera are used as advocated in the decision tree approach (Metcalfe et al., 1996), the allergenicity of the introduced protein can be determined with a high degree of confidence. However, if negative results are obtained in the immunoassays, the rDNA biotechnology-derived food or extracts of that food should be tested further using in-vivo skin-prick tests (Bock et al., 1977; Taylor and Lehrer, 1996), double-blind, placebo-controlled food challenges (Bock et al., 1988; Taylor and Lehrer, 1996), or digestive stability assessments (Astwood et al., 1996) as advocated by the IFBC-ILSI decision tree. If the immunoassays and these other tests, as appropriate, are negative, then the likelihood that the rDNA biotechnology-derived food contains an allergen would be quite small.

The most difficult assessment occurs when genes are obtained from sources with no history of allergenicity, such as viruses, bacteria, or non-food plants. The likelihood that the proteins derived from such sources of DNA will be allergens is not very high, since most proteins in nature are not allergens (Taylor, 1997). Additionally, many of these proteins will be expressed in the rDNA biotechnology-derived food at very low levels, while allergic sensitization is more likely to occur to the major proteins that exist in foods (Taylor, 1997). The key features of the allergenicity assessment for such foods involve a comparison of the amino acid sequence of the introduced protein with the amino acid sequences of known allergens and the digestive stability of the introduced protein. While the combination of these two criteria provides reasonable assurance that the introduced protein has limited allergenic potential, the ideal approaches to the application of these two criteria have been debated, and the desirability of adding other criteria for the allergenicity assessment of such products has been advocated (Wal, 1998).

The criterion of amino acid sequence homology to known allergens is a logical and increasingly powerful approach. The amino acid sequences of more than 300 known allergens are available for comparative purposes. The IFBC-ILSI strategy defines significant sequence similarity as a match of at least eight contiguous, identical amino acids based on the minimal peptide length needed for T-cell binding, which is a necessary prelude to allergic sensitization; this approach is clearly limited in that it cannot identify discontinuous or conformational epitopes that are dependent on the tertiary structure of the protein (Metcalfe et al., 1996). Others have suggested that the definition of significant sequence homology be modified to a minimal peptide length of less than eight contiguous, identical amino acids (Consumer

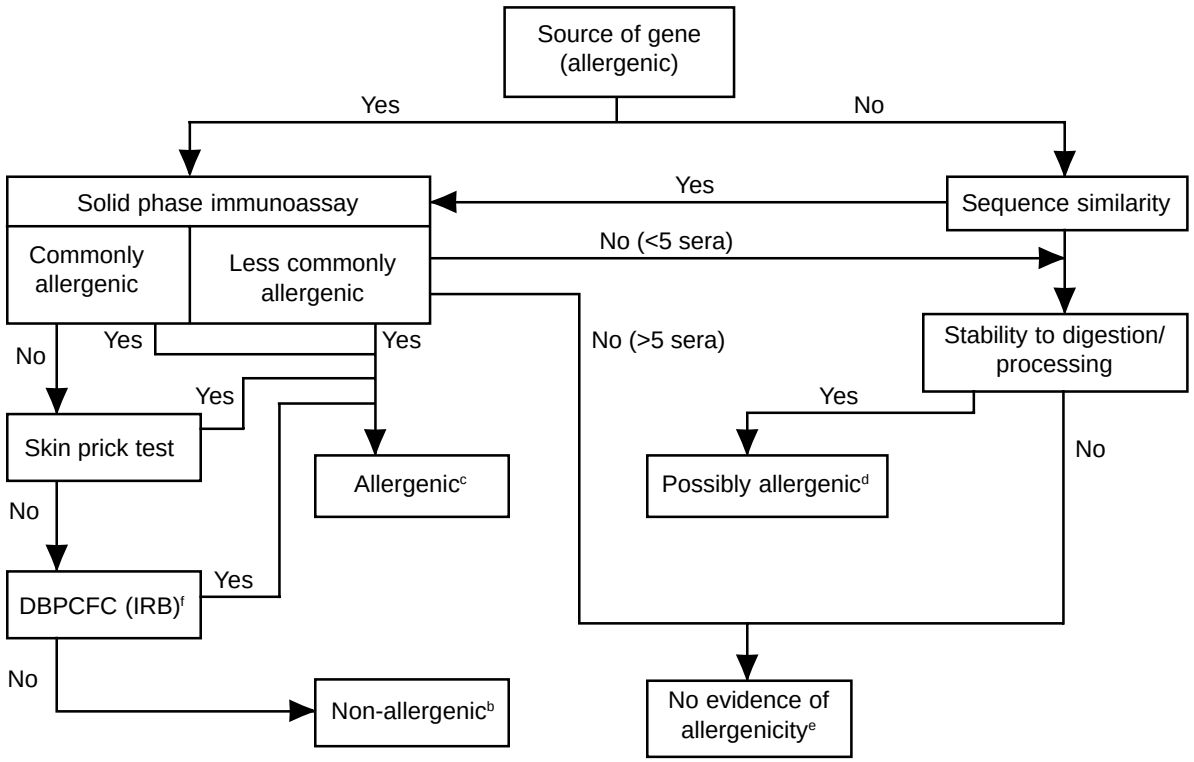
and Biotechnology Foundation, 1999). While this criterion (amino acid sequence homology to known allergens) is clearly useful, international agreement must be sought on its application.

Known food allergens tend to be quite stable to digestive proteases (Astwood et al., 1996) with the exception of the pollen-related food proteins that cause oral allergy syndrome (Taylor and Lehrer, 1996). Thus, digestive stability can be used as a criterion for the assessment of the allergenic potential of the introduced proteins. Both simulated gastric and intestinal models of mammalian digestion are advocated for such assessments (Astwood et al., 1996; Metcalfe et al., 1996). While the usefulness of this criterion is apparent, consensus is needed on the ideal protocols for assessment of digestive stability. It is recognized that novel proteins may exist that are stable to digestion but will not become allergens. Additional testing is needed to assess the allergenic potential of such proteins (FAO/WHO, 2000).

The development of additional criteria and additional tests to use in the assessment of the allergenicity of rDNA biotechnology-derived foods would be advantageous in cases where the gene is obtained from sources with no history of allergenicity. As mentioned, the level of expression of the introduced protein and the functional category of the introduced protein could be used as additional criteria (FAO/WHO, 2000). In addition, the development of suitable animal models for the prediction of the allergenic potential of the introduced proteins is anticipated in the future. While several animal models appear to be promising (Knippels et al., 1998), none has been sufficiently validated for its routine use in the assessment of the allergenicity of rDNA biotechnology-derived foods.

The existing decision-tree approach

Fig. 1—Assessment of the allergenic potential of foods derived from genetically modified crop plants[a]



[a] From FAO/WHO 2000. Adapted from decision-tree approach developed by International Food Biotechnology Council and Allergy and Immunology Institute of the International Life Sciences Institute (Metcalfe et al., 1996).

[b] The combination of tests involving allergic human subjects or blood serum from such subjects would provide a high level of confidence that no major allergens were transferred. The only remaining uncertainty would be the likelihood of a minor allergen affecting a small percentage of the population allergic to the source material.

[c] Any positive results obtained in tests involving allergic human subjects or blood serum from such subjects would provide a high level of confidence that the novel protein was a potential allergen. Foods containing such novel proteins would need to be labeled to protect allergic consumers.

[d] A novel protein with either no sequence similarity to known allergens or derived from a less commonly allergenic source with no evidence of binding to IgE from the blood serum of a few allergic individuals (<5) but that is stable to digestion and processing should be considered a possible allergen. Further evaluation would be necessary to address this uncertainty. The nature of the tests would be determined on a case-by-case basis.

[e] A novel protein with no sequence similarity to known allergens and that was not stable to digestion and processing would have no evidence of allergenicity. Similarly, a novel protein expressed by a gene obtained from a less commonly allergenic source and demonstrated to have no binding with IgE from the blood serum of a small number of allergic individuals (>5 but <14) provides no evidence of allergenicity. Stability testing may be included in these cases. However, the level of confidence based on only two decision criteria is modest. The FAO/WHO Expert Consultation suggested that other criteria should also be considered, such as the level of expression of the novel protein.

[f] Double-blind placebo-controlled food challenge (institutional review board).

Biotechnology Report: Safety

CONTINUED

has already been applied in the assessment of the allergenicity of rDNA biotechnology-derived foods. The enzyme introduced into glyphosate-tolerant soybeans has no sequence homology to known allergens and is rapidly digested in simulated mammalian digestion systems (Harrison et al., 1996). Similarly, several of the Bt proteins used in insect-resistant crops and the proteins produced by common marker genes are rapidly digested in simulated mammalian digestion systems (Astwood et al., 1996). A high-methionine protein introduced into soybeans by the transfer of a gene from Brazil nuts to correct the inherent methionine deficiency in soybeans was shown to bind to IgE from the sera of Brazil nut–allergic individuals and to elicit positive skin-prick tests in some of these patients (Nordlee et al., 1996). This protein was thus identified as the major allergen from Brazil nuts that had not previously been characterized. As a result, commercial development of this particular soybean variety was discontinued.

Clearly, the assessment of the allergenicity of rDNA biotechnology-derived foods should be a key component of the overall safety assessment process in all cases. A useful strategy has been developed for such assessments, although this strategy should be viewed as dynamic and new approaches and criteria should be added once they are validated and accepted.

Products without Conventional Counterparts

Recombinant DNA-derived biotechnology foods without conventional counterparts need to be evaluated on a case-by-case basis and would be subject to some types of toxicity assessments, depending on the nature of the modification (IFBC, 1990). This situation has not yet arisen with rDNA biotechnology derived foods, although at some point it undoubtedly will. When it does, the situation will raise a variety of issues that will need to be addressed in a scientifically based, flexible manner.

Whole foods are complex mixtures of chemical components characterized by wide variations in composition and nutritional qualities, and are not well suited for traditional toxicological studies designed to assess individual chemical entities. The testing of whole foods—rDNA biotechnology-derived or conventional—in animal feeding studies, for example, is limited by factors such as the animal's qualitative and quantitative feeding preferences and the levels of nutritional and antinutritional factors and other substances that are present. When one researcher attempted to ascertain the toxic threshold for an rDNA biotechnology-derived tomato by feeding rats freeze-dried tomato extract, the experiments were limited to the human equivalent of 13 tomatoes a day by negative effects of inorganic compounds, such as potassium, that are present in rDNA biotechnology-derived and conventional tomatoes alike. But, as noted by MacKenzie (1999), "Toxicologists still said we hadn't fed them enough to get a meaningful result."

Another limitation is that animal toxicity tests are seldom sufficiently sensitive to distinguish differences between the toxicity of a new variety and its conventional counterparts. Indeed, most foods will produce adverse effects in long-term animal feeding studies when fed in high proportions of the diet, regardless of the nature of production. The results of such studies are not easily interpreted, and apparent adverse effects are often the indirect effects of related nutritional dietary imbalance, rather than any specific compound in question. OECD (2000) recognized that there is no scientific justification for requiring long-term feeding studies for rDNA biotechnology-derived foods, and that such studies would be unlikely to provide meaningful information in the great majority of cases. FAO/WHO (2000) concurred, finding that the practical difficulties in the application of conventional toxicology studies to whole foods preclude their use as a routine safety assessment technique.

The key differences between the testing of whole foods and the testing of individual chemical substances in animal feeding studies are indicated in Table 1.

Thus, given a hypothetical rDNA biotechnology-derived food without a conventionally derived counterpart, animal studies would need to be designed to address specific nutritional or toxicological concerns. However, these studies would need to be carefully designed to avoid or minimize the limitations discussed above that are associated with the testing of whole foods or major food constituents (Munro et al., 1996). For example, toxicological studies could be used to examine the potential for acute, chronic, carcinogenic, genotoxic, reproductive, and teratogenic effects of components or fractions of concern in a food derived from a new plant variety. A complete assessment would also include pharmacokinetic data regarding absorption, distribution, metabolism, and excretion of the new product or a novel component thereof. By focusing toxicological examination on carefully se-

Table 1 Differences between animal testing of individual chemicals and whole foods[a]

Individual chemical testing	Whole foods testing
Typically a single, chemically identified substance	A complex mixture of many substances, most unidentified
Highest dose level should produce an adverse effect attributable only to the chemical	Highest dose that does not cause rejection of the diet, or nutritional imbalance, very unlikely to produce any toxic effect
Low doses, usually <1% of the diet	High doses, usually >10% of the diet
Easy to give a dose high enough to assure an adequate safety factor (>100× normal human intake)	Difficult or impossible to achieve doses more than a few multiples of human intake; therefore, no adequate safety factor
Acute effects obvious	Acute effects, other than nutritional imbalance, nearly always absent
Nutritional effects generally absent	Nutritional effects typically present
Specific routes of metabolism capable of being studied and ascertained	Complex metabolism of many ingredients, most unidentified; therefore, impossible to determine
Cause/effect relatively clear	Effects usually absent or, if observed, confused by multiple possible causes

[a]Based on Munro et al. (1986) and Hall (1981)

lected fractions or components of a food derived from a new plant variety, and excluding major components of no concern, it may be possible to reduce or eliminate the difficulties associated with testing whole foods.

The assessment of macronutrient substitutes or other major food constituents should follow a tiered approach (Munro et al., 1996), whereby the physical and chemical properties of the constituent are determined, in addition to its potential to disrupt or alter nutrient uptake. Initial predictive effect studies would dictate the physiologically relevant endpoint determinants of subsequent in-vitro and in-vivo studies (Munro et al., 1996). Further, the choice of animal model for any such in-vivo studies would have to be carefully considered for relevance when applying results to humans (Battershill et al., 1999).

Without precedence, the above discussion outlines a proposal which seems best calculated to provide the data needed for a persuasive showing of safety. Clearly, such novel foods without conventional counterparts, when they do become available, will need careful testing, evaluation, and regulatory scrutiny using a flexible process that contains case-by-case adaptation based on the novel nature of the issues presented.

Scientific Consensus About Safety

The Human Food Safety Panel reviewed available information about the safety of rDNA biotechnology-derived foods and found that there is striking congruence in the conclusions and recommendations of various international scientific groups that have considered the issue.

The National Academy of Sciences published a white paper (NAS, 1987) on the planned introduction of organisms derived using rDNA biotechnology into the environment. This white paper has had wide-ranging impacts in the United States and other countries. Its most significant conclusions and recommendations include (1) there is no evidence of the existence of unique hazards, either in the use of rDNA biotechnology techniques or in the movement of genes between unrelated organisms, and (2) the risks associated with the introduction of rDNA biotechnology-derived organisms are the same in kind as those associated with the introduction of unmodified organisms and organisms modified by other methods.

In a 1989 extension of this white paper, the National Research Council (NRC), the research arm of the NAS, concluded that "no conceptual distinction exists between genetic modification of plants and microorganisms by classical methods or by molecular techniques that modify DNA and transfer genes" (NRC, 1989). The NRC report supported this statement with extensive observations of past experience with plant breeding, introduction of rDNA biotechnology-derived plants, and introduction of rDNA biotechnology-derived microorganisms:

> The committees [of experts commissioned by NRC] were guided by the conclusion (NAS, 1987) that the *product* of genetic modification and selection should be the primary focus for making decisions about the environmental introduction of a plant or microorganism and not the *process* by which the products were obtained.
>
> Information about the process used to produce a genetically modified organism is important in understanding the characteristics of the product. However, the nature of the process is not a useful criterion for determining whether the product requires less or more oversight.
>
> The same physical and biological laws govern the response of organisms modified by modern molecular and cellular methods and those produced by classical methods.
>
> Recombinant DNA methodology makes it possible to introduce pieces of DNA, consisting of either single or multiple genes, that can be defined in function and even in nucleotide sequence. With classical techniques of gene transfer, a variable number of genes can be transferred, the number depending on the mechanism of transfer; but predicting the precise number or the traits that have been transferred is difficult, and we cannot always predict the phenotypic expression that will result. With organisms modified by molecular methods, we are in a better, if not perfect, position to predict the phenotypic expression.
>
> Crops modified by molecular and cellular methods should pose risks no different from those modified by classical genetic methods for similar traits. As the molecular methods are more specific, users of these methods will be more certain about the traits they introduce into the plants.
>
> The types of modifications that have been seen or anticipated with molecular techniques are similar to those that have been produced with classical techniques. No new or inherently different hazards are associated with the molecular techniques.

The same principles were emphasized in a comprehensive report (NIH, 1992) by the U.S. National Biotechnology Policy Board, which was established by Congress and composed of representatives from the public and private sectors:

> The risks associated with biotechnology are not unique, and tend to be associated with particular products and their applications, not with the production process or the technology per se. In fact biotechnology processes tend to reduce risks because they are more precise and predictable. The health and environmental risks of not pursuing biotechnology-based solutions to the nation's problems are likely to be greater than the risks of going forward.

These findings are consistent with the observations and recommendations of the United Kingdom's House of Lords Select Committee on Science and Technology (UK,1993), which was very critical of that nation's policy of subjecting rDNA biotechnology-derived products to additional regulatory requirements:

> As a matter of principle, GMO-derived products [i.e., those from genetically manipulated organisms, or recombinant organisms] should be regulated according to the same criteria as any other product. . . . U.K. regulation of the new biotechnology of genetic modification is excessively precautionary, obsolescent, and unscientific. The resulting bureaucracy, cost, and delay impose an unnecessary burden to academic researchers and industry alike.

Three joint FAO/WHO consultations, addressing specifically the question of the safety of rDNA biotechnology-derived foods, came to similar conclusions. The first of these expert consultations (FAO/WHO, 1991) concluded:

Biotechnology Report: Safety

CONTINUED

> Biotechnology has a long history of use in food production and processing. It represents a continuum embracing both traditional breeding techniques and the latest techniques based on molecular biology. The newer biotechnological techniques, in particular, open up very great possibilities of rapidly improving the quantity and quality of food available. The use of these techniques does not result in food which is inherently less safe than that produced by conventional ones.

The second consultation (FAO/WHO, 1996) reaffirmed the conclusions and recommendations of the first FAO/WHO consultation:

> Food safety considerations regarding organisms produced by techniques that change the heritable traits of an organism, such as rDNA technology, are basically of the same nature as those that might arise from other ways of altering the genome of an organism, such as conventional breeding. . . . While there may be limitations to the application of the substantial equivalence approach to safety assessment, this approach provides equal or increased assurance of the safety of food products derived from genetically modified organisms as compared to foods or food components derived by conventional methods.

The most recent consultation (FAO/WHO 2000) examined the evidence to date and concluded:

> A comparative approach focusing on the determination of similarities and differences between the genetically modified food and its conventional counterpart aids in the identification of potential safety and nutritional issues and is considered the most appropriate strategy. . . . The Consultation was of the view that there were presently no alternative strategies that would provide better assurance of safety for genetically modified foods than the appropriate use of the concept of substantial equivalence.

OECD (1993) offered several conclusions and recommendations that are wholly consistent with the NAS, NRC, and FAO/WHO findings:

> In principle, food has been presumed to be safe unless a significant hazard was identified.
>
> Modern biotechnology broadens the scope of the genetic changes that can be made in food organisms and broadens the scope of possible sources of foods. This does not inherently lead to foods that are less safe than those developed by conventional techniques.
>
> Therefore, evaluation of foods and food components obtained from organisms developed by the application of the newer techniques does not necessitate a fundamental change in established principles, nor does it require a different standard of safety.
>
> For foods and food components from organisms developed by the application of modern biotechnology, the most practical approach to the determination of safety is to consider whether they are *substantially equivalent* to analogous conventional food product(s), if such exist.

OECD (1998) reaffirmed the conclusions and recommendations of previous consultations of both FAO/WHO and OECD. Regarding the specific question of potential allergenicity of novel proteins introduced in rDNA biotechnology-derived foods, the report stated:

> While no specific methods can be used for proteins derived from sources with no history of allergy, a combination of genetic and physicochemical comparisons exist which can be used as a screen. The application of such a strategy can provide appropriate assurance that foods derived from genetically modified products can be introduced with confidence comparable to other new plant varieties.

In 2000, OECD acknowledged the public concerns about the safety assessment of rDNA technology (OECD 2000), stating:

> Although [the] food safety assessment is based on sound science, there is a clear need for increased transparency and for safety assessors to communicate better with the public. Much progress has already been made in this regard. . . . However, more could be done in this area.

The NRC's Committee on Genetically Modified Pest-Protected Plants published a report (NRC, 2000) that reaffirmed the principles set forth in the 1987 NAS white paper. Specifically, the committee found that "there is no strict dichotomy between, or new categories of, the health and environmental risks that might be posed by transgenic and conventional pest-protected plants" and that the "properties of a genetically modified organism should be the focus of risk assessments, not the process by which it was produced." The committee concluded that "[w]ith careful planning and appropriate regulatory oversight, commercial cultivation of transgenic pest-protected plants is not generally expected to pose higher risks and may pose less risk than other commonly used chemical and biological pest-management techniques." (While the report focused on rDNA biotechnology-derived pest-protected plants, the committee stated that many of its conclusions are also applicable to rDNA biotechnology-derived plants generally.)

In summary, the safety of rDNA biotechnology-derived foods has been extensively reviewed by a number of scientific organizations, at the national and international level. The use of rDNA biotechnology in itself has no impact on the safety of such foods. Foods derived using rDNA biotechnology are subject to rigorous and systematic scientific evaluations under existing principles of food safety—far more than are routinely applied to the products of traditional breeding. Thus, the level of field testing and premarket review for food safety provide assurance that foods derived from plants and microorganisms through rDNA biotechnology are at least as safe as existing foods, and are consistent with all existing standards of food safety.

Conclusions

Based on its evaluation of the available scientific evidence, the Human Food Safety Panel reached the following conclusions:

• Biotechnology, broadly defined, has a long history of use in food production and processing. It represents a continuum that encompasses both centuries-old tradition-

al breeding techniques and the latest techniques based on molecular modification of genetic material, which are a major step forward by virtue of their precision and reach. The newer rDNA biotechnology techniques, in particular, offer the potential to rapidly and precisely improve the quantity and quality of food available.

• Crops modified by modern molecular and cellular methods pose risks no different from those modified by earlier genetic methods for similar traits. Because the molecular methods are more specific, users of these methods will be more certain about the traits they introduce into the plants.

• The evaluation of food, food ingredients, and animal feed obtained from organisms developed with the newer rDNA biotechnology techniques of genetic manipulation does not require a fundamental change in established principles of food safety; nor does it require a different standard of safety, even though, in fact, more information and a higher standard of safety are being required.

• The science that underlies rDNA biotechnology-derived foods does not support more stringent safety standards than those that apply to conventional foods.

• The use of rDNA biotechnology and molecular techniques of genetic manipulation significantly broadens the scope of the genetic changes that can be made in food organisms and broadens the scope of possible sources of foods, but this does not inherently lead to foods that are less safe than those developed by conventional techniques. By virtue of their greater precision, such products can be expected to be better characterized, leading to more predictability and a more reliable safety assessment process.

REFERENCES

Astwood, J.D., Leach, J.N., and Fuchs, R.L. 1996. Stability of food allergens to digestion in vitro. Nature Biotechnol. 14: 1269-1273.

Battershill, J., Hattersley, S.J., and Sanderson, M. 1999. Critical issues for the safety assessment of novel foods when no conventional counterpart exists: Discussion meeting, Dept. of Health, London, UK, 12 February 1998. Food Additives and Contaminants 16(1): 37-45.

Beever, D.E. and Kemp, C.F. 2000. Safety issues associated with the DNA in animal feed derived from genetically modified crops. A review of scientific and regulatory procedures. Nutr. Abstr. Reviews, Series B: Livestock Feeds and Feeding 70: 175-182.

Bock, S.A., Buckley, J., Holst, A., and May, C.D. 1977. Proper use of skin tests with food extracts in diagnosis of hypersensitivity to foods in children. Clin. Allergy 7: 375-383.

Bock, S.A., Sampson, H.A., Atkins, F.M., Zeiger, R.S., Lehrer, S., Sachs, M., Bush, R.K., and Metcalfe, D.D. 1988. Double-blind, placebo-controlled food challenges (DBPCFC) as an office procedure: A manual. J. Allergy Clin. Immunol. 82: 986-997.

Consumer and Biotechnology Foundation. 1999. Genetically modified foods and allergenicity: Safety aspects and consumer information. Report of Workshop, Breukelen, Netherlands, May 28-29.

Donaldson, L. and May, R. 1999. Health implications of genetically modified foods. Dept. of Health. www.doh.gov.uk/pub/docs/doh/gmfood.pdf .

FAO. 1995. Report of the FAO Technical Consultation on Food Allergies, Rome, Nov. 13-14. Food and Agric. Org., Rome.

FAO/WHO. 1991. Strategies for assessing the safety of foods produced by biotechnology. Report of a Joint FAO/WHO Expert Consultation. Food and Agriculture Organization of the United Nations and World Health Organization. WHO, Geneva, Switzerland.

FAO/WHO. 1996. Biotechnology and Food Safety. Report of a Joint FAO/WHO Expert Consultation. Food and Agriculture Organization of the United Nations and World Health Organization. WHO, Geneva, Switzerland.

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. Food and Agriculture Organization of the United Nations and World Health Organization. WHO, Geneva, Switzerland.

FDA. 1992. Statement of policy: Foods derived from new plant varieties. Food and Drug Admin., Fed. Reg. 57: 22984.

FDA. 1994. Secondary direct food additives permitted in food for human consumption; Food additives permitted in feed and drinking water of animals; Aminoglycoside 3'-Phosphotransferase II; Final rule. Food and Drug Admin., Fed. Reg. 59: 26700.

Hall, R.L. 1981. Evaluating the toxicity and health hazards of dietary adjuvants (spices, herbs, etc.). In Proceedings of the Toxicology Forum, July 20–24, 1981, pp. 404. Toxicology Forum, Washington, D.C.

Harrison, L.A., Bailey, M.R., Naylor, M.W., Ream, J.E., Hammond, B.G., Nida, D.L., Burnette, B., Nickson, T.E., Mitsky, T.A., Taylor, M.L., Fuchs, R.L., and Padgette, S.R. 1996. The expressed protein in glyphosate-tolerant soybean, 5-enolpyruvylshikimate-3-phosphate synthase from Agrobacterium sp. Strain CP4, is rapidly digested in vitro and is not toxic to acutely gavaged mice. J. Nutr. 126: 728-740.

Hefle, S.L., Nordlee, J.A., and Taylor, S.L. 1996. Allergenic foods. Crit. Rev. Food Sci. Nutr. 36: S69-S89.

HHS. 2000. FDA to strengthen premarket review of bioengineered foods. Press release. May 3. U.S. Dept. of Health and Human Services, Washington, D.C.

IFBC. 1990. Biotechnologies and Food: Assuring the Safety of Food Produced by Genetic Modification. Intl. Food Biotechnology Council. Regulatory Toxicol. Pharmacol. 12(3): Part 2.

Knippels, L.M.J., Pennicks A.H., Spanhaak S., and Houben G.F. 1998. Oral sensitization to food proteins: A Brown Norway rat model. Clin. Exp. Allergy 28: 368-375.

MacKenzie, D. 1999. Unpalatable truths. New Scientist, April 17, pp. 18-19.

Metcalfe, D.D., Astwood, J.D., Townsend, R., Sampson, H.A., Taylor, S.L., and Fuchs, R.L. 1996. Assessment of the allergenic potential of food derived from genetically engineered crop plants. Crit. Rev. Food Sci. Nutr. 36: S165-S186.

Miraglia, M., Onori, R., Brera, C., and Cava, E. 1998. Safety assessment of genetically modified food products: An evaluation of developed approaches and methodologies. Microchem. J. 59: 154-159.

Munro, I.C., McGirr, L.G., Nestmann, E.R., and Kille, J.W. 1996. Alternative approaches to the safety assessment of macronutrient substitutes. Regulatory Toxicol. Pharmacol. 23: S6-S14.

NAS. 1987. Introduction of recombinant DNA-engineered organisms into the environment: Key issues. Natl. Acad. of Sciences. National Academy Press, Washington, D.C.

NIH. 1992. National Biotechnology Policy Board report. Natl. Insts. of Health, Bethesda, Md.

Nordlee, J.A., Taylor, S.L., Townsend, J.A., Thomas, L.A., and Bush, R.K. 1996. Identification of a Brazil nut allergen in transgenic soybeans. New Eng. J. Med. 334: 688-694.

NRC. 1989. "Field Testing Genetically Modified Organisms: Framework for Decisions." Natl. Res. Council. National Academy Press, Washington, D.C.

NRC. 2000. "Genetically Modified Pest-Protected Plants: Science and Regulation." Natl. Res. Council. National Academy Press, Washington, D.C.

OECD. 1993. "Safety Evaluation of Foods Derived by Modern Biotechnology: Concepts and Principles." Org. for Economic Cooperation and Development, Paris.

OECD. 1998. Report of the OECD Workshop on Toxicological and Nutritional Testing of Novel Foods. Org. for Economic Cooperation and Development, Paris.

OECD. 2000. Report of the Task Force for the Safety of Novel Foods and Feeds. Org. for Economic Cooperation and Development, Paris . 86/ADDI, May 17.

Royal Society. 1998. Genetically modified plants for food use. www.royalsoc.ac.uk/files/statfiles/document-56.pdf.

Salyers, A. 2000. Genetically engineered foods: Safety issues associated with antibiotic resistance genes. Reservoirs of Antibiotic Resistance Network. www.healthsci.tufts.edu/apua/salyersreport.htm.

Taylor, S.L. 1997. Food from genetically modified organisms and potential for food allergy. Environ. Toxicol. Pharmacol. 4: 121-126.

Taylor, S.L. and Lehrer, S.B. 1996. Principles and characteristics of food allergens. Crit. Rev. Food Sci. Nutr. 36:S91-S118.

UK. 1993. Regulation of the United Kingdom biotechnology industry and global competitiveness. October. United Kingdom's House of Lords Select Committee on Science and Technology.

Wal, J.M. 1998. Strategies for assessment and identification of allergenicity in (novel) foods. Intl. Dairy J. 8: 413-423.

WHO. 1993. Health aspects of marker genes in genetically modified plants. Report of WHO Workshop. WHO/FNU/FOS/93.6. World Health Org., Geneva.

Yunginger, J.W., Adolphson, C.R. 1992. Standardization of allergens. In "Manual of Clinical Immunology," 4th ed., pp. 678-684. Am. Soc. of Microbiology, Washington D.C.

Zitnak, A., and Johnston, G.R. 1970. Glycoalkaloid content of B5141-6 potatoes. Am. Potato J. 47: 256-260.

IFT Expert Report on Biotechnology and Foods

Labeling of rDNA Biotechnology-Derived Foods

This section begins with an overview of the United States food labeling requirements directly relevant to the labeling of recombinant DNA biotechnology-derived foods, including constitutional limitations on the government's authority to regulate food labeling and specific case studies relevant to labeling rDNA biotechnology-derived foods. Next, the report discusses labeling policies for rDNA biotechnology-derived foods in the U.S. and internationally and the impact of labeling distinctions on food product distribution systems. Finally, consumer perceptions of various label statements are discussed.

U.S. Food Labeling in General

Current Requirements, Policies, and Constraints

• Food and Drug Administration Requirements and Policies. Generally speaking, the Food and Drug Administration (FDA) has authority over food labeling, and the Federal Trade Commission (FTC) has authority over food advertising. A detailed analysis of FTC and its responsibilities regarding food advertising is beyond the scope of this paper; however, a brief overview follows later in this section.

Except for meat and poultry products regulated by the U.S. Department of Agriculture (USDA), the federal law governing the labeling of food generally is the Federal Food, Drug, and Cosmetic Act (FFDCA) [21 USC §§301–397]. The FFDCA is administered by FDA. Under this statute, FDA regulates food labeling through a series of requirements that are intended to assure that information of significance about a food product is provided and that food labeling is truthful and not misleading.

"Labeling" is defined in the FFDCA as "written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article" [21 USC §321(m)]. Thus, "labeling" includes—but is not limited to—the "label" that is physically attached to the immediate container of foods in package form [21 USC §321(k)]. Physical attachment or proximity of the material to the product is not required for the material to be considered "labeling" for purposes of the statute. In 1948, the Supreme Court found that a booklet containing information about a product that was sold separately from the product was nevertheless "labeling" for purposes of the statute because the product and the booklet "were parts of an integrated distribution scheme" [*Kordel v. United States*, 335 US 345 (1948)]. The court in *Kordel* also pointed out

that material that is not regulated as labeling by FDA will be regulated as advertising by FTC.

At the most basic level, the FFDCA and its implementing regulations specify that certain information is required on the labels of almost all foods. These label requirements are intended to assure provision of information that is fundamental to the description of the food or the operation of the food safety regulatory system. Examples of these label requirements are the common or usual name (or other name) of the food; net contents statement; an ingredient listing for food products made from more than one ingredient; name and place of business of the manufacturer, packer, or distributor; and nutrition labeling.

• Constitutional Constraints. In the American legal system, the U.S. Constitution is paramount. Therefore, all statutory labeling requirements, their implementing regulations, and FDA labeling policies must satisfy constitutional requirements. The principal constitutional consideration in food labeling matters is First Amendment constraint of government labeling regulation. The First Amendment of the U.S. Constitution states: "Congress shall make no law . . . abridging the freedom of speech." This right has recently been extended to include "commercial speech," which is commonly defined to be speech in any form that advertises a product or service for profit or for any business purpose, or as speech that proposes a legitimate business or commercial transaction [*Virginia State Bd. of Pharmacy v. Virginia Citizens Consumer Council,* 425 US 748 (1976)].

Until the 1970s, advertising or labeling restrictions were viewed as purely economic regulations that did not implicate the First Amendment. Indeed, until the late 1970s, the Supreme Court had excluded commercial speech from the coverage of the First Amendment [*Valentine v. Chrestensen,* 316 US 52 (1942)]. Today, commercial speech is protected under the First Amendment, but can be subject to more stringent government regulation than other kinds of speech, such as political commentary.

For food labeling purposes, the most important modern commercial speech case is *Central Hudson v. Public Service Com'n of N.Y.* [447 US 557 (1980)]. In *Central Hudson,* the Supreme Court held that commercial speech is protected by the First Amendment, and set forth a four-pronged test for determining permissible regulation of commercial speech. Under *Central Hudson,* the government may restrict commercial speech if (1) the speech is either misleading or concerns an unlawful activity, or if (2) the asserted governmental interest in support of the restriction is substantial, (3) the restriction directly advances the government's substantial interest, and (4) the regulation is not more extensive than is necessary to serve that interest.

The First Amendment protects both the right to speak and the right not to speak. The constitutionally protected right not to speak, the compelled speech doctrine, is clearly established in Supreme Court precedent [*Harper & Row, Publishers, Inc. v. National Enter.,* 471 US 539 (1985); *Wooley v. Maynard,* 430 US 705 (1977)]. Indeed, the Supreme Court has suggested that compelling someone to speak involuntarily is an even more serious constitutional matter than preventing speech [*West Virginia State Bd. of Ed. v. Barnette,* 319 US 624 (1943)].

The regulation of food labeling involves both the commercial speech and the compelled speech doctrines. The courts have not articulated a "compelled commercial speech" doctrine. Therefore, in assessing the constitutionality of government restrictions on commercial speech, the courts have applied the four-pronged *Central Hudson* commercial speech analysis. It should also be noted that the courts have been at least as skeptical about government requirements that compel speech as about limitations on speech.

• False or Misleading Statements. Beyond these fundamental label requirements and constitutional constraints discussed above, the food processor is generally at liberty to make use of label or labeling space in the manner it deems fit, provided that the label or labeling is not false or misleading. The FFDCA deems a food to be misbranded if "its labeling is false or misleading in any particular" [21 USC §343(a)(1)]. As noted above, the prohibition on misleading commercial speech is specifically reinforced by the Supreme Court's decision in *Central Hudson*. Under that case, government restrictions on misleading commercial speech are not subject to the rigors of the second, third, and fourth prongs of the *Central Hudson* test. The prohibition of misleading labeling is the objective of many of the specific labeling requirements of the FFDCA, as well as the basis for most FDA regulation of voluntary labeling statements.

If a statement, picture, or other representation on the label or labeling of any food product is false or misleading, the food is misbranded regardless of the importance of the representation to the consumer. The Supreme Court has held that it is not necessary to show that anyone was actually misled or deceived, or that there was any intent to deceive, in order to find that a product is misbranded under the FFDCA [*United States v. 95 Barrels-Cider Vinegar,* 265 US 438 (1924)]. Other courts have stated that the test is not the effect of the label on a "reasonable consumer" but on "the ignorant, the unthinking, and the credulous" consumer [*United States v. An Article of Food . . . 'Manischewitz . . . Diet Thins',* 377 F.Supp. 746 (1974)].

The prohibition on false or misleading labeling statements reaches far beyond patently false claims. Statements that, while not false, are misleading are also prohibited. For example, a "cholesterol-free" claim for broccoli suggests that particular broccoli is cholesterol-free, while ordinary broccoli is not cholesterol-free. Thus, the claim is misleading, since ordinary broccoli does not contain cholesterol. To reinforce this interpretation, the FFDCA explicitly prohibits a claim that states the absence of a nutrient unless the nutrient is usually present in the food [21 USC §343(r)(2)(A)(ii)(I)]. To avoid being misleading, FDA permits the claim "broccoli, a cholesterol-free food," but not "cholesterol-free broccoli" [21 CFR §101.13(e)(2)].

Just as labeling statements may be misleading because of what they say or imply, they may be misleading by virtue of what they do not say. In determining whether a food labeling statement is misleading, FDA and the courts take into account the extent to which the labeling fails to reveal any material facts [21 USC §321(n)]. There is neither a statutory nor a reg-

Biotechnology Report: Labeling

CONTINUED

ulatory definition of "material fact," and the term has not been elaborately defined by the courts. Instead, determinations of whether or not a fact is material are made on a case-by-case basis, with an extensive body of precedents.

Generally, if a new or modified food is significantly different from its conventional counterpart in composition, nutritional value, or safety, the difference in the food would be considered a material fact. For example, if a new processing technique resulted in a significant decrease in the nutrient content or change in flavor, color, or other valued characteristic of a food, a label statement would be required to inform consumers of that material fact. Absent a label statement disclosing a material fact about a food, the presentation of the food would be misleading. So the FFDCA prohibition on false or misleading labeling may effectively require that a label include a disclosure of the material fact.

While some FDA disclosure requirements are imposed to provide for safe use of food ingredients [e.g., 21 CFR §172.804, "Phenylketonurics: contains phenylalanine," and 21 USC §343(o) regarding saccharin warnings] or to provide consumer warnings, many disclosure requirements are imposed to clarify or explain an otherwise misleading label statement. For example, FDA decided that a statement of the percent reduction is necessary to clarify a claim like "reduced fat" [21 CFR §101.13(j)(2)]. The agency determined that consumers would likely be confused unless the magnitude of the reduction was specified.

• Federal Trade Commission Requirements. FTC regulates food advertising under the Federal Trade Commission Act (FTCA) [15 USC §§41-58], which is similar in structure to the FFDCA. The FTCA generally prohibits "deceptive acts or practices in commerce" [15 USC §45(a)(1)]. It prohibits false advertising that is likely to induce the purchase of foods, and declares such false advertising to be prohibited as "deceptive acts or practices" [15 USC §52]. The term "false advertising" is defined as advertising that is "misleading in a material respect" [15 USC §55(a)(1)]. These FTCA provisions are similar to the FFDCA provisions on labeling that is false or misleading. To determine if advertising is false or deceptive, FTC examines whether and to what degree the information in the advertising can be substantiated, and whether there is a reasonable basis for the claims made in the advertising.

In the past, FTC has issued enforcement policy statements stating that it will defer to FDA regarding the enforcement of certain kinds of food advertising, e.g., the use of health claims and nutrient content claims (FTC, 1994). FTC has not yet elaborated on how it plans to enforce advertising regarding rDNA biotechnology-derived foods, so it is not clear whether and to what extent FTC might follow any FDA policy that is issued with respect to rDNA biotechnology-derived foods.

Labeling Case Studies

In evaluating the labeling framework for rDNA biotechnology-derived foods, consideration should be given to at least three analogous situations: irradiated foods, milk from rBST-treated cows, and organic foods.

• Food Irradiation. Irradiation is defined by statute as a food additive, the only process that is so defined. It entails the treatment of a food with an FDA-approved energy source that kills bacteria or pests, prevents sprouting of root vegetables, or extends shelf life in some foods.

Irradiation is an example of a process that triggers a label disclosure requirement because FDA determined that irradiation can render food materially different organoleptically, e.g., taste, smell, and texture. (Although the scientific information available today might support a different agency conclusion, that view is not relevant in the context of this case study.) Therefore, FDA determined by regulation that the fact that a food is irradiated is material, justifying the labeling requirement of a logo and a phrase such as "treated with irradiation" [21 CFR §179.26(c); FDA (1986)].

Despite some limited studies indicating good consumer acceptance of irradiated food, food processors generally took a conservative position in adoption of the technology. They concluded that irradiated products with the mandatory labeling would be avoided by consumers and could result in loss of sales, bad publicity, and loss of investment. Other factors that may have inhibited use of irradiation are opposition by some activist groups, low-volume demand, overall cost of operation, high capital investment, technical expertise needed by workers, limited availability of suitable packaging, slow equipment development, and large sums of money already invested in alternative technologies. Nonetheless, there is considerable evidence that the irradiation labeling requirement slowed the food industry's adoption of this technology.

Today, there are several recent examples where consumers have preferred an irradiated product to the traditional nonirradiated product. One example is strawberries, where irradiation extends the shelf life of the raw fruit. Recent concerns about microbiological safety of foods have drawn the public's attention to the potential benefits of irradiation processing. As a result, some food processors are again considering further utilization of this technology.

In summary, FDA determined that the process of irradiation caused food to differ significantly from its conventional counterpart, thus making irradiation of food a material fact that must be disclosed. The irradiation label disclosure requirements have been cited as at least one significant factor inhibiting the use of this pathogen-reducing technology.

• Milk from rBST-Treated Cows. In the early 1990s, FDA approved treatment of dairy cows with recombinant bovine somatotropin (rBST), an rDNA biotechnology-derived version of a naturally occurring hormone that increases a cow's milk production. FDA determined that milk produced by cows treated with rBST was not significantly different from conventional milk. Nonetheless, significant controversy accompanied the introduction of rBST into the marketplace. Some manufacturers attempted to address consumer interest in avoiding milk from rBST-treated cows by labeling milk products as "rBST-free." FDA discouraged "rBST-free" claims because they implied that there is some com-

positional difference, such as the presence of rBST, between milk from treated and untreated cows. Rather, FDA encouraged the use of claims that address the production procedure rather than the product. So FDA announced that an appropriate way to phrase such an acceptable claim would be, "from cows not treated with rBST," as long as the statement also provided a context that did not imply a difference between the milks. FDA's example was to include with the claim the statement, "No significant difference has been shown between milk derived from rBST-treated and non-rBST-treated cows" (FDA, 1994).

The controversy over introduction of rBST was most pronounced in New England states where it was seen as a threat to the economic viability of the region's small dairies. The state of Vermont enacted a law requiring that milk from cows treated with rBST bear a mandatory label disclosure. The constitutionality of this state labeling requirement was challenged in *International Dairy Foods Association v. Amestoy* [92 F.3d 67 (2d Cir. 1996)]. Vermont sought to justify its law on the basis of the consumer's right to know, not on health or safety concerns. However, the U.S. Court of Appeals for the Second Circuit stated that Vermont's limited justification was understandable, as "the already extensive record in the case contains no scientific evidence from which an objective observer could conclude that rBST has any impact on dairy products." The Second Circuit applied the *Central Hudson* test for permissible commercial speech regulation, concluding that "consumer curiosity alone is not a strong enough state interest to sustain the compulsion of even an accurate, factual statement."

Thus, without a material fact that distinguishes the characteristics of milk from rBST-treated cows from other milk, there was not a "substantial government interest" to justify the labeling requirement. As a result, Vermont's disclosure requirement was unconstitutional. Voluntary label statements are required to meet the FFDCA's "truthful and nonmisleading" standard. So voluntary label statements could only be made in a manner that did not mislead consumers about the milk product on which the claim appeared or the conventionally produced milk to which it was being compared.

• Organic Foods. The term "organic" has been used to describe foods grown without certain modern farming practices that some consumers find objectionable. The organic food movement began using statements concerning the production of foods without the use of certain types of commercial pesticides and fertilizers. The focus of the organic movement has expanded and centered on the societal goals of some citizens, including a reduction in the usage of agricultural chemicals, a healthier environment, more humane treatment of animals, greater worker safety, and enhanced food safety. The movement established production criteria that not only pertained to conditions for growing crops but also for labeling and distribution of such foods. The organic movement originally enlisted several state governments to recognize or adopt documentation and inspection programs designed to demonstrate compliance with these criteria. In some cases, it has become necessary to provide separate production and distribution systems for organic and non-organic foods.

To date, scientific evidence does not demonstrate that organic foods have superior nutritional or food safety benefits over non-organic foods. Therefore, FDA has deemed some claims on organic foods misleading when the term "organic" has been used in a manner that implied that the organic food is somehow superior to a similar non-organic food.

In 1990, with the vigorous support of the organic food movement, Congress passed the Organic Food Production Act [7 USC §§6501-6522] which required USDA to develop national organic standards and establish an organic certification program based on recommendations from an expert panel. On March 13, 2000, USDA announced its National Organic Program (NOP), a comprehensive proposed rule that would set uniform national standards (USDA, 2000). USDA's goal is to issue a final NOP rule by the end of 2000. These regulations are intended to further establish a market for a niche category of "organic" foods desired by consumers. Under the proposed rule, every farm or other organic operation would have to develop and carry out an "organic plan" that would be approved and certified by a USDA-accredited agent. The NOP would include a "National List" that sets forth which chemical substances are permitted for use in organic production.

The NOP also would create three categories of permissible label claims, each with its own criteria: "100 percent organic"; "organic"; and "made with organic (specified ingredients)." Products labeled "100 percent organic" would have to be all organic product; products bearing the "organic" label would have to contain not less than 95% organically produced product; and products labeled "made with organic (specified ingredients)" would have to contain at least 50% organic ingredients. Any of the three label claims could be used, in accordance with requirements set forth in the regulations; e.g., all would have to bear the seal or logo of the certifying agent, anywhere on the package and on any other labeling or market information about the product.

With the exception of products labeled "100 percent organic," the listing for each organic ingredient would have to be qualified with the term "organic" in the ingredients statement. Products labeled "made with organic (specified ingredients)" would be subject to labeling limitations (e.g., maximum type size, no more than three organic ingredients may be listed), and, unlike products labeled "100 percent organic" or "organic," would not be allowed to bear the USDA Organic Seal.

In addition to the above categories, in order for products containing less than 50% organic ingredients to use the term "organic," the label would have to declare the total percentage of organic ingredients on the information panel (the label panel that typically includes nutrition information, the ingredients statement, and similar information) and qualify each organic ingredient with the term "organic" in the ingredients statement. The product would not be allowed to use "organic" anywhere else on the label or to bear the USDA Organic Seal or the seal or logo of any certifying agent.

The proposed NOP rule is clear that rDNA biotechnology-derived and irradiated foods are not considered "organic." Any product made with what the proposed rule terms "exclud-

Biotechnology Report: Labeling

CONTINUED

ed methods" (which include the use of rDNA biotechnology) could not be labeled as "organic." USDA made this decision based on "overwhelming public opposition" to the use of rDNA biotechnology in organic production systems, even though the agency admitted "there is no current scientific evidence that use of excluded methods presents unacceptable risks to the environment or human health" (USDA, 2000).

Thus, it may be possible for consumers wishing to avoid rDNA biotechnology-derived foods to purchase foods bearing one of the three "organic" label claims on the principal display panel. With organic products a rapidly growing percentage of the market—organic food sales in the U.S. have risen dramatically, from $78 million in 1980 to an estimated $6 billion in 2000, and projected annual growth is approximately 20%—organic foods appear to be a readily available option for consumers who wish to avoid rDNA biotechnology-derived foods.

The labeling of organic foods is an example of a voluntary program that focuses on production differences that are of significant consumer interest, even though they do not render foods materially different from their conventional counterparts. Under the constitutional restrictions described above, such distinctions may not be addressed through government-mandated disclosures, but may be freely described through voluntary label statements. To avoid confusion regarding the meaning of terms and to clarify rules in a manner that helps organic food processors and marketers avoid making misleading claims, Congress actively monitored USDA's development of standards. Improved clarity of labeling terms and greater efficiency associated with higher product volumes appear to be facilitating growth in organic foods.

Summary

In summary, the FFDCA works within the constitutional framework to address the so-called "consumer's right to know" or, more accurately, right to be informed of significant or material facts about their foods. This right is addressed through a corresponding duty for food marketers to label foods in a truthful, nonmisleading manner, including the disclosure of fundamental descriptive information about the food. The corresponding right to be informed and duty to disclose concerns all material facts regarding the food product, such as the fact that a food has been irradiated (because of FDA's conclusion that there are organoleptic changes in food treated by irradiation). However, not all facts are material. As the Vermont rBST labeling litigation demonstrates, a fact that does not render a food significantly different from its conventional counterpart is not material and therefore is insufficient to give rise to informational rights and duties.

Nonetheless, there may be extensive consumer interest in such information. As the organic foods experience demonstrates, when marketplace interest is sufficient, consumer information desires are served by the establishment of voluntary disclosure programs where necessary, with certain limitations and authorized label statements. These voluntary programs and labeling provisions have been used to achieve advantage in a competitive marketplace. Thus, the food labeling regulatory regime provides a graduated series of requirements to address consumer information rights and desires in a truthful, nonmisleading manner.

Labeling of rDNA Biotechnology-Derived Foods

U.S. Policies

FDA has not established special labeling requirements for foods derived using rDNA biotechnology. Yet, the general framework of food labeling regulation provides a series of food labeling requirements for rDNA biotechnology-derived foods.

• Mandatory Disclosures. As explained above, constitutional restrictions specified in *Central Hudson* and the FFDCA prohibition of labeling that is misleading by virtue of omission of a material fact are important factors regarding mandatory label disclosures.

Labeling requirements that apply to foods in general also apply to foods derived using rDNA biotechnology. As previously noted, to avoid a misleading presentation of the food, the label must reveal all material facts. In developing its labeling policy for rDNA biotechnology-derived foods, FDA considered public comments and scientific evidence regarding the presence of material facts about such foods. FDA concluded that rDNA biotechnology-derived foods do not differ materially as a class of food from conventional foods. On the other hand, individual rDNA biotechnology-derived foods may or may not be significantly different from their conventional counterparts.

FDA requires labeling of specific rDNA biotechnology-derived foods that differ significantly in composition, nutritional value, or safety from their conventional counterparts (FDA, 1992). Thus, if a food derived using rDNA biotechnology differs from its conventional counterpart such that the common or usual name no longer adequately describes the new food, the name must be changed or qualified to describe the difference. If a safety or usage issue exists for the new food, a statement must be made on the label to describe the issue. For example, if a food derived using rDNA biotechnology has significantly different nutritional properties, its name must reflect the difference (e.g., "high oil corn"). Likewise, if a new food includes an allergen that consumers would not expect based on the name of the food, the presence of that allergen must be stated on the label (e.g., the hypothetical use of a peanut protein in a tomato).

Some have advocated that the mandatory labeling requirements reach beyond disclosure of material facts regarding the food. They have urged a blanket requirement for disclosure when a food is derived using rDNA biotechnology. In developing its 1992 labeling policy (FDA, 1992), FDA considered public comments and all available scientific evidence in connection with a possible blanket rDNA biotechnology disclosure requirement. FDA rejected such a blanket requirement because it was "not aware of any information showing that [rDNA biotechnology-derived foods] differ from

other foods in any meaningful or uniform way, or present any different or greater safety concern than foods developed by traditional plant breeding."

In the absence of a material fact to distinguish an rDNA biotechnology-derived food from its conventional counterpart, the imposition of a blanket disclosure requirement would be constitutionally suspect. As with the Vermont rBST label disclosure requirement that was ruled unconstitutional in *International Dairy Foods v. Amestoy,* the absence of a distinguishing characteristic of the rDNA biotechnology-derived food requires the government to demonstrate a substantial government interest to justify a label disclosure requirement. The *Amestoy* court specifically rejected "consumer curiosity" as basis for a substantial government interest.

• Voluntary Claims. As noted above, required declarations only constitute a portion of the label information that serves the consumer's right to know. In a competitive marketplace, there are powerful incentives for the introduction of factors for distinguishing products that would be appreciated by significant population segments. When government action to compel labeling is involved, the distinguishing factors must be material facts regarding the food. Countless other factors may be advanced through voluntary label claims and, if appreciated by consumers, rewarded in the marketplace.

So foods that are not rDNA biotechnology-derived may be labeled as such in a truthful and non-misleading manner. Consumers who appreciate that distinction are served by such labeling. Government restrictions on misleading labeling can also influence the nature and even the availability of such voluntary claims. Naturally, the prohibition against false and misleading claims is an important service to the consumer's right to know. However, ambiguity in what may be viewed as false or misleading label statements may have a chilling effect on the marketing of such claims.

For example, a processor asserting that a product includes no rDNA biotechnology-derived ingredients must be able to substantiate that claim to provide reasonable assurance of its accuracy. Before a processor undertakes that risk, it may reasonably seek guidance as to how FDA expects such substantiation to be accomplished and what degree of purity is required to justify a claim that a product is free of rDNA biotechnology-derived ingredients. As detailed below, the answers to these questions may have significant economic effects that can greatly influence the availability of such claims.

The degree of purity is a complex issue that must be resolved with careful consideration of what such a claim is likely to mean to the consumer. For example, fat-free claims are permitted on products that have up to one-half gram of fat per serving [21 CFR §101.62(b)(1)(i)] because it is not feasible to measure lesser amounts of fat in foods. Moreover, the general public health objective is to limit fat in the diet, not eliminate it altogether. Further, the degree of purity a claim represents would be considered by FDA in determining appropriate methods of substantiation. For example, a claim like "These ingredients were not genetically modified," which addressed the process by which the food was produced, would not imply the same degree of purity as a "Free of GM ingredients" claim. Supplier certifications are generally regarded as less accurate and less expensive than product testing. FDA would seek accuracy, but would likely be reluctant to require an excessively expensive substantiation method, since its costs could discourage use of the label statement. A claim about the production process would likely be easier to verify than a claim about the composition of the food.

Moreover, the potential for a claim about the absence of rDNA biotechnology-derived ingredients to be interpreted as misleading because it inaccurately implies superiority of the food over its counterpart may also discourage such claims. One need only consider the rBST experience to see that a simple "GM-free" claim may be regarded as misleading because it implies superiority in safety or environmental effect. FDA recommended the use of terminology that disclosed the use or non-use of rBST on the cow, rather than the presence or absence of rBST in the milk.

Therefore, as was sought by the organic foods movement, clear guidance as to government's expectations regarding voluntary claims can eliminate the regulatory uncertainty that may discourage investment in a new product line of foods that are to be marketed as free of rDNA biotechnology-derived ingredients. However, establishing a clear definition of "GM-free" through legislation or a regulatory mechanism will be a difficult process that would require general agreement from most stakeholders.

In May 2000, FDA announced that it plans to develop a guidance document regarding the voluntary labeling of food about the presence or absence of rDNA biotechnology-derived ingredients (HHS, 2000). FDA stated that it would use focus groups and seek public comment on its draft guidance.

The Labeling Panel is mindful that not all voluntary claims regarding rDNA biotechnology-derived foods are claims that the food is free of rDNA biotechnology-derived ingredients. One of the first rDNA biotechnology-derived foods introduced to the market was the *FlavrSavr* tomato, which bore statements in labeling indicating that the tomato was developed through rDNA biotechnology. The issues regarding such claims are straightforward and therefore have not been addressed in this report. As discussed above, these claims also must be truthful and non-misleading.

• Summary. The following U.S. food labeling requirements apply to foods derived using rDNA biotechnology: Any material differences in the characteristics of these foods compared with their conventional counterparts must be disclosed; and voluntary label statements must be truthful and non-misleading, which entails substantiation of label claims and ensuring that the claims are not misleading, by implication or by omission.

To impose a blanket disclosure requirement for all rDNA biotechnology-derived foods would be constitutionally suspect and may inhibit consumer choice by discouraging development of the technology. Though difficult to accomplish, clear government guidance regarding such claims would lend regulatory stability and reduce a barrier to development of such products.

International Policies

Because of the world market for food and food ingredients, U.S. labeling requirements and policies should

Biotechnology Report: Labeling

CONTINUED

not be examined in isolation. Rather, the subject should be considered in the context of international requirements and policies.

In view of the growing conditions where cross-pollination might occur, the complexities of the harvesting, storage, and distribution practices, and other possibilities for inadvertent contamination of non-rDNA biotechnology-derived crops with rDNA biotechnology-derived crops, it would be necessary for any mandatory labeling program to include a level of inadvertent rDNA biotechnology-derived crop contamination above which labeling would be required. This level should be consistent with the objectives of the labeling program and be acceptable to the program's proponents. It should also be legally defensible and practical to enforce, including scientifically appropriate, practical, and affordable analytical testing. There is currently no international consensus on what such a regulatory level should be.

The regulation of rDNA biotechnology-derived foods differs widely in other countries. Some countries do not allow them to be imported at all, on the basis that not enough is known about the long-term effects of consuming rDNA biotechnology-derived foods (Anonymous, 1999a). Other countries permit such foods, with requirements that each food disclose on the label that it was produced using rDNA biotechnology (Codex, 1999). Such policies require foods at each stage of production, from raw agricultural product to finished consumer package, to bear a statement like "Contains GMO." Still other countries, like the U.S., compare the new plant variety to varieties produced using conventional breeding to identify differences for safety evaluation and to determine whether the differences need to be described on the food label. These countries do not require statements that the food was derived using rDNA biotechnology.

International debates on labeling of rDNA biotechnology-derived foods take place in a variety of forums and often are part of the discussion of the safety of the foods. Countries that require declaration of the fact that the food was derived using rDNA biotechnology tend to have less confidence in the safety of the food. This lower confidence level is not always based on scientific assessments that indicate higher potential risk. The consumer's right to know is an important factor in the rationale of those supporting mandatory labeling, particularly when consumer confidence in the regulatory system is low (Codex, 1999).

The primary international forum for discussion of labeling of rDNA biotechnology-derived foods is the Codex Alimentarius Commission. Codex implements the International Food Standards Program under the joint sponsorship of the Food and Agriculture Organization (FAO) of the United Nations and the World Health Organization (WHO). Its purpose is to harmonize international food requirements to foster public health and international trade. However, not all participating countries adopt all Codex standards.

For several years, the Codex Committee on Food Labeling (CCFL) has been discussing how rDNA biotechnology-derived foods should be labeled, with the goal of having a single approach to labeling requirements. Two basic approaches to labeling are being considered by the CCFL. One, based on the principle of comparing new varieties of foods to those produced by conventional means, would require the description of any differences on the label. That is, where the rDNA biotechnology-derived food differs significantly from the conventional version of the food in nutritional value, in physical or handling properties, or by the presence of an allergen not indicated by the name of the food, this difference would have to be disclosed on the label.

The other approach to labeling involves the conclusion that the use of rDNA biotechnology, either in the food or to produce the food, is itself a difference that requires disclosure. The U.S., Canada, and several other countries support the approach that only the significant differences need to be disclosed, while the European countries and others favor what is called the "mandatory labeling" approach (Codex, 1999). A number of countries are currently developing national policies, and several of them are likely to require mandatory labeling.

Even though the discussion is ongoing in Codex and will likely continue for several more years, the effects of differing national rDNA biotechnology labeling policies are already being felt. For example, European countries are major markets for U.S. grains and food ingredients. Some European retailers have decided to exclude rDNA biotechnology-derived ingredients from foods manufactured for their own "store brands" (Anonymous, 1999b). Some U.S. producers have decided to return to growing non-rDNA biotechnology-derived crops rather than lose this market. Some European food manufacturers, particularly infant formula firms, have said they will not accept rDNA biotechnology-derived ingredients. Some U.S. manufacturers of processed corn and soybean consumer products have announced that they will not accept any rDNA-derived biotechnology crops for processing (Anonymous, 2000).

While Codex is the major forum for discussion of international food labeling requirements, another organization has also developed a position on labeling. The Cartagena Protocol on Biosafety was adopted by more than 130 countries at the Convention on Biodiversity (CBD) in January 2000. The protocol has been interpreted to provide that "living modified organisms" (LMO) intended for "food, feed, or processing" must be identified as LMO (Codex, 2000). While the U.S. signed the Cartagena Protocol, it has not been ratified by the U.S. Senate. As a result, it has no legal effect in the U.S. at this time. As interpreted by the U.S. Department of State (USDS, 2000), the Protocol requires international shipments of bulk LMO commodities to be accompanied by documentation stating "May contain LMOs"; however, the Protocol does not impose consumer product labeling requirements.

The European Union (EU), Japan, South Korea, Australia, and New Zealand have all passed, or are considering, laws requiring that food containing rDNA biotechnology-derived ingredients be labeled. These countries are in various stages of implementing such requirements. The EU has been considering this issue for a substantial

period of time and has approved a *de minimis* threshold level of 1% (Betts, 1999; EU, 2000). This *de minimis* threshold would apply separately to each ingredient used in the product, and only apply to those situations where the presence of the rDNA biotechnology-derived material was unintentional. Many businesses in Germany and Japan require that products be certified to contain less than 0.1% or even 0.01% of rDNA biotechnology-derived ingredients.

Compliance with *de minimis* thresholds requires the availability of quantitative analytical testing methods to detect the presence of rDNA biotechnology-derived ingredients. The two most common methods for detecting rDNA biotechnology-derived materials are the polymerase chain reaction (PCR)–based methods, which detect genetically modified DNA sequences, and immunoassays, which measure levels of proteins expressed by inserted DNA sequences. For a fuller discussion of rDNA testing methods, see Anonymous (1999c, d).

Most PCR-based assays are qualitative in nature and are routinely used to determine if rDNA is present in a sample. PCR is a laboratory-based technique requiring trained staff and specialized equipment. It is extremely sensitive and capable of detecting one or a few copies of a gene. DNA extraction methods need to be optimized for each food matrix, as various food components inhibit the reagents used in the assay. In general, DNA is not detectable in highly heat-treated foods, hydrolyzed plant proteins, purified lecithin, starch derivatives, and refined oils derived from rDNA biotechnology-derived crops. The use of Real-Time PCR, which uses fluorescence to monitor the PRC amplification process, shows significant promise in resolving this problem. However, the equipment is, at present, very expensive, ranging in price from $36,000 to $95,000. Because these methods are extremely sensitive, there is a significant risk of cross-contamination resulting in false positives. Sample analysis time requires approximately one day, although turnaround times for results are typically 3–5 days. Per-sample costs range from less than $100 to more than $300. Several laboratories are developing quantitative PCR methods that will be important if PCR is to be used for determining the level of rDNA biotechnology-derived ingredients in foods.

The common protein-based test methods use antibodies specific for proteins encoded by rDNA sequences. The Enzyme Linked Immunosorbent Assay (ELISA) uses one antibody to bind the specific protein and an antibody conjugated to an enzyme whose product generates a color that can be easily visualized and quantified. Non-quantitative immunoassays are also available in the form of plate or lateral strip formats. Immunoassays are less sensitive than PCR and therefore are less susceptible than PCR to false positives caused by minor levels of contamination. Assay validation is important because of the large diversity of food matrices. In addition, it is important to determine sequence homology with other proteins that might be present in the sample. Per-sample costs are in the range of $2 to $10, although up-front costs for assay development and generation of antibodies and protein standards are high. Results are available within minutes. Immunoassays are not capable of distinguishing between different rDNA biotechnology-derived events that express similar protein characteristics (e.g., immunoassays will not determine if a specific protein such as the Bt protein came from corn or soy). Since proteins are denatured by many food processing methods, immunoassays are best used for raw commodities or minimally processed ingredients.

There are some common problems no matter which assay method is used. Currently, there are no internationally recognized sampling methods or agreement on the number or size of samples. Sampling plans must be scientifically and statistically sound and take into account the potential heterogeneity of samples due to adventitious contamination from cross-pollination or during distribution. Positive and negative reference standards are not readily available to validate analytical methods or to assess the performance of methods and laboratories. As new rDNA biotechnology-derived crops are developed, sequence information must be shared by the technology generators so that new assays can be developed. Ultimately, hundreds of different assays may be necessary.

Several agencies in Europe and the U.S., including the European Commission's Joint Research Centre, the U.S. National Institute of Standards and Technology, and USDA's Grain Inspection, Packers, and Stockyards Administration, are working on reference standards and validation programs for rDNA testing methods (Erickson, 2000). Validation and standardization of sampling and testing methods are essential to resolving disputes regarding the status of food ingredients, and for regulatory authorities responsible for enforcing mandatory labeling laws.

Impact of Market Segmentation of Crops

Labeling of rDNA biotechnology-derived foods, whether mandatory or voluntary, must be premised on discrete distribution channels for the underlying commodities, such as soybeans and corn. This section of the report examines market segmentation for key commodities. A fuller discussion of this subject appears in Nelson et al. (1999) and Bullock et al. (2000).

The majority of processed foods contain ingredients derived from corn and/or soybeans. One major trade association has estimated that 70% of processed foods contain corn or soy-derived ingredients. In fact, corn and soy serve as the source of thousands of ingredients used in processed foods. Common ingredients derived from corn include corn oil, corn starch, corn flour, corn meal, maltodextrins, corn syrup, and dextrose. Soy-derived ingredients include soy oil, bran, flour, sauce and meal, soy protein isolates and concentrates, texturized vegetable protein, lecithin, and mono- and diglycerides.

Many processed foods contain multiple corn and soy-derived ingredients. For example, a typical cake mix contains hydrogenated soybean oil, modified corn starch, mono- and diglycerides, dextrose, and soy lecithin. Some corn and soy-derived ingredients serve as secondary ingredients (e.g, carriers for flavors, colors, or vitamins) and may not be listed on the label. For many of these ingredients, substitutes are not available that provide the same functionality, texture, and taste. Since corn and soy are managed as commodity ingredients and labeling is not required in the U.S., many of the processed foods on the market today likely contain ingredi-

Biotechnology Report: Labeling

CONTINUED

ents derived from rDNA biotechnology-derived crops.

The world markets for corn and soybeans are currently undergoing a process of segmentation in response to concerns in the EU and elsewhere. It is clear that consumer concerns about rDNA biotechnology in some countries will determine the marketability of rDNA biotechnology-derived corn and soybeans. Several major food processors in different countries have announced that they will only accept non-rDNA biotechnology-derived crops. Thus, some supplies in the world market must be guaranteed rDNA biotechnology-free to meet this emerging demand.

In April 1999, two major processors announced that they would pay a premium for a particular non-rDNA biotechnology-derived soybean product that has been bred to resist one particular herbicide. In addition, they announced they would reject any rDNA biotechnology-derived corn not accepted in EU markets during the 1999 growing year (Anonymous 1999e). In 1999, this program provided an 18-cent-per-bushel premium (approximately 3.5%) for soybeans (Anonymous 1999f). A similar approach is expected for the 2000 crop year. One major supplier of rDNA biotechnology-derived seeds announced that it would help growers of its rDNA biotechnology-derived crops find domestic market outlets for varieties that are not approved by the EU. In August 1999, a major processor requested that its suppliers segregate rDNA biotechnology-derived and non-rDNA biotechnology-derived crops (Anonymous, 1999e). This segmentation goes beyond rejection of rDNA biotechnology-derived products not approved by the EU, and was said to be a response to growing consumer requests for such segmentation.

In fall 1999, some U.S. firms paid a premium for non-rDNA biotechnology-derived products, but the size of the premium and the extent of demand for non-rDNA biotechnology-derived products was very uncertain. In addition to changes in demand, another source of uncertainty is the regulatory status of rDNA biotechnology-derived crops in other major producing countries, such as Brazil. Although Brazil does not allow rDNA biotechnology-derived crops, a significant portion of the crops produced are genetically modified because seed is smuggled into the country. Whether segmentation by country source or segmentation within market channels can take place will be an important determinant of eventual marketing costs. For example, EU buyers are able to source their corn imports in 2000 from countries other than the U.S., but they must still buy a significant share of their soybean product imports from the U.S. Thus, there is greater market incentive to develop guaranteed non-rDNA biotechnology-derived soybean channels in the U.S. In spite of the market forces discussed above, as of spring 2000 there had been relatively little market differentiation of rDNA biotechnology-derived crops in the U.S.

The marketing costs and price premiums associated with the development of a segmented market include any premium paid to a producer to supply a particular variety, the costs of segregation in storage and handling, and the costs of verifying that the crop is truly not rDNA biotechnology-derived. The complexity of the U.S. grain-marketing channels makes it difficult and expensive to segregate crops when variety is the only clear difference, as testing for genetic modification is currently an expensive alternative.

Whether the objective is to label or to ban rDNA biotechnology-derived crops, only three alternative marketing strategies exist: test the product at selected points in the market channel; accept producer assurances at the first handler and maintain identity through the market channel; or use third-party supervision and certification from seed to final processing. Each alternative has its advantages and its limitations.

In May 2000, the Clinton Administration announced that USDA will work with the agricultural and food industries on the creation of reliable testing procedures and quality assurance programs to differentiate non-rDNA biotechnology-derived commodities to better meet the needs of the marketplace. USDA will do so through an Advanced Notice of Proposed Rulemaking, which will seek input on current market practice as well as the feasibility and desirability of quality assurance programs (White House, 2000).

- Final Product Testing. This approach provides assurance that the sample selected for testing meets the standards of the buyer. It focuses on the attributes of the product rather than on the process by which it was produced and delivered. The disadvantages are the costs and uncertainties of sampling and testing. Current sampling methods provide a low level of confidence that a large bulk shipment is adequately represented by the sample analyzed. The standard error for even the best sampling strategy (e.g., automatic diverter samplers in the inbound or outbound grain stream) is large for the current low tolerance levels. Sampling of inbound deliveries by farmers presents the same problem of obtaining representative samples, and it has the additional problem of time required for testing and segregating, given the speed with which inbound vehicles must be unloaded.

A single test that can be applied at the first-handler level for testing for the entire range of possible genetic modifications has not yet been developed. As discussed above, the most common rDNA biotechnology test method currently used is PCR. It is a very sensitive test which is most useful in detecting the presence of rDNA biotechnology-derived materials, but it takes 3–5 days to complete and costs several hundred dollars per sample. The ELISA approach takes 5–20 minutes and costs less than $10 per sample. However, neither approach has been accepted as being quantitatively reliable because of a lack of standardized sampling techniques and reliable control standards.

For labeling purposes, what to test for is also important. It is possible, at least with PCR, to test for the promoter or marker DNA, which is common to many rDNA biotechnology-derived organisms, or to test for the specific genes that confer the desirable traits. The first type of test would identify only whether a crop was rDNA biotechnology-derived; the second type

would identify what type of modification had taken place.

• Producer Validation and Market Segregation. This strategy segregates the non-rDNA biotechnology-derived crops at the beginning of the market channel. If the product is shipped in containers dedicated to non-rDNA biotechnology-derived grain, guaranteeing the process will also guarantee the final product. However, there are problems with this approach in addition to the cost of segregation. Although producers may know the variety and the extent of potential cross-pollination at the time of harvest, much commercial grain is delivered by commercial haulers who do not have this information. Without prior contracts or arrangements with the producer, producer validation and certifications have questionable reliability. This strategy also requires grain handling establishments to maintain separate facilities, as it is not feasible to clean facilities of all rDNA biotechnology-derived grain between loads.

Some establishments designate one of their facilities for handling non-rDNA biotechnology-derived grain, thus simplifying the problem of identification at the time of delivery. Yet a major obstacle to maintaining purity through the rest of the market channel still exists, because trucks, rail cars, barges, and port equipment must also use dedicated equipment to guarantee that all rDNA biotechnology-derived grain has been excluded.

• Third-Party Certification. This strategy reduces the danger of misinformation, questionable methods of isolation in the field, and incomplete knowledge on the part of the producer or distributor. The strategy is well known and frequently used for delivering food-quality corn and soybeans to foreign destinations.

Organic, pesticide-free, and variety-specific qualifications are common in international trade, but third-party certification adds significant costs per bushel. Illinois grain handlers currently use third-party certification from seed to river elevator and shipping in containers or small-volume segregated barge loads that are transferred directly from barge to vessel to avoid contamination. This strategy is based on the premise that it is more effective to guarantee the process than to guarantee the product. No shipper can guarantee that a very small amount of rDNA biotechnology-derived product will not be introduced into a shipment from any of many sources, including the storage facility in the destination country. Instead of guaranteeing 100% purity, this approach provides assurances that the grain has been handled in such a way as to minimize the possibility of contamination.

• Cost of Market Segregation. There will be a cost for any of the strategies described above. A survey by Bender et al. (1999) examined the marketing costs associated with specialty grains in Illinois. Such specialty grains have particular characteristics, such as oil or protein content, that bring high value in particular end-use markets. The survey reported an average additional handling cost of $0.17 per bushel for corn and $0.48 per bushel for soybeans in 1998, over and above the premium for specialty characteristics. These are similar to the 6–10% additional marketing costs estimated by Buckwell et al. (1999) in their review of several segmented or identity-preserved markets.

Interviews in May 1999 with nine firms that advertised on Internet-based e-markets to contract with farmers for non-rDNA biotechnology-derived corn or soybeans showed that the market is still sorting out methods of verification and premiums for non-rDNA biotechnology-derived crops. The current means of verification for non-rDNA biotechnology-derived products included all of the possibilities discussed above. The firms interviewed used spot testing, segregated on-farm storage, segregated on-site storage at the elevator, and segregated transportation measures. Some elevators do not do any testing and relied on the word of the farmer regarding the non-rDNA biotechnology-derived product. These firms also reported widely varying premiums for non-rDNA biotechnology-derived product that was contracted for in the previous spring (1998).

It is useful to think about rDNA biotechnology-derived and non-rDNA biotechnology-derived corn and soybeans as separate products. There is substitution in supply, but in some countries there is little substitution in demand. rDNA biotechnology-derived varieties reduce costs of production and/or increase yields for some U.S. producers. If rDNA biotechnology-derived crops have lower costs, producers presumably will look to be compensated for producing non-rDNA biotechnology-derived crops at higher cost for the EU.

The following scenario seems possible: Some portion of EU and other demand will be for guaranteed non-rDNA biotechnology-derived crops. At the same time, there will be widespread adoption of rDNA biotechnology-derived varieties in major producing countries. The demand for non-rDNA biotechnology-derived varieties will be met from segmented market channels that will develop in all exporting countries, and this supply will carry a marketing premium. In addition to this marketing premium, producers will receive a price premium to cover the higher costs of production of non-rDNA biotechnology-derived crops. However, this premium will be in relation to the somewhat lower world prices for corn and soybeans due to increased total supplies brought about by adoption of rDNA biotechnology. The costs of the producer premium and marketing premium are likely to be passed on to buyers in the EU and elsewhere. The long-run costs of this segmentation are more difficult to predict. These long-run costs arise from the disincentives to invest in rDNA biotechnology that result from lack of consumer acceptance.

Depending on the degree of purity demanded by any market segmentation, the current grain handling and distribution system may need to be modified, or a new, dedicated system for non-rDNA biotechnology-derived products developed. For example, while the practicality of currently available test methods for detecting rDNA biotechnology-derived organisms could be improved, the sensitivity of these methods greatly exceeds the capabilities of existing U.S. grain handling and distribution systems to deliver non-rDNA biotechnology-derived crops.

For example, USDA's grade standards for soybeans permit 1.0% "foreign material" in U.S. No. 1 Grade (the highest grade) soybeans, to 5.0% "foreign material" in U.S. Grade No. 4 soybeans [7 CFR §810.1604]. Similarly, the USDA grade standards for corn permit 2.0% "foreign material" in U.S.

Biotechnology Report: Labeling

CONTINUED

No. 1 Grade corn, to 7.0% "foreign material" in U.S. No. 5 Grade corn [7 CFR §810.404]. As the U.S. commercial grain handling and distribution system works within the regulatory confines of the USDA grain grade standards, it is not realistic to expect that the same handling and distribution system could achieve a threshold level of 0.01%, 0.1%, or even 1% rDNA biotechnology-derived material in non-rDNA biotechnology-derived grain. In other words, it may be unrealistic to expect a grain handling and distribution system that tolerates, for example, 1% corn as "foreign material" in soybeans to exclude a comparable, if not lower, level of rDNA biotechnology-derived soybeans—which would not even be considered "foreign material"—in a lot of non-rDNA biotechnology-derived soybeans. Yet, as discussed above, such low threshold levels are being considered in other countries.

Consumer Reactions in the U.S. and Canada

Most U.S. consumers are not concerned about the safety of foods derived using rDNA biotechnology. Eighty percent of consumers are confident that food in the supermarket is safe (Gallup, 1999; FMI, 1999). Most consumers support application of rDNA biotechnology in agriculture and food production. A majority (53%) believe that rDNA biotechnology does not pose a health hazard. A much smaller number (27%) believe that rDNA biotechnology does pose a serious health hazard, while 20% have no opinion. The majority of consumers believe that rDNA biotechnology will provide benefits for them or their families within five years (Wirthlin, 2000).

Labels are a valuable source of information for consumers. People indicate that they consult labels to obtain accurate information as to product ingredients and nutritional content (Bender and Derby, 1992; Rodolfo et al., 1998). Information on labels and in government publications generate greater trust than any other information source (Buzby and Ready, 1996).

It is well recognized that the method of asking a question can influence consumer response. Some surveys indicate that the majority of consumers want foods derived by rDNA biotechnology to be labeled; however, consumers frequently respond affirmatively when asked if they want additional information (Hoban and Kendall, 1993; Gallup, 1999). When asked if labels should contain a variety of information, 85% of consumers desired disclosure that rDNA biotechnology was used. Fewer consumers expressed interest in labeling if rDNA biotechnology was used to produce ingredients or processing aids, such as chymosin for cheese making (Hoban and Kendall, 1993). Other information, such as use of pesticides or country of production, was desired by 94% and 80%, respectively. In these surveys, consumers were not told that labeling would entail additional cost. Focus group research indicated that most consumers believed that cost would be minimal (Hoban and Kendall, 1993).

In one survey (Wirthlin, 2000), FDA labeling policy was explained as follows: "The U.S. Food and Drug Administration requires special labeling when a food is produced under certain conditions: when rDNA biotechnology's use introduces an allergen or when it substantially changes the food's nutritional content, like vitamins or fat, or its composition. Otherwise special labeling is not required." The majority of consumers supported the policy, with 42% indicating strong support; and 28% opposed the policy, with 18% strongly opposed. When presented with an alternative view, that all rDNA biotechnology-derived products should be labeled,52% continued to support FDA's policy, 43% supported labeling all products, and 5% did not know.

General consumer research has shown that label statements should be clear and not misleading and should provide salient facts to the consumer. Consumers indicated that labeling should be in laymen's terms, use consistent terminology, and follow a standard format (Hoban and Kendall, 1993).

Focus group research in Canada indicated that consumers want simple information presented in lay terminology, which links changes to nature and how products are grown, identifies product improvements, and acknowledges government approval (NIN, 1999). Consumers reacted negatively when unknown scientific terminology was used. They indicated that numerous messages on foods containing multiple ingredients derived from biotechnology would be viewed as too complex and unreadable. Most terms used today to describe rDNA biotechnology were misunderstood by consumers. Following is a summary of the consumer response to specific terms:

"Genetic," as in "genetically modified." Use of the term "genetic" was not viewed as neutral. It was often misinterpreted and frequently evoked concern. Some believed that plant products would no longer be grown in soil. Others viewed "genetically modified" as an improvement of some kind. Many were of the view that something was being added to the products, with "chemicals" frequently mentioned. Consumers wanted to be given more information, such as the method and purpose of the modification.

"Genetically enhanced." This phrase also raised concern because people were unclear about the meaning of "genetically." Some viewed products as improved. In comparison, "genetically engineered" generated the most negative feeling. The term "enhanced" was viewed with skepticism by some, being reminiscent of advertising.

"Genetically improved." This term, suggested by participants, was preferred because it was simpler and represents the appropriate reasons for change, i.e., improvement.

"rDNA biotechnology." This term was not understood, and reactions were usually negative. Individuals surveyed stated that a simpler term would be better understood.

"Does Not Contain." Messages of this type were viewed as an advertising claim to disparage competitors. Participants believed that the majority of consumers would be attracted to this type of message because the public was easily alarmed. This terminology was interpreted as guaranteeing that no genetically modified ingredients were used. Use of this phrase was criticized by participants because of the negative feelings it evoked.

"May contain." "May contain"

messages were interpreted by consumers as the failure of manufacturers to know what their products contained, because there was a mixup, the source of the product was uncertain, or the producer did not care enough to determine what was available on the market.

Consumers suggested terms that use simple language and blend science and traditional agriculture. These included "advanced growing method," "product of the new science of farming," and "enhanced farming" (NIN, 1999).

A recent survey of food industry leaders (Hoban, 2000) found that 67% believe that "organic" labeling is a reasonable alternative for consumers concerned about rDNA biotechnology.

A majority of consumers (86%) believe that simple labeling does not provide enough information for consumers (Wirthlin, 2000). Additional information should be available through the media, toll-free numbers, brochures, and Web sites (NIN, 1999).

Consumer Reactions in Other Countries

In addition to the U.S. and Canadian data discussed above, available foreign research is relevant. Most Australians believe that genetic engineering, in general, is a "good idea," with as many as 90% supporting medical and environmental applications and about two-thirds supporting food and nutritional applications (Kelley, 1995). Almost all (93%) of Japanese consumers surveyed believed that rDNA biotechnology would provide benefits to them or their families in the next five years (Hoban, 1996). Interest in purchasing was greatest in applications that reduce pesticide use.

A 1995 survey indicated that 44% of Europeans considered genetic engineering of food a serious risk (Tordjman, 1995). This was midway among potential food risks, with bacterial contamination at the top with 85% of consumers expressing concern, and sugar at the bottom with 12% expressing concern. With the exception of Austria, half or more of European consumers indicated they would purchase a product modified by genetic engineering (Hoban, 1997). Recently, response in the United Kingdom has become more conservative, with a very high percentage of consumers indicating that they would not purchase products derived using rDNA biotechnology (Blanchfield, 1999). In a survey conducted by Eurobarometer (2000), 53% of European consumers said they would pay more for non-rDNA biotechnology-derived foods.

The difference between European and U.S. consumer attitudes may be attributed to perceptions of risk, level of knowledge, or trust in regulatory authorities. Gaskell et al. (1999) indicated that those who support rDNA biotechnology believe that rDNA biotechnology is useful and morally acceptable with little risk. In regard to applications to food, this group constitutes 22% in Europe and 37% in the U.S. Risk-tolerant supporters make up 21% in Europe and 24% in the U.S. Opponents, estimated at 30% in Europe and 13% in the U.S., believe that rDNA biotechnology is risky, offers no benefit, and is morally unacceptable. Those who believe that rDNA biotechnology is useful, not very risky, but morally unacceptable constitute 2% in Europe and 1% in the U.S.

European consumers indicated that regulation of food rDNA biotechnology should rest with international organizations, such as the UN or WHO. When asked what group would be most likely to tell the truth about rDNA biotechnology-derived crops, European consumers identified environmental, consumer, and farming organizations. National public bodies received support from only 4% of respondents. In contrast, U.S. consumers indicated that they would trust statements made by U.S. regulatory agencies, with USDA generating 90% support and FDA 84% support.

European and North American consumers differed significantly in knowledge of basic concepts related to food rDNA biotechnology (Hoban, 1998). Most consumers from the Netherlands, Sweden, U.S., and Canada recognize as false the statement "Ordinary tomatoes do not contain genes, while genetically modified ones do." Only 34% of Austrian and 35% of German consumers recognized that the statement was false. Significantly more persons from the Netherlands, Sweden, U.S., and Canada recognized as false the statement "A person's genes could be changed by eating a genetically modified food." Correct responses were provided by 62% of consumers in the U.S., Canada, and Sweden, 74% in the Netherlands, but only 29% in Austria.

Conclusions

The Labeling Panel concluded that the following facts are fundamental to resolving issues regarding the labeling of rDNA biotechnology-derived foods in the U.S. The information presented on food labels is highly regarded by consumers and is considered one of the most reliable sources of information about foods. Based on these facts, the panel drew the following conclusions:

- Within the constitutional framework, the FFDCA provides for a food labeling regulatory regime that is intended to ensure that information about food products is presented to consumers in a truthful, non-misleading manner. This regulatory system requires disclosure of any significant difference in the characteristics of an rDNA biotechnology-derived food when compared with its conventional counterpart. In addition, voluntary label statements must be substantiated and not misleading, either overtly, by implication, or by omission.
- Mandatory label disclosure requirements may not reach beyond addressing material facts about a food. If rDNA biotechnology were used in the development of a plant variety but the rDNA biotechnology-derived food was not significantly different from the conventional counterpart, there would be no material fact regarding the food to disclose. Thus, absent significant differences, the fact that a food is rDNA biotechnology-derived is not by itself a material fact.
- Voluntary labeling has been used to establish markets for niche categories of foods desired by consumers.
- Any labeling requirements or policies to distinguish rDNA biotechnology-derived foods from other foods would require definitions and monitoring tools sufficiently precise to meet the objectives of the requirement or policy.
- Labeling initiatives for rDNA biotechnology-derived foods are likely to have substantial effects on the production, distribution, and cost of food to consumers.
- If a voluntary labeling initiative

Biotechnology Report: Labeling

CONTINUED

to distinguish rDNA biotechnology-derived foods is pursued, broad stakeholder agreement should be achieved regarding appropriate substantiation of claims.

• Terminology used in labeling should convey information to the public in an understandable, accurate, and non-misleading manner.

REFERENCES

Anonymous. 1999a. European Commission may tell Austria, Luxembourg to end GM corn ban. World Food Chemical News, March 3, pp. 11-12.

Anonymous. 1999b. Major European supermarkets ban GMOs in own-brand products. Food Regulation Weekly, March 22, p. 20.

Anonymous. 1999c. Food Control 10(6): 339-414.

Anonymous. 1999d. Methods for detection of GMO grain in commerce. Report prepared for Diag Work Group of the American Crop Protection Assn. www.acpa.org/public/issues/biotech/detectmeth.html.

Anonymous. 1999e. ADM joins Staley in rejecting some transgenic corn. Grainnet. April 14. www.grainnet.com/BreakingNews/articles.html?ID=3528.

Anonymous 1999f. ADM to offer premium non-genetic soy. Reuters, May 5. biz.yahoo.com.

Anonymous. 2000. Frito-Lay will stop using genetically modified corn due to consumer concern. Food Labeling and Nutrition News, Feb. 9, p. 17.

Bender, M.M. and Derby, B.M. 1992. A prevalence of reading nutritional information and ingredient information on food labels among adult Americans: 1982-1988. J. Nutr. Educ. 24(6): 292-297.

Bender, K., Hill, L., Wenzel, B., and Hornbaker, R. 1999. Alternative market channels for specialty corn and soybeans. Agric. Exp. Sta. Res. Bull. AE-4726. Univ. of Illinois, Urbana-Champaign.

Betts, K. 1999. Environmental news. Env. Sci. Technol. 33(23): 484A-485A.

Blanchfield, J.R. 1999. Personal communication. Consultant, London, U.K.

Buckwell, A., Brookes, G., and Bradley, D. 1999. "Economics of Identity Preservation for Genetically Modified Crops." Food Biotechnology Communications Initiative (unpublished work).

Bullock, D.S., Desquilbet, M., and Nitsi, E. 2000. The economics of non-GMO segregation and identity preservation. Presented at Ann. Mtg., Inst. of Food Technologists, Dallas, Tex., June 10-14. Available at www.aces.uiuc.edu/ACE/faculty/dallasbu.PDF.

Buzby, J.C. and Ready, R.C. 1996. Do consumers trust food safety information? Food Rev. 19(1): 46-49.

Codex. 1999. Report of the Twenty Seventh Session of the Codex Committee on Food Labelling. ALINORM 99/22A. Codex Alimentarius Commission, Rome.

Codex. 2000. Review of the Work by International Organizations on the Evaluation of the Safety and Nutrition Aspects of Foods Derived from RDNA Biotechnology. CX/FBT/00/3. Codex Alimentarius Commission, Rome.

Erickson, B.E. 2000. Detecting genetically modified products in food. Anal. Chem. 72(13): 454A-459A.

EU. 2000. Commission Regulation No 49/2000 of 10 January 2000 amending council regulation No 1139/98 produced from genetically modified organisms of particulars other than those provided for in Directive 79/112/EEC. Jan. 10. European Union, Brussels.

Eurobarometer. 2000. The Europeans and biotechnology. Report prepared by INRA (Europe)-ECOSA. http://europa.eu.int/comm/research/pdf/eurobarometer-en.pdf.

FDA. 1986. Irradiation in the production, processing and handling of food. Food and Drug Admin., Fed. Reg. 51: 13376.

FDA. 1992. Statement of policy: Foods derived from new plant varieties. Food and Drug Admin., Fed. Reg. 57: 22984.

FDA. 1994. Interim guidance on the voluntary labeling of milk and milk products from cows that have not been treated with recombinant bovine somatotropin. Food and Drug Admin., Fed. Reg. 59: 6279.

FMI. 1999. Consumer trends. Food Res. Group, Food Mktg. Inst., Washington, D.C.

FTC. 1994. Enforcement policy statement on food advertising. Federal Trade Comm., Fed. Reg. 59: 28388.

Gallup. 1999. What biotech food issue? Poll Release, Oct. 5, Gallup Organization. www.gallup.com/poll/releases/pr991005.asp.

Gaskell, G., Bauer, M., Durant, J., and Allum, N. 1999. Worlds apart? The reception of genetically modified foods in Europe and the US. Science 285: 384-387.

HHS. 2000. "FDA to Strengthen Pre-Market Review of Bioengineered Foods. News release, May 3. U.S. Dept. of Health and Human Services, Washington, D.C.

Hoban, T.J. 1996. How Japanese consumers view biotechnology. Food Technol. 50(7): 85-88.

Hoban, T.J. 1997. Consumer acceptance of biotechnology: An international perspective. Nature Biotechnol. 15: 232-234.

Hoban, T.J. 1998. International acceptance of agricultural biotechnology. In "Agricultural Biotechnology and Environmental Quality: Gene Escape and Pest Resistance," ed. R.W.F. Hardy and J. B. Segelken, National Agricultural Biotechnology Council Report No. 10, pp. 59-73. Natl. Agricultural Biotechnology Council, Ithaca, N.Y.

Hoban, T.J. 2000. Personal communication. North Carolina State Univ., Raleigh.

Hoban, T. and Kendall, P.A. 1993. Consumer attitudes about the use of biotechnology in agriculture and food production. North Carolina State Univ., Raleigh.

Kelley, J. 1995. Public perceptions of genetic engineering: Australia, 1994. Report prepared for Dept. of Industry, Science and Technology, Commonwealth of Australia, by Intl. Survey Program, Australian Natl. Univ.

NIN. 1999. Voluntary labeling of foods from biotechnology. Report on a qualitative study among Canadian consumers by the National Institute of Nutrition. Office of Biotechnology, Canadian Food Inspection Agency. www.cfia-acia.agr.ca/english/ppc/biotech/ninrepor. htm.

Nelson, G.C., De Pinto, A., Bullock, D., Nitsi, E.I., Rosegrant, M., Josling, T., Babinard, J., Cunningham, C., Unnevehr, L., and Hill, L. 1999. The economics and politics of genetically modified organisms in agriculture: Implications for WTO 2000. Bull. 809, Office of Research, Univ. of Illinois, Urbana-Champaign.

Rodolfo, M.N., Lipinski, D., and Savur, N. 1998. Consumers' use of nutritional labels while food shopping and at home. J. Consumer Affairs 32(1): 106-120.

Tordjman, A.S. 1995. Trends in Europe. Report prepared for the Food Mktg. Inst., Washington, D.C.

USDA. 2000. National organic program; Proposed rule. U.S. Dept. of Agriculture, Fed. Reg. 65: 13512.

USDS. 2000. Fact sheet: The Cartagena Protocol on Biosafety. Office of the Spokesman, U.S. Dept. of State, Washington, D.C., Feb. 16. www.state.gov/www/global/oes/montreal_2000-01_index.html.

White House. 2000. Clinton Administration agencies announce food and agricultural biotechnology initiatives: Strengthening science-based regulation and consumer access to information. http:/vm.cfsan.fda.gov/~lrd/whbio53.html.

Wirthlin Worldwide. 2000. U.S. consumer attitudes toward food biotechnology. Survey conducted for the Intl. Food Information Council, Washington, D.C.

Labeling Panel

John E. Vanderveen, Ph.D., Scientist Emeritus, Food and Drug Administration, San Antonio, Tex.
John W. Bode, Esq., Principal, Olsson, Frank & Weeda, P.C., Washington, D.C.
Christine M. Bruhn, Ph.D., Director, Center for Consumer Research, University of California, Davis
Elizabeth (Betty) Campbell, Senior Consultant, AAC Consulting Group, Bethesda, Md.
Susan K. Harlander, Ph.D., President, Biorational Consultants, Inc., New Brighton, Minn.
Gerald Nelson, Ph.D., Associate Professor, Dept. of Agricultural and Consumer Economics, University of Illinois, Urbana
Steve Taylor, Ph.D., Professor and Head, Dept. of Food Science and Technology, University of Nebraska, Lincoln

IFT Expert Report on Biotechnology and Foods

Benefits and Concerns Associated with Recombinant DNA Biotechnology-Derived Foods

One of the difficulties in discussing the benefits and concerns that attend any technology is consideration of the rapid and extensive advances. As a result, most of us, as consumers, are aware in detail of only those technologies with which we, as individuals, are involved. If we are keenly interested in computers, for example, we usually have considerable knowledge of the underlying technology. If we have never touched a computer, we are likely to be unfamiliar with their function. That is no less true of the technologies that support our food supply.

A few generations ago, most of our population lived on farms or in small towns. Nearly all of our food was grown at home, or nearby, and processed by our families or by people we knew. We had confidence owing to personal contact. The technologies were simple and available to all.

The remainder of that picture, however, was not so comfortable. Frozen foods, iodized salt, vitamins, enriched bread, and air transport of fresh foods were unknown. For all except the very wealthy, fresh fruits and vegetables were limited to what was seasonably available. Goiter, rickets, beri-beri, and pellagra were common.

Today, nutrient deficiency diseases in the Western world are a distant memory. A huge variety of food is available year round. For this to be possible, many of these foods are grown thousands of miles away from where we live, and processed by people we neither see nor know. Furthermore, in the United States, expenditures for food are among the lowest in the world—about 10% of average family income. Supporting those facts is an enormous breadth of science and technology, some of which we discuss in this report. That technology is no longer simple and familiar to all. It is complex, and to most consumers, unknown. Discussing the benefits and concerns that biotechnology creates requires discussing these usually unfamiliar technologies into which biotechnology fits.

History teaches another aspect that must be addressed in the course of introducing any new technology. Except for some life-saving medical advances, and sometimes not even then, it is rare for a new technology to receive a broad and enthusiastic welcome. Canned food, for its first hundred years, was viewed apprehensively, and not without reason. In those pre-bacteriology days, it was far more an uncertain art than a solid science. Pasteurized milk, a life-saving technology in its elimination of the microorganisms causing tuberculosis and undulant fever, was originally viewed with deep suspicion. Artificial insemination of farm animals—critical in selective breeding of improved

Biotechnology Report: Benefits

CONTINUED

livestock—was regarded as tampering with nature. Margarine was opposed, partly for alleged health concerns, but mostly because it was a threat to the dairy industry. All sorts of health threats—far beyond pacemaker interference—were originally attributed to microwave cooking. Such apprehensions were by no means confined to food, for which we have always understandably felt a close personal concern.

These examples, a few among thousands, illustrate the mix of motives—some rational, some not, some economic, some religious or ethical, some based only on lack of understanding—that have characteristically attended the implementation of innovation. Biotechnology is no exception. We hope that this report will be a useful contribution to civil and rational dialogue which alone can deal effectively with both scientific issues and consumer concerns.

Specific Benefits

There are numerous specific benefits of recombinant DNA biotechnology-derived foods.

With the use of rDNA biotechnology, there is the potential for enhancing plant availability and growth, and the ability to grow more and better food with increased nutritional value, including improved animal feed. rDNA biotechnology is expected to revolutionize food bioprocessing through improvements in the responsible microorganisms (e.g., bacteria, yeasts, and molds) and efficient production of specialized enzymes and ingredients via fermentation technology. rDNA biotechnology also creates the opportunity to produce edible vaccines and therapeutics for preventing and treating diseases. The use of rDNA biotechnology also has specific environmental benefits, with the development of new varieties of crops that exhibit increased resistance to pests, tolerance to more environmentally benign herbicides, and virus resistance. These and other specific benefits will be discussed in greater detail below.

Plant Attribute Benefits

In the harsh world of nature, surviving plants (and animals) have evolved to resist environmental stresses and both pest and pathogen attack. The survival of crop plants (and livestock) has been enhanced by human selection and intervention to produce food. In little more than a century, starting with hybridization, which was commercialized in the first decade of the 20th century, scientific breakthroughs enabled new types of plants, such as triticale and seedless watermelons and grapes, to be produced. Starting in the mid-1970s, genetic modification or "engineering" by molecular means became feasible.

A healthy plant produces a variety of compounds to protect itself from being eaten or destroyed (Ames et al., 1990a, b). At the levels commonly consumed in food, few of these naturally occurring compounds are deleterious to human health. However, many of these substances are hazardous if sufficient quantities of the plant are consumed under certain circumstances. Examples include glycoalkaloids in potatoes, cyanogenic glycosides in cassava, trypsin inhibitors in lima beans, and allergenic proteins in a variety of foods.

Plant breeding often has been successful in producing plants with increased pest and disease resistance, while retaining high yields and both taste and processing attributes. Synthetic pesticides are frequently used to produce high-quality and economically viable crops, such as apples and squash. Food crops can be devastated by both above- and below-ground microorganisms. While some compounds are available for combating fungi, such as the copper sprays and sulfur used by organic farmers and fungicides used by farmers and home gardeners, these are high-cost and broad-spectrum, often killing beneficial organisms as well. Except for plant breeding and use of insecticides for killing insects that transmit disease, no remedies for combating plant viruses are known (Dempsey et al., 1998). Unlike combating human bacterial infections, very limited remedies are available for preventing bacterial diseases of plants (Lucas, 1998). Antibiotics are available, but their use is not economical.

The susceptibility of a plant to biotic and environmental stresses—such as temperature extremes, chemical challenge and heavy metal exposure (e.g., selenium), and salinity and drought—are affected by the plant's genetic composition and structure. For example, some leaves have evolved to conserve moisture or resist heat or freezing. Breeders have changed leaf and stem architecture to capture more sunlight and allow for greater air flow through the leaf canopy.

All plants with genes for resistance to pests and disease are evaluated by breeders and processors during initial stages, and are either subsequently commercialized as generally recognized as safe (GRAS), or, if changed by molecular means, reviewed by federal agencies before commercialization (discussed in detail in the *Safety* section). Numerous scientific associations have become valued participants in the development and regulatory processes for these crops and food products. As examples, AOAC International and the American Association of Cereal Chemists (AACC) ensure that the current state of knowledge is applied through appropriate and standardized analytical testing procedures to ensure the safety and quality of food ingredients and resultant processed foods. Further, AACC has led the advancement in functional criteria for cereal grains such as the baking quality of wheat, relationships of the protein content of corn to product attributes, and other properties important or essential to various food products. This process may take up to l5 years from initial seed selection. Yield is very critical, as are processing properties, quality, composition, and organoleptic properties.

rDNA biotechnology offers the potential for enhancing plant availability and survival, as well as growth. For example, a severe strain of papaya ringspot virus in Hawaii threatened to kill the trees and decimate the livelihood of growers. Little resistance was available for breeding potential. Hence, the viral coat protein gene was transformed into stock, allowing the trees to grow. In 2005, methyl bromide, a soil fumigant widely used in certain areas, must be taken off the market, as a result of international treaty. At present, there is no alternative for controlling soilborne fungal pathogens in strawberry varieties grown in those regions; rDNA biotechnology offers the potential to retain the availability, at reasonable cost, of strawberries. Apple and pear production is constrained by the bacterial disease called fireblight, first described in the 1870s. No satisfactory antibacterial compounds or adequate resistance to the disease is available in apples desired by consumers. rDNA biotechnology research has produced the first trees to resist this devastating disease. Grape vines, which require multiple years to grow and mature before production of both wine and

table grapes, are subject to fungi, insects, root disease, and pest problems, which are increasingly difficult to control. Both the quality and availability of wine and whole grapes can be affected. rDNA biotechnology again offers the potential for minimizing damage caused by these agents.

The advantages of rDNA biotechnology-derived food crops—increased yield and better resistance to pests, disease, and environmental stress—are clearly apparent to growers but not to most consumers. Widespread acceptance of rDNA biotechnology-derived crops will not occur until consumers become convinced of their advantages. So, what advantages are consumers likely to derive from such crops? Here are a few:

• Food-deficient regions of the world may become less common. rDNA biotechnology-derived crops can be developed to prosper under conditions that previously limited or prevented plant growth. This approach will increase world crop production and also increase the variety of crops suitable for growth in any given area. It is unlikely that an abundance of crops of this type will ever become available in a reasonable time frame through conventional breeding practices. Increases in the food supply that are potentially achievable by rDNA biotechnology are likely to greatly exceed those accomplished during the Green Revolution, which relied on conventional breeding practices.

• Improvements in the organoleptic and nutritional quality of foods derived from plants will occur more rapidly and be more pronounced through rDNA biotechnology modification than by conventional breeding.

• Improvements in the shelf life of fresh fruits and vegetables that either cannot be obtained through conventional breeding or are obtained only at a much slower rate will be attainable through rDNA biotechnology modification.

• Reduction in crops of the types and concentrations of allergens, naturally occurring toxicants, and other undesirable constituents will be more easily achieved by rDNA biotechnology modification than by conventional breeding.

• Introduction into crops of disease-resisting and health-promoting constituents (e.g., substances that protect against cancer, lower cholesterol, lower blood pressure, ease menstrual and arthritic pain, help maintain bone density, resist infection, and reduce anxiety) which would be exceedingly difficult, slow, or more likely impossible by conventional breeding will be possible by rDNA biotechnology modification.

More and Better Food

Recently, the human population of the globe passed 6 billion, and forecasts predict that this number will grow to 9 billion by 2050 (UN, 1999). While these numbers are more modest than the prediction only five years ago that the population would double by 2030, demographers predict that the vast majority of the growth will occur in Asia, Southeast Asia, and Africa, areas already under significant strain for food production. Even though improved agricultural practices and higher-yielding crops will likely meet the minimum number of calories to sustain human life globally, there is real and significant concern that the needs for adequate nutrition will not be met.

For example, although India produces sufficient food to prevent starvation, more than 30% of its population is malnourished. The situation is even more pressing in Africa, where diseases such as AIDS have reduced the numbers of farming women and children. Furthermore, periodic famines in arid regions in Africa continue to drive increasing numbers of people to malnutrition and starvation. Recent studies have shown that an infant born of a malnourished mother carries the effects of malnutrition into the fourth generation beyond the mother (Galler et al., 1996).

The challenge is not simply to provide a steady supply of food, but a nutritious and safe food supply that improves the health and productivity of the global population. The past 10 years have seen the development of rDNA biotechnology that can play an important, but certainly not the sole, role in increasing the supply and quality of foods for peoples in the developing economies.

Despite the modest "farm surpluses" currently being produced in some areas (e.g., North America, Australia), the world does not yet grow nearly enough food to meet the demands of the 21st century. Even with human population stability expected by 2050, the world will need farm outputs that are 2.5–3 times greater than current harvests to provide high-quality diets to the world population just five decades from now (McCalla, 1995). Technologies such as hybrid seeds, irrigation, nitrogen fertilizer, and integrated pest management are already in broad use on the world's best farmlands. Extending the known non-rDNA biotechnology farming systems to the world's low-yield farming sectors might not even double current world farm output (Waggoner, 1994). rDNA biotechnology is the most important unused technology available to meet this last, huge surge in global farm demand.

Seven academies of science from around the world, including five from developing nations, issued a white paper (NAS, 2000) spelling out the promise of agricultural biotechnology to alleviate hunger and poverty in the Third World. The academies reported that it is essential that we improve food production and distribution to feed and free from hunger a growing world population, while reducing environmental impacts and providing productive employment in low-income areas. This will require a proper and responsible utilization of scientific discoveries and new technologies. The developers and overseers of rDNA biotechnology applied to plants and microorganisms should make sure that their efforts address such needs. The academies stated that foods can be produced through the use of rDNA biotechnology that are more nutritious, stable in storage, and in principle health promoting—bringing benefits to consumers in both industrialized and developing nations.

Any shortfall in the effort to triple current yields on the world's existing farmlands over the next 50 years is likely to mean massive malnutrition for the world's poorest peoples. It is also likely to mean the plowdown of millions of square miles of forests and wildlands and thus the probable sacrifice of millions of irreplaceable wild species (Avery, 1997).

Organic farming is often held up as the agricultural ideal for the 21st century. Unfortunately, the U.S. has only about one-third of the organic nitrogen needed to support current U.S. farm output (Van Dyne and Gilbertson, 1987). Countries such as India and China have even less of the organic nitrogen that would be needed; they already feed much of their biomass to livestock and burn animal feces for cooking. The world as a whole may have only one-fourth of the organic nitrogen necessary to support its current food production, let alone triple for 2050.

In addition to sheer caloric needs, hundreds of millions of the world's poor people are still short of the protein and micronutrients needed to ensure long and healthy lives. rDNA biotechnology has already demonstrated, through such

Biotechnology Report: Benefits CONTINUED

successes as chymosin, "golden rice," and acid-tolerant crops, that it is one of the most promising ways to meet these urgent needs.

"Golden rice" has been genetically modified through rDNA biotechnology to have increased beta-carotene content, which may help to overcome the severe vitamin A deficiencies which cause millions of poor children to go blind or die every year in low-income, rice-consuming cultures. A related product of rDNA biotechnology may also help eliminate the iron deficiency which threatens hundreds of millions of rice-culture women and their babies with birth complications each year (Gura, 1999). Toxic metals, such as aluminum and manganese, are widely present in "acidic" tropical soils, which account for nearly half the arable land in the tropics. These metals reduce root growth, cutting yields by up to 80%. To produce acid-tolerant crops, two researchers in Mexico inserted a gene from a bacterium into tobacco and papaya. The plants thus secrete citric acid from their roots, chelating these toxic metals (De la Fuente et al., 1997). The yield gains now anticipated from making such soils accessible will be critical to protecting the tropical forests, which contain most of the world's species of plants and animals. These examples are discussed in greater detail below.

rDNA biotechnology should also be able to play key roles in protecting, preserving, and processing foods, to minimize food losses, maintain or improve quality, and increase processing efficiency. The result should be better health, greater food enjoyment, and still less competition between people and wildlife for scarce land.

If the need for improved farming and food technologies is viewed in purely economic terms, the 21st century will see a huge increase in the demand for farm exports. The rapidly rising affluence and demonstrated protein hunger in such densely populated countries as China, India, and Indonesia virtually guarantee that the temperate-zone countries well endowed with farmland (such as the U.S., Canada, Argentina, France, and Germany) will have the opportunity to help meet the soaring food demand in the emerging economies. Agriculture in the developed countries thus could make a major environmental contribution while increasing production each year for additional farm exports. Hundreds of thousands of additional urban jobs would also be created by such an expansion of farm exports, in food processing, transportation, and many associated fields.

Food Technology and Bioprocessing Benefits

Production of various foods and food ingredients through fermentation, also called bioprocessing, has occurred since the earliest records of man's preservation of foods. Microorganisms and enzymes are used widely for the conversion of raw food substrates (e.g., milk, cereals, vegetables, and meats) into a plethora of fermented products (e.g., cheeses, cultured milks, sourdough bread, pickles, wine, beer, and sausages). Bioprocessing technology has been further developed for specialized production of food ingredients (e.g., organic acids, amino acids, vitamins, and gums), or processing aids (enzymes). rDNA biotechnology is expected to revolutionize food bioprocessing across all of these arenas through improvements in the responsible microorganisms (e.g., bacteria, yeasts, and molds) and efficient production of specialized enzymes and ingredients via fermentation technology.

Ingredients made by bioprocessing are among some of the most attractive products of rDNA biotechnology. An understanding of metabolism and the ability to redirect metabolic pathways provide opportunities to produce food ingredients of higher quality and purity, as well as new ingredients for purification or synthesis that are not available through conventional methods. As discussed below, key ingredients targeted by rDNA biotechnology include organic acids, bacteriocin preservatives, enzymes, and microorganisms used for processing aids. rDNA biotechnology is also important in the production of vitamins and amino acids.

• Organic Acids. Organic acids are commonly used as food acidulants and are among the most versatile food and beverage ingredients because of their solubility, hygroscopic, buffering, and chelation properties (Moresi and Parente, 1999). Lactic, citric, gluconic, and propionic acids are all naturally occurring and produced by fermentation. Citric acid has the widest range of applications and with acetic acid accounts for 75% of food acidulant usage. Citric acid is produced by several molds, yeasts, and bacteria by fermentation of glucose via glycolysis. Mutants of fermentation strains have been selected with steps in the Krebs cycle blocked to maximize accumulation of citric acid. Improvements via rDNA biotechnology have increased the rate of glucose fermentation and eliminated enzymes that degrade citrate in the production organisms.

Lactic acid is used as an acidulant for cheeses, meats, jellies, and beer. Derivatives of ammonium lactate are used as sources of non-protein nitrogen in animal feeds, and sodium or calcium stearoyl lactylates are used as emulsifiers and dough conditioners. Fermentation processes produce both the D and L isomers of lactate via the two stereospecific lactic dehydrogenases—L-LDH and D-LDH. L-lactate is the natural and preferred form for food use because it is the form used by humans and the D-form is considered slightly toxic. Two key improvements have occurred via rDNA biotechnology. First, elimination of D-LDH by gene replacement leads to pure L-lactate production in *Lactobacillus* species (Bhowmik and Steele, 1994; Lapierre et al., 1999). Second, the bovine L-LDH gene was introduced into *Kluyveromyces lactis*, leading to significant yield increases in L-lactate (Porro et al., 1999).

Lactic acid bacteria show considerable promise for metabolic engineering because their biosynthetic pathways are completely separate from their energy-generating pathways. As a result, either pathway can be manipulated without affecting the other. In a landmark example, the homolactic pathway of *Lactococcus lactis* was redirected to a homoalanine fermentation (Hols et al., 1999). Stereospecific production (>99%) of the preferred form, L-alanine, was achieved, using metabolic engineering to produce a product (alanine) that is not a normal product of the organism's metabolism. Industrial production of this stereoisomer in food products or bioreactors is now possible.

• Bacteriocin Preservatives. Bacteriocins are peptide antimicrobials that kill bacteria. Nisin is notable among these because of its broad killing range against Gram-positive pathogens and its GRAS status based on its safe consumption in dairy products for centuries. Genetic approaches to understanding the regulation

of nisin biosynthesis in *Lactococcus* have identified the fermentation conditions where nisin, or other enzymes/proteins, can be overproduced, approaching 50% of the cells' protein (Kleerebezem et al., 1997). The increased availability of nisin has led to expanded applications for this preservative in foods. Moreover, expression systems using the nisin-inducible promoter are already providing powerful tools for production of food-grade enzymes and protein ingredients by *L. lactis*.

• Enzymes. Enzymes were important agents in food production (e.g., milk clotting, bread production, juice clarification, alcoholic beverage production) long before modern rDNA biotechnology was developed. Today, enzymes are indispensable to modern food processing technology. The U.S. market for enzymes used in food manufacture is expected to grow to $214 million by 2006 (Roller and Goodenough, 1999). An increasing variety of food enzymes has been produced using rDNA biotechnology. Their accepted use in foods is based on the following facts: enzymes produced by rDNA biotechnology are identical to their natural counterparts (e.g., chymosin); enzyme preparations are free of any deleterious substances that could be introduced during the bioprocessing and purification steps (e.g., endotoxins from *Escherichia coli*); and viable rDNA biotechnology-derived microorganisms are not present in the final preparation.

The first example of a processing enzyme produced by rDNA biotechnology for use in food was chymosin (reviewed by Roller and Goodenough, 1999). Chymosin is the most important enzyme used in the dairy industry to clot milk. Its specific hydrolysis of kappa-casein destabilizes milk micelles and leads to rapid coagulation, clean flavor, and maximum protein yields from cheese curds. Traditionally, chymosin was obtained from rennet extracted from the stomachs of young calves. Rennet supplies faced major declines as calf slaughter decreased during a period of increasing worldwide cheese production. Several commercial entities undertook efforts to clone and express chymosin, in its exact natural form, from bacteria (*E. coli*), yeast (*K. lactis*), and molds (*Aspergillus niger* var. *awamori*). Chymosin that was produced in bioreactors was identical to the animal-derived enzyme and was substantially purer (>95% chymosin) than traditional rennet (containing only 2% chymosin).

Since these were the first products of rDNA biotechnology targeted for use in human foods, extraordinary precautions were taken to assure that the enzyme preparations were free of toxins, had no live recombinant organisms, and exhibited no ill effects in animal studies. Indeed, although *E. coli* is not a food-grade organism, the Food and Drug Administration concluded that chymosin produced from recombinant *E. coli* was identical to its conventional counterpart and, therefore, could be considered to be a GRAS substance acceptable for use in foods (FDA, 1990). Estimates of the use of rDNA biotechnology-derived chymosin now exceed 80% of the market in the U.S. and Canada, where cheese produced using rDNA biotechnology-derived chymosin is regarded as vegetarian, kosher, and halal.

The chymosin example established the basis for production of a variety of safe and functional rDNA biotechnology-derived food-grade enzymes. Improvements are readily apparent in enzyme availability, purity, and cost, which benefit and improve the quality of foods available to consumers. Commercial and near-market rDNA biotechnology-derived food enzymes are listed in Table 1.

Because of the considerable benefits to be realized, it is probable that most food processing enzymes eventually will be rDNA biotechnology-derived. Enzymes of higher purity and specificity can be obtained, which will improve processing efficiencies and quality, while

Table 1 Commercial and near-market rDNA biotechnology-derived food enzymes[a]

Enzyme	Application	Source/producing organisms	Status
Chymosin	Milk clotting in cheese manufacture	*Escherichia coli, Kluyveromyces lactis, Aspergillus niger*	Commercial, >80% of market
Lactase	Lactose hydrolysis	*K. lactis*	Commercial
Alpha-amylase	High-fructose corn syrup (HFCS)	*Bacillus subtilis*	Commercial
Amyloglucosidase	HFCS	*B. subtilis*	Commercial
Acetolactate decarboxylase	Beer aging and diacetyl reduction	*B. subtilis*	Commercial, UK approval pending
Maltogenic alpha-amylase	Anti-staling in bread	*B. subtilis*	Commercial
Xylanase	Bread dough processing, crumb structure, and loaf volume	*Aspergillus oryzae*	In review
Hemicellulases	Bread dough processing, crumb structure, and loaf volume	*B. subtilis, A. niger*	Approved
Lipase	Interesterification of palm oil for cocoa butter	*A. oryzae*	Under development
Cyclomaltodextrin glycoslytransferase	Cyclodextrans for flavor and aroma binding	*Bacillus species*	Under development

[a]Compiled from Roller and Goodenough (1999)

Biotechnology Report: Benefits

CONTINUED

reducing energy costs, waste, and environmental impacts.

• Processing Aids—Microorganisms. Many beneficial microorganisms are directly responsible for the preservation and processing of food, including primarily yeasts (*Saccharomyces cerevisiae*), beneficial molds, and lactic acid bacteria. rDNA biotechnology offers considerable promise for the beneficial modification of microorganisms that drive food fermentations. Examples of microorganisms modified through rDNA biotechnology for bioprocessing that are currently approved for food use are listed in Table 2.

In those examples where rDNA biotechnology modifications were made in yeast, self-cloning was used. This concept is based on the fact that DNA rearrangements occur naturally and often within the genome of any given organism. Self-cloning protocols require that only DNA originating in the host organism can be manipulated and reintroduced to create an improved microorganism.

For bioprocessing microorganisms, there remain many attractive targets for improvement through rDNA biotechnology. Most of these offer improved product quality, better control of fermentations, and thus enhanced food safety. It is pertinent to note that progress in molecular biology and genomics has provided both the tools and targets for precise genetic modification of microorganisms. Specific genes and DNA sequences can be introduced, eliminated, or altered in a precise manner in microorganisms in many cases. If desirable, marker genes and extraneous DNA can be removed. These specific changes are superior to nondiscriminating strategies that have been used historically to mutagenize DNA, in chance efforts to select more-efficient organisms. History claims many successes in the selection of improved organisms (e.g., 10,000-fold increase in penicillin production from Alexander Fleming's original *Penicillium* strain). However, the mutations are random and nondiscriminating, and any effects of secondary mutations are not known. In contrast, rDNA biotechnology has provided the tools and information to make more-specific genetic changes, ensuring both performance and safety.

Animal Benefits

• Animal Feed. Over the past century, a remarkable revolution in both animal and plant agriculture has led to a relatively stable and cheap supply of food for the developed world. In parallel with the Green Revolution, there has emerged an equally important revolution in animal feed efficiency. This was essential to provide for the developed world's demands for high protein content of their diets. For example, 56% of the protein in the developed world's diets comes from animal products, compared with only 11–26% in the developing countries (Delgado et al., 1998). In the U.S. at the turn of the century, it took about 6 pounds of feed to produce a single pound of weight gain in a chicken. Today, only 1.5 pounds of feed are required (Gordon, 1996; Williams, 1997). Similar improvements have been seen in hog production. However, this revolution in animal genetics has led to a significant increase in animal nutritional requirements, which are poorly met by current crop plants. In essence, animal nutritional needs now exceed that which can be provided by the basic commodity plants on which animals rely for calories (Olsen and Frey, 1987).

This divergence between plant supply and animal demand has occurred because selection for improved plant productivity has focused primarily on plant yield per acre of land and has largely ignored the nutritional needs of the animal. In parallel with this, improvements in animal genetics have focused primarily on increased efficiency of feed conversion, assuming a near optimal feed composition. Thus, plant and animal breeders have been inadvertently widening the gap between the increasing nutritional needs of the animal and the ability of the crops used for feed to meet those nutritional needs.

To optimize animal nutrition, the animal feed industry has flourished during the last century. The growth in the feed supplements business was critical to meet the demand for macro- and micronutrients as feed additives. By monitoring essential feed components, least-cost feed formulations have evolved. Coupled with a vertically integrated system from farm to consumer, this has resulted in a supply of high-quality meat at affordable prices in the developed world. The basic commodity-feed components of calories and protein supplied by the crop plants are the base of the supply chain. Today, a significant proportion of world crop production is directed into animal feed in the form of

Table 2 GMOs approved for use in food processing[a]

Microorganism	Function/benefit	Genetic modification	Regulatory status
Saccharomyces (Bakers yeast)	Gas production in sweet, high-sugar dough	Switched promoter elements to allow constant expression of enzymes necessary for maltose fermentation	Approved in UK, 1990; not commercially used
Saccharomyces cerevisiae (Brewers yeast)	Manufacture of low-calorie beer—starch degradation	Introduction of glucoamylase for degradation of dextran and production of fermentable glucose	Approved in UK, 1994
Lactococcus lactis	Phage resistance, lactose metabolism, proteolytic activity, bacteriocin production	Conjugal transfer of naturally occurring plasmids into industrial dairy starter cultures	Commercially employed since 1985

[a]Compiled from Hill and Ross (1999) and Roller and Goodenough (1999)

forage, silage, or grain (Bradford, 1999). For example, 80% of U.S. maize production is used for feed for poultry, hogs, and cattle (USDA/ERS, 2000a). Although the developed world's meat consumption is projected to be stable, world meat consumption is expected to rise very significantly during this century because of increased demand for animal products in the developing world (Delgado et al., 1998).

By examining today's animal feed conversion ratios, it becomes clear that the greatest efficiencies in animal productivity are primarily based on chickens and hogs. For every pound of weight gained by a chicken, approximately 1.5 pounds of feed is required. For hogs, the feed requirement is approximately 4 pounds for every pound gained, whereas for beef cattle the feed requirement is more than 10 pounds. These conversion ratios demonstrate the importance of a high density of essential nutrients as well as calories. The shortfall in calories and essential amino acids available from cereal feed is partially offset by mixing corn with soybean to make a mixed soybean/corn feed. To improve the caloric value further, feed is supplemented with fats such as animal offal and feed-grade animal and vegetable fats which include by-products of the restaurant, soap, and refinery industries. Other nutritional needs are met by adding various feed additives to the mix. Productivity is enhanced by managing an optimal environment for the animals to grow. It is here where significant emphasis is placed on animal health as it relates to carcass quality.

The first major improvement in animal nutrition was the addition of vitamin D, which allowed chickens to be raised in controlled environments. This in turn minimized losses due to environmental changes, predators, and disease. Further improvements came with diets supplemented with vitamin E as an antioxidant, methionine to improve immune function, conjugated linoleic acids to improve feed efficiency and carcass quality, enzymes to improve digestion and remove antinutritional factors and toxins, antibiotics to optimize animal health and stabilize weight gain, prebiotics and probiotics to improve gut microflora, and growth hormones to improve feed efficiency. Today, there are many feed supplements and additives with varying efficacies (Kellems and Church, 1998). Some are macronutrients and others micronutrients, yet others are more veterinary pharmaceutical in nature. Most are aimed at improving carcass quality while maintaining or improving animal feed efficiency. A wide array of methods for producing these feed additives are used across the world, from fermentation to synthetic chemistry, and some already rely on the application of rDNA biotechnology. The key emphasis is placed on quality linked to the cost of production.

As we move forward in the new century, a new revolution is occurring. Through dramatic advances in genetics and rDNA biotechnology, it is now possible to envision ways of enhancing animal feed by directing the plant itself to produce a more nutritious product (Bonneau and Laarveld, 1999). With this advance comes the opportunity to redesign and rethink the basic composition of feeds derived from silage, forage, and grain. This change will go beyond plant yield as a commodity product and enter the realm of value-added crops. In the developing countries, where meat consumption is very much lower than in the developed world, these rDNA biotechnology-driven advances in plant composition for animal feed present another opportunity to improve human nutrition.

Collectively, these genetic improvements in crop composition have been termed the "output traits" to distinguish them from the input traits that were the hallmark of the first wave of rDNA biotechnology-derived products, which included resistance to herbicides, insects, and viral diseases. Thus, a new industry to improve feed crops is emerging as an adjunct to the existing feed supplement industry. The seed genetics industry, linked to rDNA biotechnology, is altering seed and plant traits to improve basic plant components.

Some output traits already on the market include silage corn improved by the mutant brown-midrib trait, producing so-called BMR-corn (Mazur et al., 1999). This corn has a mutation in the pathway leading to lignin deposition that significantly increases its digestibility for ruminant animals. A more recent improvement in maize was the development of corn with a higher-oil content. In this case, the maize seed was selected to have a significant increase in oil content, from 3.5% in conventional maize to about 6% oil in higher-oil corn. Varieties having the higher oil content have grown significantly in market share over the last few years. A further improvement came with the development of corn with increased protein and essential amino acids necessary for optimal animal growth.

In soybeans, improvements such as altered oligosaccharides to reduce nondigestible components (stachyose, galactose, and raffinose) and increased oleic acid composition have emerged. Increased plant resistance to fungal infections will reduce the risk of serious contamination with mycotoxins (discussed in the food safety improvements section below). In all crops, it seems reasonable to expect additional improvements through further enhancements in oil, fatty acid, protein, starch, carbohydrate, vitamin, antioxidant, and mineral composition.

A new area of animal feed improvement aids control of environmental pollution. In the intensive livestock industry, there are significant problems with odors and controlling the release of unused nutrients, such as nitrogen and phosphorus from animal waste (Dourmad et al., 1999; Poulsen et al., 1999). A significant step forward in resolving the major political and economic issue of phosphorus pollution was the identification of approaches to control phytic acid content of feed by reducing the phytate content of seed via rDNA biotechnology or adding phytase to feed via supplementation. A new development involves reducing the phytate content of the seed significantly by introducing the lpa1-mutant of corn. Low-phytate corn is new on the market. Recent studies have revealed that it has an unexpected nutritional enhancement, namely, an increased bioavailability of amino acids. Phytate also strongly chelates iron, calcium, zinc, and other divalent mineral ions, making them no longer bioavailable. This means less phosphorus waste as well as reductions in nitrogen waste.

Collectively, these genetic enhancements in feed composition have been achieved by introducing valuable traits directly into the commodity component, the plant itself. This is a significant technical challenge for both conventional plant breeding and rDNA biotechnology. Nevertheless, significant progress has already been made through a combination of conventional breeding, germplasm screening linked with high throughput tests of specific traits, rDNA biotechnology-aided breeding using

Biotechnology Report: Benefits

CONTINUED

DNA markers, selection for mutants carrying specific traits, and rDNA biotechnology (transgenic) approaches, which involve isolating, characterizing, and modifying individual genes followed by plant transformation and trait analysis. In all of these approaches there is an overriding imperative to maximize plant yield, because the least-costs feed analysis will continue to rule this market sector. Thus, it will be necessary to provide a platform which will continue to be based on delivering products using the cheapest methods available. This is perhaps the most challenging step of all, since yield requires many genes all functioning optimally in the plant. These enhancements are a key next step in securing and improving the world food supply in the new century for both the developed and the developing nations. Furthermore, these enhancements are expected to also alleviate some environmental problems associated with intensive livestock production.

• Plant-Based Animal Vaccines. Animal health benefits appear to be possible, as certain vaccines and growth hormones are amenable to an rDNA biotechnology approach (McKeever and Rege, 1999). At present, animals receive multiple injections to maintain their optimal health and high feed efficiency. This is inconvenient, causes some distress to the animal, and can cause some meat spoilage. By engineering a plant to express some of these products it appears to be possible to circumvent these concerns. Further advances seem highly likely in this type of technology.

Howard (1999) demonstrated production in plants of a vaccine against transmissible gastroenteritis virus which protected swine in clinical trails against the virulent pathogen. Dalsgaard et al. (1997) demonstrated that a cowpea plant-based vaccine protected mink against the diarrhea and anorexia caused by mink enteritis virus (MEV), a member of a group of viruses that is also responsible for disease in cats and dogs. To develop the plant-based vaccine, a segment coding for the epitope (antibody binding site on an antigen/allergen) of MEV was fused into the coat protein gene of a cowpea mosaic virus. Mink immunized by injection with the chimeric virus obtained from the rDNA biotechnology-derived plants resisted subsequent challenge with MEV; most of the unimmunized animals quickly succumbed to the disease.

Environmental Benefits

Farmers and producers have enthusiastically embraced the new varieties of rDNA biotechnology-derived crops that exhibit increased resistance to pests (e.g., corn, canola, cotton, and potatoes with *Bacillus thuringiensis* (Bt) genes for insecticidal proteins); tolerance to more environmentally benign herbicides (e.g., corn, cotton, soybeans); and virus resistance (e.g., squash, cucumbers, papaya).

Although a major driving force for adoption of these crops is economic, farmers also welcome the environmental benefits of fewer pesticide residues and simplification of farming practices. In general, farmers who use the new varieties have realized significant savings in production costs, as well as increased yields (USDA/ERS, 2000b). These savings occurred despite the increased costs of seeds and "technology fees" that were added by seed producers to recover expenses for research and development.

A recently released summary of the proceedings of the Ceres Conference on Agricultural Biotechnology (Doyle, 1999) describes the results of independent third-party studies to document farmer acceptance and profitability of rDNA biotechnology-derived crops. For example, 45% of farmers had higher yields of Bt corn compared to conventional corn in 1998, and nearly 26% of farmers growing Bt corn reported a decrease in pesticide use. Studies have demonstrated that farmers can save as much as $27 per acre in overall growing costs with glyphosate-tolerant soybeans. Data indicate that some farmers earned a net profit of about $40 more per acre for rDNA biotechnology-derived cotton compared to the conventional varieties. Data from the Canola Council of Canada for the 1998 season (Doyle, 1999) showed that, compared to conventional canola, glyphosate-tolerant varieties produced greater yields (31 bushels/acre compared to 28.6 bushels/acre) and greater profits ($86 per acre compared to $52 per acre). In addition to economic advantages, the number of pesticide applications is typically reduced. As an example, canola fields require only one herbicide application (instead of two), and glyphosate provides broader-spectrum weed control. Certainly, rDNA biotechnology can play an important role in development of agriculture that uses fewer and more-benign agrochemicals than needed with traditional crop varieties.

Researchers found that glyphosate-tolerant soybeans offered easier weed management, less injury to crops, no restrictions on crop rotations, increase in no-till agriculture, and reduced costs. U.S. farmers using glyphosate-tolerant soybeans saved an estimated $220 million in 1998 due to lower herbicide costs. The broad spectrum of weeds controlled by glyphosate means that soybean growers no longer need to make multiple applications of complex combinations of herbicides.

Before the introduction of tolerance genes from other organisms, herbicides were selected by screening for chemicals that caused minimal crop damage while killing as many common target weeds as possible. Broad-spectrum herbicides like glyphosate were most often used to kill vegetation in places like railroad tracks, paths, and parking lots. Glyphosate inhibits an enzyme essential for the synthesis of aromatic amino acids in plants. Researchers found a form of the enzyme that carries out the same step in a bacterium and which is not inhibited by this herbicide. Glyphosate-tolerant soybeans carry the bacterial gene and are relatively insensitive to the herbicide. Extensive tests by the manufacturer of glyphosate have shown that it has a very low mammalian toxicity and is rapidly degraded in the soil after application (Padgette et al., 1996). Its microbial degradation ultimately produces carbon dioxide and water. No toxic intermediates or derivatives have been identified among its breakdown products (Sanders et al., 1998). Unlike earlier herbicides that persisted in the environment and contaminated ground water, glyphosate appears to be safe and to disappear rapidly.

Similarly, rDNA biotechnology is now being used to develop varieties of soybeans and other crops that are tolerant to other herbicides, which would otherwise kill them. Two other herbicides with different modes of action, glufosinate and imidazolinone, are also being used on crops protected with transgenes. Corn resistant to sulfanyl urea has also been produced by the selection of mutants in tissue culture.

The introduction of herbicide tolerance has contributed to the development of no-till agriculture and crop rotation with benefits that include savings on fossil fuel in preparing seedbeds, and reductions in soil erosion and in air pollution from burning crop residues.

Economic Benefits

The most widespread rDNA biotechnology-derived crops in the U.S. at the present time are cultivars of soybean, cotton, and corn. In the U.S. in 1999, 35% of the corn acreage (77.4 million acres) was made up of either insect-tolerant (23%) or herbicide-tolerant cultivars; 45% of the cotton acreage (14.8 million acres) was insect tolerant; and 54% of the soybean acreage (72.9 million acres) was herbicide tolerant. A USDA/ERS (1997) study found that herbicide-tolerant soybeans reduced farm input costs by 3–6% and increased average yields by more than 13–18% in most regions of the U.S. Estimated benefits of herbicide-tolerant corn and canola range from $15 to $24 per acre (James, 1998). Considering that the planted area of rDNA biotechnology-derived crops more than doubled in 1998 to nearly 69 million acres (James, 1998), many farmers have obviously become convinced that rDNA biotechnology-derived varieties have superior characteristics.

Certain segments of the commercial seed markets have already become highly concentrated. Two companies together account for more than 50% of North American sales of corn seed and nearly 40% of North American soybean seed sales (Hayenga, 1998). Based on data contained in their recent annual reports, two other companies account for more than 40% of global commercial sales of fruit and vegetable seed.

Even in the relatively concentrated U.S. hybrid corn seed market, increases in seed costs have been less than half the value of yield increases attributable to new varieties for the period 1975 through 1998 (Artuso, 2000). A recent study of the distribution of benefits resulting from introduction of Bt cotton estimated that the biotechnology firms involved captured 44% of the value of the innovation, with farmers receiving 48% and consumers 8% (Falck-Zepeda et al., 2000). The estimated benefit shares derived in the study were based on data for 1997, which was only the second year in which the Bt variety was available. As competitors develop their own varieties of Bt cotton, the premium that can be charged for this variety can be expected to decline. The effect of competition can already be seen in the market for herbicide-tolerant soybeans. In this more-competitive market, the share of the economic benefits captured by the companies that introduced the first of these varieties is estimated at less than 25% (Falck-Zepeda et al., 2000).

Diet, Nutrition, and Health Benefits

rDNA biotechnology has the potential to improve the nutritional status of populations throughout the world. Both developed and developing societies can benefit from rDNA biotechnology-derived plants that will provide increased quantities of foods, as well as foods with unique and more-effective nutritional composition and qualities that will satisfy the individual needs of different populations.

There are many types of malnutrition, but all can be traced to two major sources, the lack of proper quantity and quality of foods. rDNA biotechnology offers unique opportunities to increase the quantity of food that is available in developing countries. In both developing and developed countries, rDNA biotechnology can also improve the nutritional quality of foods. Specific foods can be developed to correct malnutrition problems that are unique to different regions of the world. As discussed above, plants can be modified to grow well in areas of low production potential. They also can be modified to provide increased and more-stable quantities of essential amino acids, vitamins, or desirable fatty acids. For example, deficiencies of vitamin A and iron are serious, life-threatening health problems in many regions of the developing world. Vitamin A deficiency can increase susceptibility to infections and cause blindness. An inadequate consumption of iron results in anemia. According to the World Health Organization, vitamin A deficiency affects approximately one quarter of a billion children, with child death rates as high as one out of four in some regions of the world. Iron deficiency affects 3.7 billion people (Gura, 1999). rDNA biotechnology-derived golden rice with increased content of beta-carotene, the precursor to vitamin A, is under development, and foods with enhanced iron content are also in the research pipeline.

Other regions of the world suffer malnutrition because their dietary sources of protein are inadequate. Because diets provide an inadequate source of protein, children suffer from stunted growth, increased susceptibility to infections, and impaired intellectual development. Approximately 195 million children worldwide are so affected. Through the use of rDNA biotechnology, the essential amino acids content of cereal grains such as corn and rice can potentially be increased to improve both the protein quality and quantity, thereby eliminating this form of malnutrition (Larkins, 1999). Similar efforts to improve protein content and quality through conventional methods have met with only limited success.

Research is being conducted to produce plants with altered nutrient composition, such as increased fiber content, to produce oils that have better nutritional quality and stability, and to enhance components that may be useful in reducing the incidence of several cancers and other chronic diseases (USDA/ERS, 1999). As the science of nutrition improves and develops our understanding of the relationships between genetics, diet, and degenerative diseases, recommendations for dietary consumption practices will also change. In addition to classical nutrients, other plant components (i.e., phytochemicals), are now recognized for their contributions to improved health and the prevention of some degenerative diseases. It will also be important to provide foods of appropriate composition to achieve maximum benefits.

Scientists predict that in the near future rDNA biotechnology-derived foods with improved levels of phytochemicals and micronutrients will be developed. Some have predicted that these and other products will be well received by health-conscious consumers, who spend more than $6 billion annually on over-the-counter food supplements.

Probiotics are living microorganisms, typically delivered through foods, that offer benefits to health and well-being that are beyond basic nutrition, such as increased resistance to food-borne illness, decreased risk of some cancers, and potential lowering of blood cholesterol (Sanders, 1999). Selected members within the *Lactobacillus* and *Bifidobacterium* genera are considered key probiotic species as they are able to survive stomach and intestinal

Biotechnology Report: Benefits

CONTINUED

transit, exert health benefits (e.g., stimulation of the mucosal immune system), and favorably affect the microbial ecosystem. rDNA biotechnology and genomics are expected to play an important role in identifying the probiotic strains that are capable of eliciting certain health benefits.

rDNA biotechnology also offers the opportunity to decrease or eliminate the allergenic proteins that occur naturally in specific foods. For example, rDNA biotechnology has already been used to dramatically reduce the levels of the major rice allergen (Matsuda et al., 1993). Similar approaches could be attempted with more commonly allergenic foods such as peanuts.

Medical Benefits

Plants have been a valuable source of pharmaceuticals for centuries. During the past decade, however, intensive research has focused on expanding this source through rDNA biotechnology. The research brings closer to reality the prospect of commercial production in plants of edible vaccines and therapeutics for preventing and treating animal and human diseases. Possibilities include a wide variety of compounds, ranging from vaccine antigens against hepatitis B and Norwalk viruses (Arntzen, 1997; Dixon and Arntzen, 1997; Mason et al., 1992, 1998) and *Pseudomonas aeruginosa* and *Staphylococcus aureus* (Brennan et al., 1999) to vaccines against cancer and diabetes. In addition, genetically modified strains of probiotic microorganisms are also possible vehicles for successful delivery of vaccines and digestive aids (e.g., lactase) through the stomach and the small intestine.

Two seminal papers supported the use of rDNA biotechnology-derived plants for pharmaceutical production (Ma et al., 1995, 1997). These reports were soon followed by one (Ma et al., 1998) describing results of successful human clinical trials with an edible vaccine against a pathogenic strain of *E. coli* and a monoclonal antibody against cariogenic *Streptococcus mutans*. Haq et al. (1995) reported the expression in potato plants of a vaccine against *E. coli* enterotoxin that provided an immune response against the toxin in mice. Human clinical trials suggest that oral vaccination against either of the closely related enterotoxins of *Vibrio cholerae* and *E. coli* induces production of antibodies that can neutralize the respective toxins by preventing them from binding to gut cells. Ma et al. (1995, 1998) showed that tobacco plants could express secretory antibodies or "plantibodies" against the cell surface adhesion protein of *S. mutans*. Used as a bactericidal mouthwash, the antibodies prevented bacterial colonization by the microorganism and development of dental caries for four months.

A similar approach showed that soybean-produced antibodies protected mice against infection by genital herpes (Zeitlin et al., 1998). Compared to antibodies produced in mammalian cell culture, the plantibodies had similar physical properties, remained stable in human reproductive fluids, and exhibited no differences in their affinity for binding and neutralizing herpes simplex virus. Hence, the difference in the glycosylation processes of plants and animals does not appear to affect the immune functions of the plant-derived antibodies.

Non-Hodgkins B-cell lymphoma, the most widespread cancer of the lymph system, is difficult to treat because the B-cell tumors are variable and response to treatment can vary from person to person. Hence, effective therapy requires "personalized medicine" tailored to the genetic makeup of each patient's tumor. Unfortunately, conventional treatment methods do not meet the needs for rapid production of customized antibodies in sufficient quantities. Monoclonal antibodies used in conventional treatment also tend to be expensive and unreliable, and those produced in bacteria have solubility and conformation problems.

A system using tobacco mosaic virus (TMV) was developed to produce in tobacco plants *(Nicotiana benthamiana)* a therapeutic vaccine against non-Hodgkin's B-cell lymphoma in a mouse model (McCormick et al., 1999). Using cells cloned from malignant B-cells of mice, TMV DNA was modified with a tumor-specific sequence from the gene coding for the immunoglobin cell surface marker. Plants were then infected with the modified virus, resulting in expression of cancer-specific antibodies. B-cell proteins were then extracted from the plant leaves for vaccination of the mice. Eighty percent of the mice receiving the plant-derived vaccine survived the lymphoma, while all untreated mice died within three weeks of contracting the disease.

A similar approach was used to develop a vaccine against insulin-dependent diabetes mellitus (IDDM), an auto-immune disease in which insulin-producing cells of the pancreas are destroyed by the cytotoxic T lymphocytes. The "oral tolerance" method of preventing or delaying autoimmune disease symptoms involves the ingestion of large amounts of immunogenic proteins that turn off the autoimmune response. This method of vaccination is gaining recognition as a potential alternative to systemic drug therapy, which is often ineffective. Insulin and pancreatic glutamic acid decarboxylase (GAD), which are linked to the onset of IDDM, are candidates for use as oral vaccines. Blanas et al. (1996) described the development in a mouse model of a potato-based insulin vaccine that is almost 100 times more powerful than the existing vaccine in preventing IDDM. Feeding diabetes-prone mice potatoes engineered to produce immunogenic GAD reduced the incidence of disease and immune response severity.

rDNA biotechnology-derived vaccines are potentially cheap, convenient to distribute, and simple and safe to administer. Production of medically important substances via rDNA biotechnology engineering of plants and microorganisms offers multiple advantages. For plants, production can be done virtually anywhere and has the potential to address problems associated with delivery of vaccines to people in developing countries. Products from these alternative sources do not require a so-called "cold chain" of refrigerated transport and storage, although they will require segregation from conventional foods to prevent inappropriate consumption. Pharmaceuticals or therapeutics produced via genetic engineering of plants also offer an alternative delivery method, feeding versus injection (Howard, 1999), and an alternative to extraction from animal sources. Furthermore, rDNA biotechnology-derived vaccines may also be safer than many conventional vaccines because they consist of pathogen or antibody subunits rather than whole microorganisms. The use of plants can facilitate abundant production of therapeutic proteins without the risk of contamination by animal pathogens, and at substantially reduced cost.

Food Safety Improvements

Preliminary studies have shown the potential for food safety benefits from rDNA biotechnology-derived foods and food ingredients. For example, preliminary studies have shown that Bt corn had levels of fumonisin, a potential cancer-causing agent often found at elevated levels in insect-damaged kernels, that were up to 30- to 40-fold lower than in non-Bt corn varieties (Dowd et al., 1999). Mycotoxins like fumonisin are both a public health issue and an export issue, as European and Asian markets have refused to import U.S. corn because of what they view as unacceptable levels of mycotoxins.

The actual amount of reduction of fumonisin appears to depend on environmental conditions and the specific Bt corn hybrid, but those corn varieties in which the Bt protein is expressed throughout the plant rather than only in specific areas had the lowest fumonisin levels. Bt corn is modified primarily to resist European corn borers, but it also showed lower mycotoxin levels when corn earworms were present in growing fields. However, the mycotoxin reduction was not as significant as when the primary insect pest was the European corn borer. This preliminary result may lead to the creation of corn varieties with greater resistance to a variety of insects, leading to greater protection from mycotoxins.

Evaluation of Concerns

Changes to our foods have always produced public concerns. This was the case for hybrid corn, margarine, artificial insemination of farm animals, pasteurization of milk, and microwave cooking, and is the case for rDNA biotechnology-derived foods. The transition from traditional plant breeding to rDNA biotechnology-derived crops has raised several issues that need to be addressed. Upon examination, many of these issues turn out to be without merit.

Economic and Access Concerns

• Public Sector Access. Some critics contend that the increasing role of the private sector in research and aggressive patenting of genes and research resources (materials and techniques) is limiting the access to the necessary materials and processes for pioneering research in the public sector. To examine this issue, the National Research Council convened a workshop in 1996 (NRC, 1997), and another in 1999 with the National Academy of Sciences (NRC, 1999). The National Agricultural Biotechnology Council also explored the issue during an annual meeting (NABC, 1995).

A key issue is the scope of patents granted on genes and genetic information as well as on transformation tools and other platform technologies. If concentrated private-sector control of critical genes and technologies becomes a problem, appropriate policy responses include reducing the scope of patents on genes and platform technologies, including obligatory licensing requirements in patent awards, and increasing public-sector funding of basic research to increase the amount of plant genetic information and rDNA biotechnology information in the public domain. One significant industry response to this concern is one firm's decision to make its extensive rice genome data available to the public for research purposes. In addition, one major biotechnology company recently announced that it will grant patent licenses without charge for the introduction of an rDNA biotechnology-derived crop that will have significant health and nutrition benefits in developing countries (golden rice).

Access to rDNA biotechnology is needed to help meet the need for increasing the world food supply and improving the quality of foods in developing countries (Gilmore, 2000; Pinstrup-Anderson and Pandya-Lorch, 1999). Some believe that a strong public-sector agricultural research effort is necessary to provide the benefits of plant rDNA biotechnology to the world's poorest people (Conway and Toenniessen, 1999). The agribusiness input industry will need to find ways to donate technology for use in these poor parts of the world where there are few opportunities for commercial returns. There are organizations that seek to facilitate such transfers, such as the U.S. Agency for International Development (USAID). There is also need for increased funding of rDNA biotechnology research at international crop research centers that are part of the Consultative Group on International Agricultural Research (CGIAR) system.

The seven academies of sciences (NAS, 2000) stated that it is imperative that (1) public funding of research is maintained at least at its present level in both CGIAR and national research institutions; (2) governments, international organizations and aid agencies should acknowledge that plant research is a legitimate and important object for public funding and that the results of such research should be placed in the public domain; and (3) innovative and vigorous forms of public/private collaboration are urgently required if the benefits of rDNA biotechnology are to be brought to all the world's people.

• Agribusiness Consolidation and Competition. As noted above, certain segments of the commercial seed markets have already become highly concentrated. Even in highly concentrated markets, abuses of market power by dominant firms can be restrained by both actual and potential competition. If competing firms can easily enter profitable markets, dominant firms will be prevented from charging exorbitant prices. There are at least four or five large agricultural and life science companies that are aggressively competing for market share in the corn, soybean, oilseed, and vegetable seed markets. In addition to the two dominant firms referred to above, one company has expanded its corn and soybean seed sales in the North American market and has realized strong sales growth for vegetable and horticultural seeds. Yet another company is actively marketing herbicide-tolerant corn and canola seed and has recently established itself as a strong competitor in the vegetable seed market with the acquisition of two smaller companies. In addition, a new joint venture has been formed for development of advanced cottonseed, and another joint venture is competing in the maize, cotton, and oilseed markets.

To its proponents, continued advances in rDNA biotechnology will be needed to feed a growing world population in an environmentally sustainable manner. For example, the further development and application of rDNA biotechnology to agriculture will lead to improved efficiencies in food production. Strong intellectual property rights are defended as a prerequisite for the private-sector investment needed to realize these potential benefits. Yet some consumer and environmental advocacy groups are concerned that widespread adoption of rDNA biotechnology-derived crop varieties will leave farmers increasingly vulnerable to increases in

Biotechnology Report: Benefits

CONTINUED

farm input prices and create unknown risks to the environment and public health. These critics also have concerns about the continuing decline of the small family farmer and the further industrialization of farming.

Critics of rDNA biotechnology contend that the combination of strong patent rights for rDNA biotechnology-derived crop varieties as well as technological constraints on seed reproduction (e.g., sterility genes) could eventually provide major firms with sufficient market power to charge monopoly prices. But the appropriate public-sector response to potential abuses of market power by agricultural biotechnology companies is not to constrain the use of rDNA biotechnology in agriculture, but rather to maintain a vigilant antitrust policy. The potential for restricted competition did, in fact, become an issue in one recent acquisition, where the U.S. Department of Justice (DOJ) required the acquiring firm to enter into binding commitments to license corn germplasm developed by the acquired firm to 150 other seed companies (DOJ, 1998). Antitrust concerns raised by DOJ derailed another planned acquisition (Monsanto, 1999).

To the degree that direct gene transfer may eventually enable crop breeders to incorporate elite traits into even relatively inferior germplasm, advances in rDNA biotechnology breeding techniques could facilitate the entrance of new competitors into profitable seed markets. However, to promote this type of innovative competition, it will be necessary to maintain widespread access both to the technologies necessary for gene transfer as well as to specific genes that code for important agronomic traits. Access to rDNA biotechnology was in fact an issue raised by DOJ in its review of the acquisition discussed above. As a result, the acquiring firm agreed to spin-off its claims to the *Agrobacterium* method for genetic transformation of corn (DOJ, 1998). As agricultural biotechnology companies continue to increase their investments in genomic research, the requirements for, and scope of, patents granted for genetic information will become an increasingly important policy issue.

From the perspective of economic theory, patent rights should be defined to maximize benefits derived from increased inventive activity net of any costs resulting from monopoly control of new inventions. In 1985, the Board of Appeals and Interferences of the U.S. Patent and Trademark Office (PTO) ruled in *Ex parte Hibberd* that patents could be issued for inventions relating to any plant, plant seeds, and plant genes (Fuglie et al., 1996). This ruling was followed by a significant and continuing increase in the number of utility patents granted by the PTO for inventions involving plants (Artuso, 2000). A similar relationship can be seen between the approval in 1994 of amendments to the U.S. Plant Variety Protection Act, which strengthened plant breeders' rights, and the subsequent increase in the number of applications for Plant Variety Protection Certificates (PVPCs) submitted each year to USDA (Artuso, 2000). Although plant utility patents and PVPCs are imperfect measures of innovation in crop breeding, these trends do suggest that there is a close relationship between intellectual property rights and inventive activity by private-sector plant breeders. But the benefits and costs of expanded patent rights need to be evaluated from a long-term perspective, taking into account that subsequent inventive activity will be dependent on the scope of intellectual property rights previously awarded. If patents for rDNA biotechnology and genetic information are defined too broadly, this could inhibit future research and development activities.

• Research Incentives. Fruits and vegetables are considered important for a healthy diet. Most rDNA biotechnology-derived crops commercialized and in the pipeline are considered major crops, e.g., cotton, corn, soybeans, wheat, potatoes, rice, canola, sunflowers, peanuts, sugar beets, and sugarcane (Thayer, 1999). Because the development, testing, and commercialization of rDNA biotechnology-derived minor crops (e.g., fruits and vegetables) are often not economically feasible for private-sector firms, the predominant source of rDNA biotechnology-derived minor crops will be the public sector, as it was for virus-resistant papaya. There is a need for public research funds, as well as access to genes and tools for research and commercialization of rDNA biotechnology-derived minor plants.

It is possible that agricultural biotechnology companies will focus on crops and trait improvements that are expected to generate relatively high profits, while ignoring other research opportunities for which societal benefits may be substantial but not easily appropriated (Byerlee, 1996; Pray and Umali-Deininger, 1998). While this potential problem is not unique to rDNA biotechnology-derived crop research, it could become more pronounced as the cost of research, development, and regulatory review of rDNA biotechnology-derived varieties increases. One response to this problem is to reorient public funding for crop breeding to minor crops and crop traits in which there is perceived to be under-investment by the private sector.

An alternative, although not mutually exclusive, policy option is to provide a set of incentives to increase private-sector research on crops and traits perceived to have high public benefits. The Orphan Drug Act of 1983 provides a case study of a set of targeted research incentives applied to the pharmaceutical sector. The Act provided tax credits, research grants, regulatory assistance, and seven years of exclusive marketing rights to developers of drugs for diseases that afflict fewer than 200,000 people in the U.S. or otherwise would have limited commercial potential. One study found that the Act has been relatively effective in providing incentives for drug development efforts that would not have occurred without this support (Shulman et al., 1992).

To date, there have been no systematic studies of the costs of developing new crop varieties using rDNA biotechnology. This is a stark contrast to the situation in the pharmaceutical sector, where the cost of developing a new drug is the focus of continual research and policy analysis. Like pharmaceutical product development, crop breeding requires lengthy and repeated trials of potential new products. Regulatory review of rDNA biotechnology-derived crop varieties also requires closely monitored field trials, environmental assessment, and food safety analyses. There remains considerable debate over whether these regulatory processes are excessive or too lenient, but it is difficult to evaluate the merits of alternative regulatory approaches in the absence of information

about how these changes might affect the cost and time required to develop new crop varieties. Indeed, improved information regarding both conventional and rDNA biotechnology-derived crop breeding costs would be a substantial benefit to the development of appropriate regulatory, antitrust, and patent policies for rDNA biotechnology.

Environmental Concerns

• General. Environmental concerns have been raised about the impact of pest and disease resistance and herbicide-tolerant plants. All of the new products are carefully tested for safety to mammals and other animal and microbial life. Soil persistence and the likelihood of subsoil water and stream contamination are taken into account by the Environmental Protection Agency (EPA) in deciding whether to register the products for use. Scientists performing these tests and regulators together design testing programs most appropriate for the new products using the most current scientific knowledge and procedures, as it is very important for all agricultural chemicals to be properly regulated and monitored.

• Pest and Disease Resistance. Corn and potato plants have both been successfully transformed with genes from various strains of the soil bacterium *B. thuringiensis*. These genes encode toxic proteins with specific effects on certain groups of insects. The pollen of Bt plants was reported to be toxic to the larvae of monarch butterflies feeding on the leaves of milkweed plants (Hansen Jesse and Obrycki, 2000; Losey et al., 1999). The Losey et al. (1999) laboratory study was flawed because it did not include a standard dose response, nor quantification of the amount of Bt pollen used. In spite of these serious limitations, almost all print media featured highly critical front-page stories that Bt corn pollen was killing monarch butterfly larvae. The Hansen Jesse and Obrycki (2000) study exposed butterfly larvae to pollen in a laboratory, rather than a field, setting. Other studies, however, have shown that in or close to cornfields the concentration of pollen grains found on milkweed plant leaves is, for the most part, well below the threshold level that has any effect on monarch butterfly larval growth or viability (Sears, 2000).

Field studies at multiple locations—Maryland, Iowa, Nebraska, and Ontario—found that a lethal dose of Bt pollen spreads only a few feet from its source, not the hundreds of feet reported earlier, and there is little overlap between time of corn pollen shedding and monarch larvae feeding on milkweed leaves (ESA, 1999; Nüler, 1999). Furthermore, at the time of approval of Bt crops in 1995 and 1996, EPA required applicants to provide information on effects on non-target organisms and beneficials, e.g., monarchs, lacewings, honey bees, and parasitic wasps. Little effect was noted. EPA considered the effect of Bt crops on non-target organisms, including such insects as monarch butterflies, and concluded that there was no greater effect on them than with insecticide use. EPA's recent suggestion that farmers locate the required 20% corn refuge areas around the perimeter of the fields, coupled with the limited movement of corn pollen, would virtually eliminate any remaining risk of Bt pollen to monarch butterfly larvae.

Pimentel and Raven (2000) assessed the overall picture of the effect on the survival of butterfly populations of Bt corn pollen dusting their larval food plants, and concluded that although Bt corn pollen under certain circumstances has the potential to adversely affect the population levels of Monarch butterflies and other nontarget Lepidoptera, these impacts are minimal compared with habitat loss and the widespread use of pesticides throughout the ecosystem. Reporting on experiments on the effect of Bt corn on populations of black swallowtail larvae under field conditions, Wraight et al. (2000) concluded that there was no relationship between mortality and proximity to the field or pollen deposition on host plants. They determined that pollen from these same plants failed to cause mortality in the laboratory at the highest pollen dose tested, a level that far exceeded the highest pollen density observed in the field, and concluded that Bt pollen of the variety tested is unlikely to affect wild populations of black swallowtails.

Studies to examine the breakdown of Bt toxin present in debris from corn and other crops with the Bt transgene indicated that the Bt toxin is rapidly broken down by microbial activity (Sims and Ream, 1997) and that it has no detectable effects on a range of soil organisms that were tested (Sanders et al., 1998). However, Crecchio and Stotzky (1998) suggested that Bt toxin could persist in the soil bound to humic acids and clay, where it may pose a hazard to non-target insects and enhance the selection of toxin-resistant target species. A recent rigorous assessment carried out by EPA, however, concluded that plants registered for environmental release that express Bt toxins derived by rDNA biotechnology do not cause unreasonable adverse effects (EPA, 2000). Since *B. thuringiensis* is widely used in organic pesticides and is a common soil organism, the exposure of other soil organisms to its toxin is hardly novel.

Resistance to all methods of pest control has been and continues to be a major problem in agriculture. For the first time in the case of rDNA biotechnology-derived products, government, industry, and farmers are trying to manage the use of Bt corn to extend its useful life. Since the widespread use of rDNA biotechnology-derived Bt is likely to shorten its useful life and that of Bt used as an insecticidal spray, refuges that contain non-rDNA biotechnology-derived crop plants to reduce the selection pressure on target insects (Peck et al., 1999) are being employed to delay the accumulation of resistant forms. It is too soon to know how effective this strategy will be. Another approach is to use plant chloroplast-encoded Bt transgenes. The levels of expression of the Bt toxin can be 20,000– to 40,000-fold higher via chloroplast gene expression than nuclear rDNA biotechnology-derived plants (Kota et al., 1999). These high levels are lethal to resistant insect larvae that can grow on sprayed plants but may be so high as to present other hazards in residues from crop debris.

• Transgene Spread by Pollen. There is a concern that the genes for herbicide tolerance may spread via pollen from rDNA biotechnology-derived crops to other native plants. It is theorized that these genes might become established in weed populations, creating forms that would be difficult to control in the future. For soybean, corn, and most other crops in the U.S., this outcome is unlikely because of the absence of related wild species that are either already weeds or have the potential to become weeds.

For those crops that are themselves of weed origin, this problem is a more serious issue. For example, hybrid sugar beet normally takes two years to flower. Its roots are harvested near the end of the first year of growth before flowering. Plants that flower prematurely, or bolt,

Biotechnology Report: Benefits CONTINUED

produce seeds that contaminate the field and give rise to non-hybrid, lower-yielding plants in subsequent crops. In Europe, where bolting is sometimes a problem, a tractor-drawn wick, held above the leaves and soaked with an herbicide, is used to selectively kill the taller-flowering sugar beet plants, which contact the wick. Herbicide-tolerant bolters will reduce the choice of herbicides that can be used in this way. In some rice-growing regions, red rice is a weed in rice paddies. Because it readily hybridizes with cultivated rice, it would be very unwise to use herbicide-tolerant rice in such regions, since the red rice population would rapidly acquire herbicide tolerance, denying rice farmers a tool for controlling it. It is also generally regarded as unwise to produce herbicide-tolerant sorghum for use in the U.S. because of the likelihood of outcrossing to Johnson grass (Arriola and Ellstrand, 1997), which is a particularly difficult weed to control in agriculture.

In Canada, volunteer canola plants that arise from spilled seed from the previous season's crop can be a problem for subsequent crops of canola and other species. Canola resistant to three commonly used herbicides have arisen in Alberta, Canada, from intercrossing among two adjacent crops that gave rise to doubly resistant volunteers that, in the following year, crossed with a nearby crop tolerant to the third herbicide (MacArthur, 2000). Farmers usually seed a cereal crop after canola and apply a phenoxy herbicide to kill canola volunteers. If the treatment is done properly, the herbicide-resistant volunteers will be eliminated. Although the triply resistant forms can be controlled by other herbicides, such as 2-4 D, their origin points to a failure to manage the release of the original varieties in a way that will safeguard their continued usefulness in agriculture. In short, growing adjacent crops with different transgenes that are better kept apart is not prudent.

A relatively new technology introduces transgenes, such as those for herbicide tolerance, in the DNA carried by plant chloroplasts (Maliga et al., 1994; Zoubenko et al., 1994). Chloroplasts usually are not carried in pollen grains, so the spread of these transgenes is limited to the seeds produced by the rDNA biotechnology-derived plant. This technology shows promise in restricting the spread of transgenes (Daniell et al., 1998). Chloroplast transformation is technically more difficult to carry out than nuclear transformation, so rDNA biotechnology-derived crops produced in this way are not yet commercially available.

Herbicide tolerance that has spread to weeds is very unlikely to be a problem in the absence of selective pressure from herbicide application and is thus unlikely to be a threat that extends beyond agriculture and cultivation (Duke, 1998).

There is some concern that transfer of genes like Bt to related wild species by out-crossing could increase their competitiveness and lead either to enhanced weediness or to undesirable changes in the wild population. In parts of Mexico, corn and teosinte freely intercross in farmers' fields. If insect damage exercises significant control of the teosinte population, there could be strong selection for resistance with undesirable consequences for those farmers. However, conventional breeding for insect resistance in corn has not engendered similar concerns.

• Organic Crops. The organic farming community has decided at this time not to use rDNA biotechnology-derived crops. Thus, if an organic crop, grown for its harvested seed, is planted near an rDNA biotechnology-derived crop of the same species, it is likely that some seeds will result from fertilization by pollen carrying a nuclear transgene. With the sensitive DNA detection techniques that are now available, if the transgene signature is detected, it could invalidate the crop's organic certification. Chloroplast-encoded transgenes will avoid this problem, but so will observing reasonable isolation distances between crops. These isolation distances are used to ensure the genetic purity of named conventional crop varieties grown for seed. The purity of organic crops is addressed in the *Labeling* section of this report.

• Virus Resistance. The ability to confer viral resistance by using transgenes that incorporate a part of the viral genome, such as a gene encoding the viral coat protein, or a gene responsible for organizing the movement of virus particles from cell to cell through the minute pores (plasmodesmata) that connect them, has had a dramatic impact on several crops. For example, in Hawaii the papaya industry was devastated by ring-spot virus, which has now been successfully controlled by planting rDNA biotechnology-derived papaya with a gene encoding the viral coat protein (Gonsalves, 1998). The viral coat protein gene is used because, above a certain concentration, in or on the plant, the viral coat protein inhibits further growth of the virus. Presumably, this trait evolved so that the virus did not kill its host too promptly.

In the U.S., squash plants resistant to the aphid-borne zucchini yellows virus have been developed and provide effective control (Fuchs et al., 1998). This example has been criticized on the grounds that tests which found that native populations of wild squash relatives (cucurbits) did not harbor the virus and therefore are unlikely to be controlled by it, were on too small a scale. Others have pointed to examples where multipartite viruses may be reassembled by crossing different rDNA biotechnology-derived parents that carry the separate components. It can be theorized that recombination in an rDNA biotechnology-derived host plant between a systemically expressed viral component and the genome of another, randomly infecting virus might result in a new form that could create a serious problem. While conceivable, opportunities of this kind occur all the time when plants become naturally infected with more than one kind of virus.

Recombination between a virally derived transgene and another virus has been suggested as a possible source of a new virus with enhanced virulence. Such recombination has been shown in laboratory studies, especially with high selection pressure (Matthews, 1991). A recent NRC committee concluded that "most virus derived resistance genes are unlikely to present unusual or unmanageable problems that differ from those associated with traditional plant breeding for resistance" (NRC, 2000).

The S35 promoter from cauliflower mosaic virus (CaMV) is used in almost all commercialized rDNA biotechnology-derived crops. A recent, much-publicized article (Hodgson, 2000) suggests that the CaMV35S promoter will cause large-scale genomic rearrangement, with the extreme suggestion that it could cause cancer. Scientists knowl-

edgeable about CaMV35S note that about 10% of the cauliflower and cabbage produced are infected with CaMV, thereby providing 10,000 times greater 35S promoter in the diet than in rDNA biotechnology-derived crops. No evidence of 35S promoter transfer has been observed, in spite of human consumption of CaMV35 in cauliflower and cabbage throughout history.

• Monoculture and rDNA Biotechnology. Conventional plant breeding and improvements in agronomy have helped farmers to maximize yields and profits (Silvey, 1994). Yield trials of the crop varieties available usually reveal one—or a few that are very similar—that is best for an agricultural region. The dense, uniform crop stands that cover very large areas are an invitation to epidemic pests and diseases that are kept in check by breeding for resistance and by pesticide applications. The Southern corn leaf blight epidemic of 1969–70 revealed the inherent weakness of a crop whose hybrid seed production depended on cytoplasmic male sterility to avoid removing the pollen-bearing tassels (NRC, 1972). The resultant high degree of cytoplasmic uniformity among North American corn hybrids made them acutely susceptible to a strain of a fungal pathogen that devastated about 15% of the corn crop in the U.S. However, the availability of alternative genetic varieties limited this problem to a single year.

A similar level of dependence on a particular transgene could easily arise, as has been shown by the very rapid adoption in the U.S. of herbicide-tolerant soybean and insect-resistant corn. Even though the risk is probably not high, it would be prudent to adopt the same strategy advocated following the Southern corn leaf blight, which was to diversify the germplasm. This is to make sure that there is adequate backup capability that can provide alternative varieties in the event of catastrophic failure. The best way of doing this is still to safeguard germplasm collections and to encourage a broad spectrum of plant breeding activities.

Monitoring Concerns

• Food Safety Monitoring. The initial safety evaluation of rDNA biotechnology-derived foods addresses both short-term and long-term potential food safety issues. The issue of long-term human food safety was considered by a recent consultation of the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO). The consultation concluded that the possibility of long-term effects being specifically attributable to genetically modified foods is highly unlikely (FAO/WHO, 2000):

> In considering the issue, the consultation noted that very little is known about the potential of long term effects of any foods. In many cases, this is further confounded by wide genetic variability in the population, such that some individuals may have a greater disposition to food-related effects. In this context, the consultation acknowledged that for genetically modified foods, the premarketing safety assessment already gives assurance that the food is as safe as its conventional counterpart. Furthermore, it was recognized that observational epidemiological studies would be unlikely to identify any such effects against the background of undesirable effects of conventional foods.

• Environmental Monitoring. Genetic modification of plants through plant breeding is well established as a major contributor to increased yield and value addition to our food and feed supply. Plant breeding is conducted in both the public and private sector, with the private sector in recent years dominating the major crops, e.g., corn, cotton, sorghum, and soybeans. Extensive field testing involving multiple sites and several years typically occurs before seed multiplication and release of a commercial seed product. Most states test and release public varieties in a tracked process that produces certified seed. Most states also provide public testing in a fee-based evaluation at a few sites. Private-sector seeds are sometimes submitted for public testing, but usually undergo similar field evaluations and, in the case of large seed companies, may be tested at hundreds of sites.

The ultimate test in all cases is in commercial farmers' fields. Almost all farmers monitor their crops from planting to harvest by regular field examinations. This key monitoring activity is done by the growers or, in the case of large acreage, may be performed by hired consultants or scouts. Consultants or scouts are frequently used for cotton but are less common for soybeans. This "on-the-farm" monitoring follows emergence, growth, nutrient limitations, flowering, fruit set, maturation, insect pests, disease, weed control, and other key events. Finally, the yield for each crop in each field is measured at harvest. The experience of the farmer or consultant for specific crops in specific locations represents a baseline. In addition to the farmers and consultants, there are also extension agents and industry representatives who do a modest amount of monitoring.

Monitoring by the farmer or hired consultant has proven to be effective and serves as the first alert for untoward effects. For example, farmers were the first to identify herbicide-tolerant weeds, e.g., atrazine-resistant pigweed in Ontario in the 1950s to 1960s. Untoward environmental or performance effects of rDNA biotechnology-derived seeds—as is the case for traditional seeds—would normally be identified by the farmer or consultant. Examples are the reduced boll set of herbicide-tolerant cotton in the Mississippi delta in the introductory year of this product, as well as periodic herbicide performance problems. Special monitoring by the seed company is required for Bt crops to provide early identification of Bt-resistant insect pests (Anderson, 1999). The farmer and consultant monitors, however, are likely to provide an early alert for actual pest resistance.

The road map for rDNA biotechnology-derived seeds from initial generation through testing and regulatory approval is similar to that for traditional seeds, with additional steps to meet regulatory requirements. To date, almost all the commercialized rDNA biotechnology-derived seeds have been developed by the private sector, with four large firms as the primary technology developers. From several hundred up to a thousand transformants with the desired gene or trait, one or a few are selected for development. The selected transformants are evaluated for efficacy in standard (e.g., Crocker 305 in the case of cotton) and other genetic backgrounds, agronomic characteristics (e.g., maturity, vigor, standability), and genetics (e.g., single gene, stability, purity). Equivalency testing is performed at multiple locations by the seed company. In addition, the rDNA biotechnology-derived seed is analyzed to pro-

Biotechnology Report: Benefits

CONTINUED

vide data for regulatory review.

Questions remain as to long-term effects on organisms (e.g., birds, plants, animals) and microorganisms in the environment. These questions are the same as those that need to be raised for introducing any new types of plants or even new varieties of an established plant. Hypothetical deleterious changes in producing modified foods are possible, as such changes have occasionally occurred in nature and in conventional plant breeding. Such plants rarely make it to the marketplace and, if they do, can be readily removed. With a higher degree of regulatory oversight for all foods derived by rDNA biotechnology, there is less likelihood of adverse reactions to consumers than with conventional foods. rDNA biotechnology will require continued research and management, as well as monitoring and surveillance, to produce high-quality and affordable foods.

Allergenicity Concerns

Food allergies involve abnormal immunological responses to substances in foods, usually naturally occurring proteins. The majority of food allergies are traced to eight commonly allergenic foods or food groups: milk, eggs, fish, crustacea, peanuts, soybeans, tree nuts, and wheat (FAO, 1995), although other sources of genetic material can possess genes encoding for environmental allergens such as pollen allergens. Allergic reactions can be manifested by symptoms ranging from mild cutaneous or gastrointestinal symptoms to life-threatening anaphylactic shock reactions. Virtually all food allergens are proteins, although only a small fraction of the proteins found in nature (and in foods) are allergenic. Since genetic modifications involve the introduction of new genes into the recipient plant and since these genes would produce new proteins in the improved variety, the potential allergenicity of foods developed through rDNA biotechnology has been a source of some concern. (This topic is also discussed in the *Safety* section.)

Despite the concerns, no unique allergic reactions have yet occurred to any of the foods derived through rDNA biotechnology. Of course, a consumer with a soybean allergy is likely to be reactive to an rDNA biotechnology-derived soybean as well. But no new and novel allergens have been introduced into foods through rDNA biotechnology. In fact, the proteins introduced into rDNA biotechnology-derived foods to confer traits such as insect resistance and herbicide tolerance are unlikely to be allergenic because they are expressed at very low levels in the modified food, they have no amino acid sequence homology to known allergens, and they are readily digested (Astwood et al., 1996; Harrison et al., 1996; Metcalfe et al., 1996).

The potential allergenicity of rDNA biotechnology-derived foods can be assessed using a decision-tree strategy developed by the International Food Biotechnology Council (IFBC) and the Allergy and Immunology Institute of the International Life Sciences Institute (ILSI) in 1996 (Metcalfe et al., 1996). The utility of this approach was recently recognized by FAO/WHO (2000). This strategy focuses on specific scientific criteria, including the source of the gene(s), the sequence homology of the newly introduced protein(s) to known allergens, the immunochemical reactivity of the newly introduced protein(s) with immunoglobulin E (IgE) antibodies from the blood serum of individuals with known allergies to the source from which the genetic material was obtained, and the physicochemical properties (e.g., digestive stability) of the introduced protein (see discussion in the *Safety* section).

If genes are obtained from known allergenic sources, the possibility of the transfer of a known allergen must be carefully examined. The potential hazards are illustrated by the case of a soybean variety constructed to correct the inherent methionine deficiency existing in soybeans. A high-methionine protein was introduced into soybeans by one firm using a gene from Brazil nuts. Brazil nuts are known to be allergenic, but, at the time of this development, the allergens from Brazil nuts had not been identified. The high-methionine protein from Brazil nuts was identified as the major allergen in research sponsored by that firm (Nordlee et al., 1996). As a result, commercial development of that particular soybean variety ceased.

Antibiotic Resistance Transfer

Genetic transformation of plant cells is an inherently infrequent event. The challenge that the researcher faces is to identify the few cells that have integrated the introduced DNA from a large population of non-transgenic cells. This is most often done by introducing a selectable marker that permits growth of only cells containing the newly introduced DNA. In plant transformation, a gene for resistance to the antibiotic kanamycin dominated early rDNA biotechnology-derived crops (see the *Safety* section for additional information).

Concerns have been raised about the potential for horizontal gene transfer of the antibiotic resistance gene from an rDNA biotechnology-derived plant to microorganisms, thereby reducing the efficacy of the antibiotic. However, both scientists and most regulators around the world generally believe that this risk is virtually nonexistent. The conclusion derives from a number of facts. First, the marker gene has been altered to express in plant cells. Even though, as discussed in the *Introduction* section, genes are not unique to specific organisms, the controlling elements that permit gene expression are very different in plants and microorganisms. One would not expect that a gene engineered to work optimally in plant cells would work effectively in bacteria. Second, the antibiotic-resistance genes are stable when integrated into plant DNA. Plant DNA, upon exposure to the gastrointestinal environment, would be rapidly hydrolyzed to small, nonfunctional pieces long before it came into contact with microflora. Third, DNA uptake into bacteria is an extremely inefficient process requiring either transformation competence or specific DNA transfer mechanisms employed between bacteria. There are no known mechanisms for transfer of DNA from plant cells to bacteria, and the bacteria in the digestive system would not be competent to take up free DNA.

Fourth, even if such mechanisms for DNA uptake were in place, stable integration of that DNA into bacteria requires extensive DNA sequence homology between the incoming DNA and the host chromosome. Such homology would not exist unless bacteria already possessed the antibiotic resistance gene prior to DNA uptake. Fifth, even if such unlikely transfer were to occur, positive selection pressure would be required; e.g., the person would have to be taking

the antibiotic to which the resistance was encoded at the time of such transfer. Finally, there are no authenticated reports of any horizontal DNA transfer occurring from food plants to bacteria within the gastrointestinal tract of humans. Even if this occurred by some unknown mechanism at some vanishingly small frequency, there would be no consequence, because of the existing level of antibiotic resistance already present in gut microflora.

A recent FAO/WHO joint consultation (FAO/WHO, 2000) addressed the concern that there might be transfer of antibiotic resistance from the widely used antibiotic resistance marker genes and concluded that no health risk is presented:

> The Consultation considered horizontal gene transfer from plants and plant products consumed as food to gut microorganisms or human cells as a rare possibility, but noted that it cannot be completely discounted. The most important consideration with respect to horizontal gene transfer is the consequence of a gene being transferred and expressed in transformed cells. The Consultation further noted that the antibiotic resistance markers currently used in genetically modified plants have been previously reviewed for safety. It has concluded that there is no evidence that the markers currently in use pose a health risk to humans or domestic animals.

In addition, non-antibiotic resistance markers have mainly replaced kanamycin in products now in the pipeline. These include removable selectable marker genes such as using the Cre-lox site-specific recombination system or transposable elements. Cre is a recombinase; lox is a 32-base-pair recognition site. Positive selection systems will probably dominate in the future. One system (termed BOGUS) uses an exclusive energy source, cellobiuronic acid, a disaccharide that, when transported into the cell, is metabolized to glucose by beta-glucuronidase. Another example involves the use of phosphomannose isomerase (PMI). Plant cells without this enzyme are unable to survive in a tissue culture medium containing mannose-6-phosphate as a sole carbon source.

Concerns with Naturally Occurring Toxicants

The great majority of food plants, and many animals used for food, produce or carry naturally occurring toxic substances (IFBC, 1990; Liener, 1980; NAS, 1973). The only categories of organisms used as human food that have essentially no or only a very rare content of naturally occurring toxicants are the cereal grains and domestic animals. Even among these, an exception must be made for milk, discussed below. The absence of toxicants from these food sources is entirely due to man's interference with nature—millennia of selective breeding and centuries of careful husbandry have reduced their original toxicant content. Plants, and many animals, produce toxicants for a variety of reasons. Some kill or repel predators, pests, or diseases (Ames et al., 1990a, b). Others are pollenator attractants. Some inhibit competitive species. Others are metabolic "dead ends"— a means for a plant to sequester a plant toxicant it can neither avoid nor excrete (IFBC, 1990). While the vast majority of toxicants occur at levels so low that they carry no threat to human safety, there are more than twenty for which there are well-documented reports of human injury or death from their consumption in or on food (IFBC, 1990).

The largest known number of naturally occurring toxicants are endogenous, or "constitutive"; i.e., they are produced by the normal metabolic processes of the organism that is the food source. An example is solanine, a neurotoxin in potatoes that has been the cause of numerous outbreaks of human poisoning when potatoes were grown under unfavorable conditions or when they formed a large part of the diet. Another example is cyanogenic glycosides, found in several foods such as lima beans and bamboo shoots. In these and other crops, conventional breeding has been used to decrease toxicant levels.

Another group that has received much scientific and regulatory attention is the "acquired" toxicants. These are formed in or on food as the result of naturally occurring processes, which can often be minimized but never eliminated. An example are the mycotoxins, such as the aflatoxins, caused by mold contamination. Aflatoxin B_1, in combination with hepatitis B, is responsible for the very high levels of liver cancer found in the Qidong region of China (Qian et al., 1994; Wang et al., 1999). Susceptibility of plants to mold infections is affected by both genetic and environmental factors.

A third group, only known within the past few decades, is the "derived" toxicants. These occur in food as a result of storage or normal, traditional processing. Examples are the highly mutagenic and carcinogenic polynuclear aromatic amines formed in meats and other foods by conventional roasting, baking, or cooking. Although a risk is clearly present, the size of that risk and the extent of actual human harm, if any, from their consumption are as yet unknown.

A fourth group is the "pass-through" toxicants that occur in food as a result of being acquired by the food organism from its own environment or food supply. The organism that becomes or provides the human food is simply a passive vehicle. Although extremely rare in modern times, the toxicants that occur in milk and honey provide examples of human deaths, among them that of Abraham Lincoln's mother (IFBC, 1990; Liener, 1980; NRC, 1996).

Given the near ubiquity and occasional demonstrated harm from toxicants that are naturally and unavoidably occurring in most traditional food sources, it is entirely rational to take every reasonable precaution to assure that breeding—by either traditional or rDNA biotechnology methods—does not result in an increase in risk and, if possible, decreases any risk.

Other Concerns

L-tryptophan for food and feed use, manufactured by bacterial fermentation, is contaminated by a number of secondary substances. These impurities are removed by treatment with activated carbon and reverse osmosis. A Japanese manufacturer in late 1988 and early 1989 made a number of simultaneous changes in manufacturing, including the use of a genetically engineered organism, *Bacillus amyloliquefaciens*, to increase production of L-tryptophan. At the same time, the purification procedure was altered by eliminating reverse osmosis and reducing the amount of activated carbon used. The illness of 1,500 people and the death of 37 in the U.S. from eosinophilia-myalgia syndrome from consumption of this L-tryptophan has been incorrectly attributed to the rDNA biotechnology-derived organism,

Biotechnology Report: Benefits

CONTINUED

rather than to the failure to perform standard purification to remove impurities. In three lawsuits, there was overwhelming evidence that the rDNA biotechnology-derived organism was not responsible for the illnesses and deaths (Hill et al., 1993; Kilbourne et al., 1996 Philen et al., 1993).

Conclusions

A number of issues have been advanced by some scientists and opponents of rDNA biotechnology-derived foods as major environmental or human health risks. Examination of all the science eliminates or diffuses many of these so-called risks. Other suggested risks are less severe, or no more severe, than those risks associated with the more conventional breeding techniques that have been practiced for centuries. This body of science leads to the conclusion that there is no increased adverse environmental effect inherently attributable to the use of rDNA biotechnology in food production. There is some evidence of overall improved environmental safety due to wider use of rDNA biotechnology. That is not to say that all rDNA biotechnology-derived products will be safe—they must be examined on a case-by-case basis before being commercialized.

Many of the environmental and consumer groups that have been pressing for stronger regulatory controls are also concerned about the effects of market power in the agricultural biotechnology industry. While rigorous testing and evaluation are required for any new item introduced into the food supply, adding unnecessary time-consuming and expensive testing requirements will only increase the pressure for consolidation in the industry, while creating new barriers to entry for small start-up companies. The agricultural biotechnology industry would benefit from a regulatory system that increases consumer confidence in the safety of rDNA biotechnology-derived food products and provides support for claims regarding the health benefits of rDNA biotechnology-derived foods with enhanced nutritional qualities.

Based on its evaluation of currently available scientific information, the Benefits and Concerns Panel concluded that further development and use of food rDNA biotechnology provides a number of benefits:

- A more abundant and economical food supply for the world.
- Continued improvements in nutritional quality, including foods of unique composition for populations whose diets lack essential nutrients.
- Fresh fruits and vegetables with improved shelf life.
- Foods with reduced allergenicity.
- The development of functional foods, vaccines, and similar products that may provide health and medical benefits.
- Further improvements in production agriculture through more efficient production practices and increased yields.
- The conversion of nonproductive toxic soils in developing countries to productive arable land.
- More environmentally friendly agricultural practices through improved pesticides and pesticide usage practices, less hazardous animal wastes, improved utilization of land, and reduced need for ecologically sensitive land such as rain forests.

With regard to a number of environmental and economic concerns about rDNA biotechnology-derived food products, the Benefits and Concerns Panel reached the following conclusions:

- New rDNA biotechnology-derived foods and food products do not inherently present any more serious environmental concerns or unintended toxic properties than those already presented by conventional breeding practices, which have an impressive safety record.
- Appropriate testing by technology developers, producers and processors, regulatory agencies, and others should be continued for new foods and food products derived from all technologies, including rDNA biotechnology.
- Programs should be developed to provide the benefits of safe and economical rDNA biotechnology-derived food products worldwide, including in less-developed countries.

REFERENCES

Ames, B.N., Profet, M., and Gold, L.S. 1990a. Nature's chemicals and synthetic chemicals: Comparative toxicology. Proc. Natl. Acad. Sci. 87: 7782-7786.

Ames, B.N., Profet, M., and Gold, L.S. 1990b. Dietary pesticides (99.99% all natural). Proc. Natl. Acad. Sci. 87: 7777-7781.

Anderson, J.L. 1999. Testimony before the committee on Science, Subcommittee on Basic Research, U.S. House of Representatives, Washington, D.C., Oct. 19. Director, Biopesticides and Pollution Prevention Division, Office of Pesticide Programs, Office of Prevention, Pesticides, and Toxic Substances, Environmental Protection Agency, Washington, D.C.

Arntzen, C.J. 1997. High-tech herbal medicine: Plant-based vaccines. Nature Biotech. 15: 221-222.

Arriola, P.E. and Ellstrand, N.C. 1997. Fitness of interspecific hybrids in the genus Sorghum: Persistence of crop genes in wild populations. Ecological Applics. 7: 512-518.

Artuso, A. 2000. Life science industries: Comparative analysis of market structure, R&D investment and innovation in agricultural biotechnology and pharmaceuticals. Unpublished working paper, Dept. of Agricultural Food and Resource Economics, Rutgers Univ.

Astwood, J.D., Leach, J.N., and Fuchs, R.L. 1996. Stability of food allergens to digestion in vitro. Nature Biotechnol. 14: 1269-1273.

Avery, D. 1997. "Saving Nature's Legacy through Better Farming. Issues in Science and Technology." National Academy of Sciences and the University of Texas, Dallas.

Bhowmik, T. and Steele, J.L. 1994. Cloning, characterization and insertional inactivation of the *Lactobacillus helveticus* D(-) lactate dehydrogenase gene. Appl. Microbiol. Biotechnol. 41: 432-9.

Blanas, E., Carbone, F.R., Allison, J., Miller, J.F.A.P., and Heath, W.R. 1996. Induction of autoimmune diabetes by oral administration of autoantigen. Science 274: 1707-1709.

Bonneau, M. and Laarveld, B. 1999. Biotechnology in animal nutrition, physiology and health. Livestock Production Sci. 59: 223-241.

Bradford, G.E. 1999. Contributions of animal agriculture to meeting global human food demand. Livestock Production Sci. 59: 95-112.

Brennan, F.R., Bellaby, T., Helliwell, S.M., Jones, T.D., Kamstrup, S., Dalsgaard, K., Flock, J.I., and Hamilton, W.D.O. 1999. Chimeric plant virus particles administered nasally or orally induce systemic and mucosal immune responses in mice. Journal of Virology 73: 930-935.

Byerlee, D. 1996. Modern varieties, productivity and sustainability: Recent experience and emerging challenges. World Development 24: 697-718.

Church, D.L. and Kellems, R.O. 1998. High-energy feedstuffs. In "Livestock Feeds and Feeding," 4th ed., pp. 105-134. Prentice Hall, New Jersey.

Conway, G. and Toenniessen, G. 1999. Feeding the world in the twenty-first century. Nature 402 (Suppl.): C55-C58.

Crecchio, C. and Stotzky, G. 1998. Insecticidal activity and biodegradation of the toxin from *Bacillus thuringiensis* subsp. *Kurstaki* bound to humic acids from soil. Soil. Bio. Biochem. 30: 463-470.

Dalsgaard, K., Uttenthal, A., Jones, T.D., Xu, F., Merryweather, A., Hamilton, W.D.O., Langeveld, J.P.M., Boshuizen, R.S., Kamstrup, S., Lomonossoff, G.P., Porta, C., Vela, C., Casal, J.I., Meloen, R.H., and Rodgers, P.B. 1997. Plant-derived vaccine protects target animals against a viral disease. Nature Biotechnol. 15: 248-252.

Daniell, H., Datta, R., Varma, S., Gray, S., and Lee, S.B. 1998. Containment of herbicide resistance through genetic engineering of the chloroplast genome. Nature Biotechnol. 16: 345-348.

De la Fuente, J.M., Ramirez-Rodriguez, V., Cabrera-Ponce, J.L. and Herrera-Estrella, L. 1997. Aluminum

tolerance in transgenic plants by alteration of citrate synthesis. Science 276: 1566-1568.
Delgado, C.L., Courbois, C.C., and Rosegrant, M.L. 1998. Global food demand and the contribution of livestock as we enter the new millennium. Intl. Food Policy Research Inst., Washington, D.C. In press.
Dempsey, D.A., Silva, H., and Klessig, D.F. 1998. Engineering disease and pest resistance in plants. Trends Microbiol. 6: 54-61.
Dixon, R.A. and Arntzen, C.J. 1997. Transgenic plant technology is entering the era of metabolic engineering. Trends in Biotechnol. 15: 441-444.
DOJ. 1998. Justice Department approves Monsanto's acquisition of Dekalb Genetics Corporation. Press release, Nov. 30. U.S. Dept. of Justice, Washington, D.C.
Dourmad, J.Y., Seve, B., Latimier, P., Boisen, S., Fernandez, J.A., van der Peet-Schwering C., and Jonbloed, A.W. 1999. Nitrogen consumption, utilization and losses in pig production in France, the Netherlands and Denmark. Livestock Production Sci. 58: 261-264.
Dowd, P.F., Bartelt, R.J., Behle, R.W., McGuire, M.R., Lagrimini, L.M., Estruch, J.J., Kendra, D.A., Hill, M., Privalle, L.S., Wright, M., Molid, G., Haase, I., and Duvick, J.P., 1999. Advances in insect-oriented IPM of mycotoxigenic fungi in corn in the Midwest–FY 1998. Presented at Aflatoxin Elimination Workshop, St. Louis, Mo., Oct. 25-27.
Doyle, E. 1999. Environmental benefits and sustainable agriculture through biotechnology. Executive Summary of the Ceres Forum at Georgetown Univ., Nov. 10-11.
Duke, S.O. 1998. Herbicide-resistant crops–Their impact on weed science. J. Weed Sci. Technol. 43(2): 94-100.
EPA. 2000. Greenpeace petition response submitted. Environmental Protection Agency, Washington, D.C. www.epa.gov/oppbppd1/biopesticides/news/news-greenpeace.htm.
ESA. 1999. Workshop on the Impact of transgenic pollen on Monarch butterflies, Dec. 14, Atlanta, Ga. Entomological Soc. of America. Lanham, Md.
Falck-Zepeda, J.B., Traxler, G., and Nelson, R.N. 2000. Rent creation and distribution from biotechnology innovations: The case of Bt cotton and herbicide-tolerant soybeans. Agribusiness 16: 21-32.
FAO. 1995. Report of the FAO Technical Consultation on Food Allergies. Nov. 13-14. Food and Agriculture Organization of the United Nations, Rome.
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, May 29-June 2. World Health Organization, Geneva, Switzerland.
FDA. 1990. Direct food substance affirmed as generally recognized as safe; Chymosin enzyme preparation derived from *Escherichia coli* K-12. Food and Drug Admin., Fed. Reg. 57: 10932.
Fuchs, M., Tricoli, D.M., Carney, K.J., Schesser, M., McFerson, J.R., and Gonsalves, D. 1998. Comparative virus resistance and fruit yield of transgenic squash with single and multiple coat protein genes. Plant Disease 82: 1350-1356.
Fuglie, K., Ballenger, N., Day, K., Klotz, C., Ollinger, M., Reilly, J., Vasavada, U., and Yee, J. 1996. Agriculture research and development: Public and private investments under alternative markets and institutions. Econ. Res. Service, U.S. Dept. of Agriculture, Washington, D.C.
Galler, J.R., Shumsky, J.S., and Morgane, P.J. 1996. Malnutrition and brain development. In "Nutrition in Pediatrics," ed. W.A. Walker and J.B. Watkins, pp. 196-212. B.C. Decker, Inc., Hamilton, Ontario, Canada.
Gilmore, R. 2000. Agbiotech and world food security—Threat or boon? Nature Biotechnol. 18: 361.
Gonsalves, D. 1998. Control of papaya ringspot virus in papaya: A case study. Ann. Rev. Phytopathol. 36: 415-437.
Gordon, J.S. 1996. The chicken story. Am. Heritage 47: 52-67.
Gura, T. 1999. The new genes boost rice nutrients. Science 285: 994-995.
Haq, T., Mason, H.S., Clements, J.D., and Arntzen, C.J. 1995. Oral immunization with a recombinant bacterial antigen produced in transgenic plants. Science. 268: 714-716.
Hansen Jesse, L.C. and Obrycki, J.J. 2000. Field deposition of Bt transgenic corn pollen: Lethal effects on the monarch butterfly. Oecologia, DOI 10.1007/s004420000502.
Harrison, L.A., Bailey, M.R., Naylor, M.W., Ream, J.E., Hammond, B.G., Nida, D.L., Burnette, B.L., Nickson,T.E., Mitsky, T.A., Taylor, M.L., Fuchs, R.L., and Padgette, S.R. 1996. The expressed protein in glyphosate-tolerant soybean, 5-enolpyruvylshikimate-3-phosphate synthase from *Agrobacterium* sp. strain CP4, is rapidly digested in vitro and is not toxic to acutely gavaged mice. J. Nutr. 126: 728-740.
Hayenga, M. 1998. Structural change in the biotech seed and chemical industry complex. AgBio Forum 1(2): 43-55.
Hill, C. and Ross, R.P. 1999. Starter cultures for the dairy industry. In "Genetic Modification in the Food Industry," ed. S. Roller and S. Harlander, pp. 174-192. Blackie Academic & Professional, London.
Hill, R.H. Jr., Caudell, S.P., Philen, R.M., Bailey, S.L., Flanders, W.D., Driskell, W.J., Kamb, M.L., Needham, L.L., and Sampson, E.J. 1993. Contaminants in L-tryptophan associated with eosinophilia myalgia syndrome. Arch. Environ. Contam. Toxicol. 25(1): 143-142.
Hodgson, J. 2000. Scientists avert new GM crisis. Nature Biotech. 18: 13.
Hols, P., Kleerebezem, M., Schanck, A.N., Ferain, T., Hugenholtz, J., Delcour, J., and de Vos, W.M. 1999. Conversion of *Lactococcus lactis* from homolactic to homoalanine fermentation through metabolic engineering. Nature Biotechnol. 17: 588-592.
Howard, J. 1999. Plant-based production of xenogenic proteins. Current Opinion in Biotechnol. 10: 382-386.
IFBC. 1990. Assuring the safety of foods produced by biotechnology. Intl. Food Biotechnology Council. Reg. Toxicol. Pharmacol. 12(3), Part 2 of 2 parts, Dec.
James, C. 1998. Global review of commercialized transgenic crops. Intl. Service for the Acquisition of Agri-biotech Applications, Ithaca, N.Y.
Kellems, R.O. and Church, D.C. 1998. "Livestock Feeds and Feeding," 4th ed. Prentice Hall, Upper Saddle River, N.J.
Kilbourne, E.M., Philen, R.M., Kamb, M.L., and Falk, H. 1996. Tryptophan produced by Shava Danko and epidemic eosinophilia myalgia syndrome. Rheumatol. 46 (Suppl.): 81-91.
Kleerebezem, M., Beerthuyzen, M.M., Vaughan, E.E., de Vos, W.M., and Kuipers, O.P. 1997. Controlled gene expression systems for lactic acid bacteria: Transferable nisin-inducible expression cassettes for *Lactococcus, Leuconostoc,* and *Lactobacillus* spp. Appl. Environ. Microbiol. 63: 4581-4584.
Kota, M., Daniell, H., Varma, S., Garczynski, S.F., Gould, F., and Moar, W.J. 1999. Overexpression of the *Bacillus thuringiensis* (Bt) Cry2Aa2 protein in chloroplasts confers resistance to plants against susceptible and Bt-resistant insects. Proc. Natl. Acad. Sci. 96: 1840-1845.
Lapierre, L., Germond, J.E., Ott, A., Delley, M., and Mollet, B. 1999. D-lactate dehydrogenase gene (ldhD) inactivation and resulting metabolic effects in the *Lactobacillus johnsonii* strains La1 and N312. Appl. Environ. Microbiol. 65: 4002-4007.
Larkins, B.A. 1999. Testimony submitted to the U.S. House of Representatives, Subcommittee on Basic Research, hearing on Plant Genome Research: From the Lab to the Field to the Market, Part II, Oct. 5. Serial No. 106-60. U.S. Govt. Printing Office, Washington, D.C.
Liener, I.E. 1980. "Toxic Constituents of Plant Foodstuffs," 2nd ed. Academic Press, New York.
Losey, J.E., Rayor, L.S., and Carter, M.E. 1999. Transgenic pollen harms monarch larvae. Nature 399: 214.
Lucas, J.A. 1998. "Plant Pathology and Plant Pathogens," 3rd ed. Blackwell Science Ltd. Oxford, U.K.
Ma, J.K-C., Hiatt, A., Hein, M., Vine, N.D., Wang, F., Stabila, P., van Dolleweerd, C., Mostov, K., and Lehner, T. 1995. Generation and assembly of secretory antibodies in plants. Science 268: 716-719.
Ma, S.W., Zhao, D.L., Yin, Z.Q., Mukherjee, R., Singh, B., Qin, H.Y., Stiller, C.R., and Jevnikar, A.M. 1997. Transgenic plants expressing autoantigens fed to mice to induce oral immune tolerance. Nature Med. 3: 793-796.
Ma, J.K-C., Himat, B.Y., Wycoff, K., Vine, N.D., Chargelegue, D., Yu, L., Hein, M.B., and Lehner, T. 1998. Characterization of a recombinant plant monoclonal secretory antibody and preventative immunotherapy in humans. Nature Med. 4: 601-606.
MacArthur, M. 2000. Triple-resistant canola weeds found in Alta. www.producer.com/articles/20000210/news/20000210news01.html.
Maliga, P., Staub, J., Carrer, H., Kanevski, I., and Svab, Z. 1994. Homologous recombination and integration of foreign DNA in plastids of higher plants. In "Homologous Recombination and Gene Silencing in Plants," ed. J. Paszkowski, pp. 83-93. Kluwer Academic Publishers, Dordrecht, Netherlands.
Mason, H.S., Losonsky, G., Clements, J.D., Levine, M.M., and Arntzen, C.J. 1998. Immunogenicity of a recombinant bacterial antigen delivered in a transgenic potato. Nature Med. 4: 607-609.
Mason, H.S., Lam, D.M., and Arntzen, C.J. 1992. Expression of hepatitis B surface antigen in transgenic plants. Proc. Natl. Acad. Sci. 89: 11745-11749.
Matsuda, T., Alvarez, A.M., and Tada, Y. 1993. Gene engineering for hypo-allergenic rice: Repression of allergenic protein synthesis in seeds of transgenic rice by antisense RNA. Proc. Intl. Workshop on Life Science in Production and Food-Consumption of Agricultural Products. Tsukuba, Japan. Oct. 24.
Matthews, R.E.F. 1991. "Plant Virology," 3rd ed. Academic Press, San Diego.
Mazur, B., Krebbers E., and Tingey, S. 1999. Gene discovery and product development for grain quality traits. Science 285: 372-375.
McCalla, A. 1995. Agriculture and food needs to 2025: Why we should be concerned. Department of Agricultural and Natural Resources, World Bank, Washington, D.C.
McCormick, A.A., Kumagai, M.H., Hanley, K., Turpen, T.H., Hakim, I., Grill, L.K., Tusé, D., Levy, S., and Levy, R. 1999. Rapid production of specific vaccines for lymphoma by expression of the tumor-derived single-chain Fv epitopes in tobacco plants. Proc. Natl. Acad. Sci. USA 96: 703-708.
McKeever, D.J. and Rege, J.E.O. 1999. Vaccines and diagnostic tools for animal health: The influence of biotechnology. Livestock Production Sci. 59(2-3): 257-264.
Metcalfe, D., Astwood, J.D., Townsend, R., Sampson, H.A., Taylor, S.L., and Fuchs, R.L. 1996. Assessment of allergenic potential of foods derived from genetically engineered crop plants. Crit. Rev. Food Sci. Nutr. 36S: S165-S186.
Monsanto. 1999. Filing for approval of merger between Monsanto and Delta & Pine Land canceled in light of regulatory issues. Press release, Dec. 20. Monsanto Co., St. Louis, Mo.
Moresi, M. and Parente, E. 1999. Production of organic acids. In "Encyclopedia of Food Microbiology," Vol. 2, ed. R.K. Robinson, C.A. Batt, and P.D. Patel, pp. 705-717. Academic Press, San Diego.
NABC. 1995. "Genes for the Future: Recovery, Ownership, Access." National Agricultural Biotechnology Council, Ithaca, N.Y.
NAS. 1973. "Toxicants Occurring Naturally in Foods," 2nd ed. Natl. Acad. of Sciences, Washington, D.C.
NAS. 2000. "Transgenic plants and world agriculture." Report prepared by a working group of the Royal Society of London, the U.S. National Academy of Sciences, Brazilian Academy of Sciences, Chinese Academy of Sciences, Indian National Science Academy, Mexican Academy of

Biotechnology Report: Benefits

CONTINUED

Sciences, and the Third World Academy of Sciences. National Academy Press, Wash., DC.

Nordlee, J.A., Taylor, S.L., Townsend, J.A., Thomas, L.A., and Bush, R.K. 1996. Identification of a Brazil nut allergen in transgenic soybeans. New Eng. J. Med. 334: 688-694.

NRC. 1972. "Genetic Vulnerability of Major Crops." Committee on Genetic Vulnerability of Major Crops. Natl. Res. Council. National Academy Press, Washington, D.C.

NRC. 1996. "Carcinogens and Anticarcinogens in the Human Diet: A Comparison of Naturally Occurring and Synthetic Substances," pp. 29-30. Natl. Res. Council, Natl. Academy Press, Washington, D.C.

NRC. 1997. "Intellectual Property Rights and the Dissemination of Research Tools in Molecular Biology: Summary of a Workshop." Natl. Res. Council, Natl. Academy of Sciences, Washington, D.C.

NRC. 1999. "Priority Issues of Access to Research Resources." Natl. Res. Council. National Academy of Sciences, Washington, D.C.

NRC. 2000. "Genetically modified pest protected plants: Science and Regulation." Natl. Res. Council. Natl. Academy Press, Washington, D.C.

Nüler, E. 1999. GM corn poses little threat to monarch. Nature Biotechnol.17: 1154.

Olsen, R.A. and Frey, K.J. 1987. "Nutritional Quality of Cereal Grains: Genetic and Agronomic Improvement," Agronomy: A Series of Monographs, No. 28. Am. Soc. of Agronomy, Madison, Wis.

Padgette, S.R., Re, D.B., Barry, G.F., Eichholtz, D.E., Delannay, X., Ruchs, R.L., Kishore, G.M., and Fraley, R.T. 1996. New weed control opportunities: Development of soybeans with a Roundup Ready gene. In "Herbicide Resistant Crops: Agricultural, Environmental, Economic, Regulatory and Technical Aspects," ed. S.O. Duke, pp. 53-84. CRC Press Inc., Boca Raton, Fla.

Peck, S.L., Gould, F., and Ellner, S.P. 1999. Spread of resistance in spatially extended regions of transgenic cotton: Implications for management of *Heliothis virescens* (*Lepidoptera: Noctuidae*). J. Econ. Entomol. 92(1): 1-16.

Philen, R.M., Hill R.H. Jr., Flanders, W.D., Caudell, S.P., Needham, L.L., Sewell, L., Sampson, E.J., Faulk, H., and Kilbourne, E.M. 1993. Tryptophan contaminants associated with the eosinophilia myalgia syndrome. Am. J. Epidemiol. 138(3): 154-159.

Pimentel, D.S. and Raven, P.H. 2000. Bt corn pollen impacts on nontarget *Lepidoptera*: Assessment of effects in nature. Proc. Natl. Acad. Sci. 97: 8189-8199.

Pinstrup-Andersen, P. and Pandya-Lorch, R. 1999. Securing and sustaining adequate world food production for the millennium. In "World Food Security and Sustainability: The Impact of Biotechnology and Industrial Consolidation," pp. 27-48. Natl. Agricultural Biotechnology Council, Ithaca, N.Y.

Porro, D., Bianchi, M.M., Brambilla, L., Menghini, R., Bolzani, D., Carrera, V., Lievense, J., Liu, C.L., Ranzi, B.M., Frontali, L., and Alberghina, L. 1999. Replacement of a metabolic pathway for large-scale production of lactic acid from engineered yeasts. Appl. Environ. Microbiol. 65: 4211-5.

Poulsen, H.D., Jongbloed, A.W., Latimier, P., and Fernandez, J.A. 1999. Phosphorus consumption, utilization and losses in pig production in France, The Netherlands and Denmark. Livestock Production Sci. 58: 251-259.

Pray, C.E. and Umali-Deininger, D. 1998. The private sector in agricultural research systems: Will it fill the gap? World Development 26: 1127-1148.

Qian, G-S., Ross, R.K., Yu, M.C., Yuan, J.-M., Gao, Y.-T., Henderson, B.E., Wogan, G.N., Groopman, J.D. 1994. A follow-up study of urinary markers of aflatoxin exposure and liver cancer risk in Shanghai, People's Republic of China. Cancer Epidemiol. Biomarkers & Prevention 3: 3-10.

Roller, S. and Goodenough, P.W. 1999. Food enzymes In "Genetic Modification in the Food Industry," ed. S. Roller and S. Harlander, pp. 101-128. Blackie Academic & Professional, London.

Sanders, M.E. 1999. Probiotics. A Scientific Status Summary of the Institute of Food Technologists' Expert Panel on Food Safety and Nutrition. Food Technol. 53(11): 67-77.

Sanders, P.R. Lee, T.C., Groth, M.E., Astwood, J.D., and Fuchs, R.L. 1998. Safety assessment of insect-protected corn. "Biotechnology and Safety Assessment," 2nd ed., ed. J.A. Thomas, pp. 241-256. Taylor and Francis, Philadelphia.

Sears, M. 2000. (Quoted in) New research suggests Bt corn not harmful to Monarch butterfly. Science Daily News. Feb. 9. www.sciencedaily.com/releases/2000/02/000208094017.htm.

Shulman, S., Bienz-Tadmoor, B., and Son-Seo, P. 1992. Implementation of the Orphan Drug Act: 1983-91. Food Law J. 47(4): 363-404.

Silvey, V. 1994. Plant breeding in improving crop yield and quality in recent decades. Acta Horticulturae, No. 355, pp. 19-34.

Sims, S.R. and Ream, J.E. 1997. Soil inactivation of the *Bacillus thuringiensis* subsp. *kurstaki* CrylIA insecticidal protein within transgenic cotton tissue: Laboratory microcosm and field studies. J. Agric. Food Chem. 45: 1502-1505.

Thayer, A.M. 1999. Transforming agriculture. Chem. Eng. News 77(16): 21-35.

UN. 1999. "The State of the World Population: A Time for Choices." United Nations, New York.

USDA/ERS. 1997. Agricultural resource management Study. Economic Research Service, U.S. Dept. of Agriculture, Washington, D.C.

USDA/ERS. 1999. Value-enhanced crops: Biotechnology's next stage. Agricultural Outlook, March, pp. 18-25. Economic Research Service, U.S. Dept. of Agriculture, Washington, D.C.

USDA/ERS. 2000a. "Feed Outlook Yearbook." Economic Research Service, U.S. Dept. of Agriculture, Washington, D.C.

USDA/ERS. 2000b. Genetically engineered crops for pest management in U.S. agriculture. Report No. 786 (AER-786). Economic Research Service, U.S. Dept. of Agriculture, Washington, D.C.

Van Dyne, D.L. and Gilbertson, C.B. 1987. Estimating U.S. livestock and poultry manure nutrient production. Economics, Statistics, and Cooperatives Service, U.S. Dept. of Agriculture, Washington, D.C.

Waggoner, P. 1994. How much land could 10 billion people leave for nature? Council for Agricultural Science and Technology, Ames, Iowa.

Wang, J-S., Shen, X., He, X., Zhu, Y-R., Zhang, B-C., Wang, J-B., Qian, G-S., Kuang, S-Y., Zarba, A., Egner, P.A., Jacobson, L.P., Munoz, A., Helzlsouer, K.J., Groopman, J.D., and Kensler, T.W. 1999. Protective alterations in phase 1 and 2 metabolism of aflatoxin B_1 by Oltipraz in residents of Qidong, People's Republic of China. J. Natl. Cancer Inst. 91: 347-54.

Williams, P.E.V. 1997. Poultry production and science: Future directions in nutrition. Worlds Poultry Sci. J. 53: 33-48.

Wraight, D.L., Zangerl, A.R., Carroll, M.J., and Berenbaum, M.R. 2000. Absence of toxicity of *Bacillus thuringiensis* pollen to black swallowtails under field conditions. Proc. Natl. Acad. Sci. 97: 7700-7703.

Zeitlin, L., Olmstead, S., Moench, T., Co, M., Martinell, B., Paradkar, V., Russell, D., Queen, C., Cone, R., and Whaley, K. 1998. A humanized monoclonal antibody produced in transgenic plants for immunoprotection of the vagina against genital herpes. Nature Biotech. 16: 1361-1364.

Zoubenko, O.V., Allison, L.A., Svab, Z., and Maliga, P. 1994. Efficient targeting of foreign genes into the tobacco plastid genome. Nucleic Acids Res. 22(19): 3819-3824.