CITIZEN PETITION BEFORE THE UNITED STATES FOOD AND DRUG ADMINISTRATION

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CENTER FOR FOOD SAFETY,
666 Pennsylvania Ave., S.E.
Suite 302
Washington, DC 20003,

et al.,
Petitioners,

Filed With:

JANE HENNEY,

in her official capacity as,
Commissioner
Food and Drug Administration
Parklawn Building, Room 1471
5600 Fishers Lane
Rockville, MD 20857

PETITION SEEKING THE ESTABLISHMENT OF MANDATORY PRE-MARKET SAFETY TESTING, PRE-MARKET ENVIRONMENTAL REVIEW & LABELING FOR ALL GENETICALLY ENGINEERED FOODS

Pursuant to the Right to Petition Government Clause contained in the First Amendment of the United States Constitution,[(1)] the Administrative Procedure Act,[(2)] and the Food and Drug

Administration's (FDA) implementing regulations,[3] the undersigned submit this citizen petition for rulemaking and collateral relief under the Federal Food Drug and Cosmetic Act (FFDCA), and National Environmental Policy Act (NEPA) to request the Commissioner to prevent the commercial sale of all genetically engineered foods until the agency undertakes the following actions:

(1). Rescind its 1992 Statement of Policy: Foods Derived From New Plant Varieties and implement new regulations that subject all genetically engineered foods and/or genetically engineered food additives to the food additive petition process. Such a process should include:

> (A). Pursuant to the procedures outlined in 21 C.F.R. § 170.38, the Commissioner shall issue a notice in the Federal Register determining that all genetically engineered food additives are not Generally Recognized As Safe (GRAS) and are food additives subject to section 409 of the FFDCA;
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> (B). Amend the current text of 21 C.F.R. §170.3 to include the following:
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> > (p) *Genetically engineered food* means food that contains or was produced with a genetically engineered material.
> >
> > > (1) *Genetically engineered material* means material derived from any part of a genetically engineered organism, without regard to whether the altered molecular or cellular characteristics of the organism are detectable in the material.
> > >
> > > (2) *Genetically engineered organism* means (A) an organism that has been altered at the molecular or cellular level by means that are not possible under natural conditions or processes (including, but not limited to, recombinant DNA and RNA techniques, cell fusion, microencapsulation, macroencapsulation, gene deletion and doubling, introducing a foreign gene, and changing the positions of genes), other than a means consisting exclusively of breeding, conjugation, fermentation, hybridization, in vitro fertilization, or tissue culture, *and* (B) an organism made through sexual or asexual reproduction (or both) involving an organism described in(A), if possessing any of the altered molecular or cellular characteristics of the organism so described.
> > >
> > > (3) *Genetically engineered food additive* means a genetic construct, its protein or expression product, vector, promoter, or marker system that are used or

created individually or together as a result of a genetically engineered food.

(2). Enact additional regulatory protocols within the food additive petition review process for genetically engineered foods or genetically engineered food additives that assess potential allergencity, toxicity and unintended effects. Such protocols should include, but not be limited to the following:

(A). Allergenicity. The FDA must develop and mandate specific testing protocols for the assessment of allergenicity for all genetically engineered food additives. In instituting these new mandatory pre-market regulations, the agency should include requirements that all food additives be subject to allergenicity screening that includes, but is not limited to:

(i). Prick-puncture skin testing to determine whether the food additive triggers a specific IgE antibody response;

(ii). In vitro testing screening for specific IgE (radioallergosorbent tests [RAST]) responses to a genetically engineered food additive;

(iii). Use of T Cell marker assays;

(iv). Complete molecular characterization of known allergens; and

(v). Consistent with regulatory requirements concerning informed consent, pursuant to 21 C.F.R. part 50 and 45 C.F.R. part 46, subpart A and part 690 (as applicable), an assessment of the ethical and reasonable outcomes of conducting limited double-blind placebo controlled food challenges.

(B). Toxicity and Unintended Effects. The FDA must develop and mandate specific testing protocols for the assessment of toxicity and other unintended effects for all genetically engineered food additives. In instituting these new mandatory pre-market regulations, the agency should include requirements that all food additives be subject to toxicity and other screening that includes, but is not limited to:

(i). Determination of the potential for unexpected effects using molecular characterization biochemical characterization, mRNA profiling or other

techniques, long-term feeding studies or as appropriate a combination of such techniques;

(ii). Review of required information on the glycosylation patterns of all transgenes expressed in GE foods;

(iii). Use of material derived from the transgenic plants themselves in all required toxicity studies rather than bacterially-derived proteins;

(iv). Submission of data for each separate transgenic line. Specifically for every line, the FDA should require a complete molecular characterization of each line with respect to the identity, stability and unintended positional and pleiotropic effects;

(v). Complete molecular characterization for molecular identity for each transgenic or transformed line, to include the following components:

(a). Total number of inserts of transgenic DNA;

(b). Location of each insert (organelle [chloroplast, mitochondria, etc.] or chromosomal);

(c). Exact chromosomal position of each insert;

(d). Structure of each insert (whether duplicated, deleted, rearranged, etc.);

(e). Complete genetic map of each insert including all elements (coding region, noncoding regions, marker gene, promoters, enhancers, introns, leader sequences, terminators, T-DNA borders, plasmid sequences, linkers, etc. including any truncated, incomplete sequences);

(f). Complete (nucleotide) base sequence of each insert; *and*

(g). (Nucleotide) base sequence of at least 10kbp (10,000 base pairs) of flanking host genome DNA on either side of the insert, including changes in methylation patterns

(3). Immediately comply with the NEPA including undertaking the following actions:

(A). Pursuant to 42 U.S.C. § 4332(c), complete a programmatic environmental impact statement (Programmatic EIS) assessing the agency's program on genetically engineered foods and genetically engineered food additives under the food additive petition process; and

(B). Find that 21 C.F.R. §§ 25.30, 25.32 are not applicable to all genetically engineered food additive petitions, and therefore, such petitions are not categorically excluded from NEPA review.

(4). Enact new labeling regulations under 21 C.F.R. part 101 to require as follows: "If the food contains a genetically engineered material, or was produced with a genetically engineered material, unless it bears a label (or labeling, in the case of a raw agricultural commodity, other than the sale of such a commodity at retail) that provides notices in accordance with the following:

(A) "A notice as follows: 'GENETICALLY ENGINEERED'.

(B) "A notice as follows: 'UNITED STATES GOVERNMENT NOTICE: THIS PRODUCT CONTAINS A GENETICALLY ENGINEERED MATERIAL, OR WAS PRODUCED WITH A GENETICALLY ENGINEERED MATERIAL'.

(C) "The notice required in clause (A) immediately precedes the notice required in clause (B) and is not less than twice the size of the notice required in clause (B).

(D) "The notice required in clause (C) is of the same size as would apply if the notice provided nutrition information."

PETITIONERS

Petitioner *Center for Food Safety* (CFS) is a non-profit, membership organization located at 666 Pennsylvania Ave., SE, Suite 302, Washington, DC 20003. Petitioner was established in 1997 to address the increasing concerns about the impacts of our food production system on human health, animal welfare and the environment.

Petitioner *American Corn Growers Association* (ACGA) is located c/o 7125 S. Indianapolis Ave., Tulsa, OK 74136. Petitioner is America's leading progressive commodity association, representing the interests of thousands of corn producers in 28 states. Since it's inception in 1987, the ACGA has worked tirelessly to protect farm income and rural communities. The ACGA recognizes that farmers need to have the opportunity to be rewarded for their time, investment and risk.

Petitioner *American Humane Association* (AHA) is located at 236 Massachusetts Ave., NE, Suite 203, Washington, DC 20002. Headquartered in Denver, CO, AHA is the national, non-profit organization dedicated to protecting children and animals from cruelty , neglect and exploitation. It has 6500 organizational members and 160,000 individual members nationwide.

Petitioner *Beyond Pesticides/National Campaign Against the Misuse of Pesticides* is located at 701 E Street, SE, Suite 200, Washington, DC 20003. Petitioner began in 1981 as the National Coalition Against the Misuse of Pesticides, a non-profit membership organization that was formed to serve as a national network committed to pesticide safety and the adoption of alternative pest management strategies which reduce or eliminate a dependency on toxic chemicals. Petitioner is governed directly by their membership, including individuals and organizations, which elects a 15- member board of directors.

Petitioner *California Public Interest Research Group* (CALPIRG) is located at 11965 Venice Boulevard, Suite 408, Los Angeles, CA 90066. Petitioner's mission is to deliver persistent, result-oriented public interest activism that protects our environment, encourages a fair, sustainable economy, and fosters responsive, democratic government.

Petitioner *The Campaign to Label Genetically Engineered Foods* is located at P.O. Box 55699, Seattle, WA 98155. Petitioner seeks to create a national grassroots consumer campaign for the purpose of lobbying Congress and the President and to pass legislation that will require the labeling of genetically engineered foods in the United States.

Petitioner *Cancer Prevention Coalition* (CPC) is located at c/o School of Public Health University of Illinois Medical Center, 2121 West Taylor Street, Chicago, IL 60612. Petitioner is a nationwide coalition of leading independent experts in cancer prevention and public health, together with citizen activists and representatives of organized labor, public interest environmental and women's health groups. Petitioner's goal is to reduce cancer rates through a comprehensive strategy of outreach, public education, advocacy and public policy initiatives to establish prevention as the nation's foremost cancer policy.

Petitioner *Center for Ethics and Toxics* (CETOS) is located at P.O. Box 673, Gualala, CA 95445. Petitioner is a non-profit organization located on the coast of Northern California which focuses on reducing the amount of chemicals used in the environment and protecting susceptible individuals from exposure to toxic chemicals.

Petitioner *Center Valley Organic Farm* is located at 8364 South SR 39, Clayton, IN, 46118. Petitioner is an organic vegetable farm in Hendricks County Indiana.

Petitioner *Citizens for Health* is located at P.O. Box 2260, Boulder, CO 80306. Petitioner is the national grassroots organization committed to protecting and advancing consumer access, choice, information and safety for natural health products and therapies.

Petitioner *Community Nutrition Institute* (CNI) is located at 910 17th Street, N.W., #413, Washington, D.C. 20006. Petitioner is a non-profit organization founded in1969 with a special focus on food policy. From the beginning, CNI has been a leading advocate for consumer protection, food program development and management, and sound federal diet and health policies. The Institute provides policy analysis, information, and education to consumers, program managers, federal agencies, and lawmakers.

Petitioner *Council for Responsible Genetics* (CRG) is located at 5 Upland Road, Suite 3, Cambridge, MA 02140. Petitioner is a non-profit organization representing over 1,000 scientists, ethicist and concerned citizens which seeks to educate the public regarding the social and environmental impacts of genetic engineering.

Petitioner *Demeter Association, Inc.* is located at Britt Road, Aurora NY 13026. Petitioner is an independent international agency that certifies organic and biodynamic farms in the United States and abroad. Petitioner's mission is to foster, encourage, and improve Biodynamic methods and practices by certifying growers, processors, and manufacturers of Biodynamic foodstuffs, and by carrying out other activities and education programs as may be appropriate. Demeter operates exclusively for agricultural and horticultural purposes. Demeter certifies farms as either Biodynamic, or in conversion to Biodynamic.

Petitioner *Ecological Health Organization* (ECHO) is located at P.O. Box 0119, Hebron, CT 06248-0119. Petitioner is a statewide organization providing advocacy, support, educational information and referrals for people with Multiple Chemical Sensitivity (MCS), Sick Building Syndrome, others made ill by chemicals in our modern environment (perfumes, pesticides, exhaust, cleaning products, etc.) and those who care about the prevention of chemical injury. Founded in 1992, ECHO is one of the first organizations in Connecticut linking environmental issues and public health.

Petitioner *The Edmonds Institute* is located at 20139 92nd Avenue West, Edmonds, WA 98020. Petitioner is a non-profit, public interest organization committed to the health and sustainability of ecosystems and their inhabitants. It seeks to engage in projects that foster respect for and protection of the rights and health of all communities. The Institute focuses its efforts on understanding and sharing information about environmental, human rights and human health, and economic impacts of new technologies and intellectual property policies. The current emphasis of its programs is on: (a) biosafety and the legally-binding international regulation of modern biotechnologies, (b) intellectual property rights and just policies for the maintenance and protection of biodiversity, including policies that foster recognition and sustenance of agricultural biodiversity, and (c) exploration of the ethical implications of new technologies.

Petitioner *Farm Verified Organic, Inc.* (FVO) is located at 5449 45th Street SE, Medina, ND 58467. Petitioner is an international organic certification organization established in the early 1980's.

Petitioners certify as "organic" over 115 family farms, cooperatives, processors, handlers and manufacturers around the world.

Petitioner *Food First/Institute for Food and Development Policy* (Food First) is located at 398 60th Street, Oakland, CA 94618. Petitioner is a member-supported, non-profit "peoples" think tank and education-for-action center. Its work highlights root causes and value-based solutions to hunger and poverty around the world, with a commitment to establishing food as a fundamental human right.

Petitioner*Friends of the Earth* is located at 1025 Vermont Ave., NW, Suite 300, Washington, DC 20005. Petitioner is a national environmental organization dedicated to preserving the health and diversity of the planet for future generations. As the largest international environmental network in the world with affiliates in 63 countries, Friends of the Earth empowers citizens to have an influential voice in decisions affecting their environment.

Petitioner *Florida Certified Organic Growers and Consumers, Inc.* (FOG) is located at P.O. box 12311, Gainesville, FL 32604. FOG is a non-profit organization committed to educating farmers, gardeners, the press, homeowners, agricultural information providers and consumers about organic and sustainable farming practices.

Petitioner *Green Alliance* is located at P.O. Box 8094, St. Louis, MO 63156. Founded in 1990, petitioner is the St. Louis chapter of the The Greens/Green Party USA. The group is dedicated to raising issues of environmental, social, and political importance. To promote discussion on issues that directly impact the environmental health of communities and to engage citizens in proactive campaigns regarding environmental and regulatory policies.

Petitioner *Government Accountability Project* is located at 1402 Third Avenue, Ste. 1215, Seattle, WA 98101. Every year, thousands of Americans witness wrongdoing on the job. Some speak out. Their actions may ultimately save lives and billions of dollars. But rather than receive praise for their integrity, these brave whistleblowers are often targeted for harassment, intimidation, demotion, and dismissal. In 1977, the petitioning organization was created to help these employees, who, through their individual acts of conscience, protect each and everyone of us.

Petitioner *Greenpeace, Inc*. is located at 1436 U Street NW, Washington, DC, 20009. Petitioner is the U.S. headquarters of one of the world's major environmental organizations with offices in 33 countries and over 3 million donating supporters worldwide with offices in 33 countries. Petitioner is a non-profit organization devoted to the protection of the environment with an emphasis on global environmental problems such as climate change and protection of the stratospheric ozone layer, prevention of nuclear, chemical and biological pollution, defense of biodiversity.

Petitioner *Humane Society of the United States* (HSUS) is located at 2100 L Street, NW, Washington, DC 20037. Petitioner is the nation's largest animal-protection organization, with more than 7 million constituents. The HSUS was founded in 1954 to promote the humane treatment of animals and to foster respect, understanding, and compassion for all creatures.

Petitioner *Institute for Agricultural and Trade Policy* (IATP) is located at 2105 1st Avenue South, Minneapolis, MN 55404-2505. Petitioner is a research and education organization that acts locally, nationally and internationally to develop and support policies and strategies that expand choices and

opportunities to farmers, farm workers and local communities around the world, regenerate the natural resource base, take a precautionary approach to the use of chemicals and genetic manipulation and avoids dependence on purchased inputs and external energy sources, and tackle the causes rather than the consequences of unsustainability, looking for positive, progressive and proactive ways of solving problems. IATP works with farmers, consumers, unions, environmental organizations, citizens groups and others both in the U.S. and around the world.

Petitioner *Kirschenmann Family Farms* is located at R.R. 1, Box 73, in Windsor, ND. Petitioner is a second generation family farm of diversified grain and livestock production that has been managed as a 100% organic farm since 1980.

Petitioner *Maine Organic Farmers and Gardeners Association* is located at P.O. Box 2176, Augusta, ME 04338-2176. Petitioner is the oldest and largest state organic organization in the USA and seeks to help farmers and gardeners grow organic food, to protect the environment, to promote stewardship of natural resources, to increase local food production, to support sustainable rural communities, and to illuminate for consumers the connections among healthful food, environmentally sound farming practices, and vital local communities.

Petitioner *Maine Right to Know Coalition* is located at HC 35, Box 205, South Gouldsboro, Maine 04607. Petitioner is an organization created to advocate the Maine citizens initiative

Petitioner *Massachusetts Public Interest Research Group* (MASSPIRG) is located at 29 Temple Place, Boston, MA 02111. Petitioner is a nonprofit, nonpartisan organization dedicated to serving as a watchdog for the state's citizens and environment. With tens of thousands of members and a staff of policy specialists, petitioner combines the expertise of professionals with the power of citizens in defense of clean air and water, strong safeguards for consumers, a free and vigorous democracy, and a way of living today that ensures a better quality of life tomorrow.

Petitioner *Michaela Farm* is located P.O. 100, Oldenburg, IN 47036. Petitioner is a 300 acre organic farm, which nurtures sustainable relationships among land, plants, animals, and humans. The Michaela Farm Members and Oldenburg Franciscans, foster these relationships and share what they learn through food production, responsible use of resources, community building, and spiritual awareness.

Petitioner *Michigan Organic Food and Farm Alliance* is located at 11230 W. Mt. Morris Road, Flushing, MI 48433. Petitioner is a statewide organization dedicated to promoting the development of viable organic food systems.

Petitioner *Mothers & Others for a Liveable Planet* is located at 40 West 20th Street, 11th Floor, New York, NY 10011-4211. Mothers & Others, a national nonprofit education organization, works to promote consumer choices which are safe and ecologically sustainable for this generation and the next. By providing strategies that can reduce individual and community consumption of natural resources, and by mobilizing consumers to seek sustainable choices, petitioner aims to effect lasting protection of public health and the environment.

Petitioner *National Environmental Trust* is located at 1200 18th Street, NW, 5th Floor, Washington, DC 20036. Petitioner is a non-profit, non-partisan membership group established in 1994 to inform

citizens about environmental problems and how they effect our health and quality of life. Through public education, NET helps people understand an issue and express their concerns to public officials.

Petitioner *Natural Cotton Colours, Inc., Vreseis Limited*, is located at P.O. Box 69, Guinda, CA 95637. Petitioner markets and wholesales products, including clothes, made from organic cotton. Through the commercialization of organic cotton, petitioner works to aid farmers in the transformation of cotton production systems so that sustainability is achieved throughout the entire life cycle of cotton products.

Petitioner *Natural Resources Defense Council* (NRDC) is located at 40 West 20th St., New York, NY 10011. Petitioner is a national non- profit membership environmental organization of scientists, lawyers and environmental specialists dedicated to protecting public health and the environment. Founded in 1970, NRDC has more than 400,000 members nationwide and offices in New York city, Washington, D.C., Los Angeles and San Francisco. NRDC's mandate includes maintaining and enhancing environmental quality and monitoring federal agency actions to ensure that federal statutes enacted to protect human health and the environment are fully and properly implemented. To achieve these objectives, NRDC and its members engage in legislative activities, litigation, administrative actions, and public education efforts to inform others about the environmental impacts of government and private sector activities.

Petitioner *New Hampshire Health Freedom Coalition* is located c/o Boston College, 66 Commonwealth Ave., Chestnut Hills, MA 02467.

Petitioner *New Jersey Environmental Federation* is located at 223 Park Ave., Marlton, NJ 08053. Petitioner is a non profit organization fighting to protect natural resources and clean up pollution in New Jersey. NJEF is the New Jersey chapter of Clean Water Action, a 25 year old national organization based in Washington DC, and dedicated to organizing citizen efforts to protect the environment.

Petitioner *Northeast Organic Farming Association of New York, Inc.* (NOFA-NY) is located at P.O. Box 21, South Butler, NY 13154—0021. Petitioner is a non-profit association of *1100* members including farmers, gardeners, and consumers, committed to local, organic agriculture.

Petitioner *Northeast Organic Farming Organization, Vermont Chapter* (NOFA-VT) is located at P.O. Box 697, Richmond, VT 05477. Petitioner is a non-profit association of 650 members including farmers, gardeners, and consumers, committed to local, organic agriculture.

Petitioner *Organic Ag Advisors* is located at PO Box 403, Cedar Ridge, CA, 95924. Petitioner is an independent research and consulting firm providing technical advice to over 1400 farmers growing nearly 400,000 acres of crops in California, Oregon, Washington, Arizona, Hawaii, and Latin America.

Petitioner *Organic Consumers Association* (OCA) is located at 6114 Highway 61, Little Marias, MN 55614. Petitioner is a nationwide grassroots public interest organization dealing with issues of food safety, industrial agriculture, and genetic engineering while promoting organic and sustainable agriculture.

Petitioner *Organic Growers of Michigan* is located at 11230 W. Mt. Morris Road, Flushing, MI 48433.

Petitioner *Pesticide Action Network - North America* (PANNA) is located at 49 Powell St., Suite 500 San Francisco, CA 94102. Petitioner has campaigned to replace pesticides with ecologically sound alternatives since 1982. PANNA links over 100 affiliated health, consumer, labor, environment, progressive agriculture and public interest groups in Canada, Mexico and the U.S. with thousands of supporters worldwide to promote healthier, more effective pest management through research, policy development, education, media, demonstrations of alternatives and international advocacy campaigns.

Petitioner *Physicians for Social Responsibility* is located at 1101 14th Street Northwest, Suite 700, Washington, D.C. 20005. Petitioner is working to create a world free of nuclear weapons, global environmental pollution, and gun violence. The active conscience of American medicine, PSR uses its members' expertise and professional leadership, influence within the medical community and strong links to policy makers to address this century's greatest threats to human welfare and survival.

Petitioner *Pine Creek Organics* is located at 200 Pine Swamp Road, Danville, PA., 17821. Petitioner is an organic vegetable farm.

Petitioner *Public Citizen* is located at 1600 20th St. NW Washington, DC. 20009. Founded by Ralph Nader in 1971, Public Citizen is the consumer's eyes and ears in Washington. With the support of more than 150,000 people, petitioner fights for safer drugs and medical devices, cleaner and safer energy sources, a cleaner environment, fair trade, and a more open and democratic government. Petitioner *Rfarm* is located at 1318 Bruce Street, Chico, CA 95928. Petitioner is a community supported agriculture farm that seeks to support small family farmers.

Petitioner *Rodale Institute* is located at 611 Siegfriedale Road, Kutztown, PA 19530. Petitioner is a nonprofit charity located in Kutztown, Pa. The Institute shares its expertise on organic/regenerative farming methods with people worldwide to achieve a regenerative food system that renews environmental and human health. "Healthy Soil, Healthy Food, Healthy People®" has been The Rodale Institute's message for the past 51 years. Funded in large part by donations from individuals, government agencies, private foundations and corporations, The Rodale Institute continues to promote soil quality practices to farmers worldwide.

Petitioner *Rural Advancement Foundation International-USA* (RAFI-USA) is located at 21 Hillsboro Street, Pittsboro, NC. Petitioner is dedicated to community, equity and diversity in agriculture. While focusing on North Carolina and the southeastern United States, petitioners also works nationally and internationally. Petitioner plays a leadership role in responding to major agricultural trends and creating movement among farm, environmental and consumer groups to promote sustainable agriculture, strengthen family farms and rural communities, protect the diversity of plants, animals and people in agriculture and ensure responsible use of new technologies.

Petitioner *Rural Vermont* is located at 15 Barre Street, Montpelier VT 05602 . Petitioner is a statewide grassroots organization dedicated to building a prosperous rural life and committed to broad based sustainable agriculture in harmony with the needs of the family, community, and the environment for future generations.

Petitioner *Sierra Club* is located at 85 Second Street, Second Floor, San Francisco CA, 94105-3441, Petitioner is one of the world's leading conservation organizations, as well as one of the oldest, with over 550,000 members in the United States. It's the largest grassroots conservation organization in the United States. The purposes of the Sierra Club include protecting the quality of the natural and human environment and using all lawful means to carry out its objectives.

Petitioner *Sustain* is located at 920 N. Franklin Street, Suite 206, Chicago, IL 60610-3121. Petitioner is a non-profit organization that uses innovative communications strategies to help win environmental victories. Petitioner partners with other non-profits that have legal, policy, and organizing expertise on particular issues.

Petitioner *United States Public Interest Research Group* (U.S. PIRG) is located at 218 D Street, S.E., Washington, DC, 20003. Petitioner is the national office for the State PIRGs, a network of groups with offices around the country working on consumer rights, good government, and environmental issues. For over 25 years the PIRGs have been one of the nation's leading nonprofit, nonpartisan groups acting on behalf of the public.

Petitioner *Union of Concerned Scientists* is located at 2 Brattle Square, Cambridge, MA 02238. Petitioner seeks to persuade the government to encourage innovative ways to grow plants and animals, protect the safety of food, and ensure that consumers and citizens can make choices about how food is produced. Working in coalition with the environmental community, progressive farmers, and other pubic interest organizations, we urge new policies, analyze agency actions, and engage the public in advocacy efforts to improve our food web -- the interlinked systems of agriculture, food, and the environment.

Petitioner *Vermont Public Interest Research Group* (VPIRG) is located at 64 Main Street, Montpelier, VT 05602. Established in 1972, VPIRG has grown into Vermont's largest consumer and environmental organization with over 20,000 members. Petitioner is a statewide non-profit organization dedicated to education, lobbying and advocacy on fundamental issues affecting Vermonters. They have prioritized the issues of environmental health, energy conservation and consumer protection.

Petitioner *Virginia Association of Biological Farmers* is located at Box 252, Flint Hill, VA. Petitioner is an state-wide network of growers, marketers, educators, and consumers of ecologically produced food and fiber.

STATEMENT OF GROUNDS

I. Statement of the Law

Administrative Procedure Act, 5 U.S.C. § 551, *et seq.*
Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301, *et seq.*
National Environmental Policy Act, 42 U.S.C. § 4321, *et seq.*
Council on Environmental Quality, 40 C.F.R. §§ 1500-1508 (1996).
U.S. Department of Health and Human Services, 45 C.F.R. part 46, subpart A (1999).
Food and Drug Administration, 21 C.F.R. parts 10, 25, 50, 101 and 170 (1999).
National Science Foundation, 45 C.F.R. part 690 (1999).

All other applicable statutes and regulations.

II. Statement of Fact

Genetic engineering encompasses a wide range of new techniques that allows scientists to alter the molecular biology of an organism using genes from entirely unrelated organisms. Unlike traditional breeding, these techniques artificially breach natural reproductive barriers and combine genes from distant species in ways that could never occur in nature. Thus, biotechnicians are suddenly altering genetic patterns that have developed over millions of years.[i]

The genetic manipulation of food shuffles the deck of genes in ways that are entirely new and creates foods that have never before existed.[ii] Plants are genetically engineered for various reasons; e.g., to alter processing performance, to modify nutritional content, to confer pest resistance, or to improve flavor, appearance or smell. In order to effect these desired performance and organoleptic changes, highly sophisticated manipulations of genetic material and other biologically important chemicals are required.[iii]

To do so, scientists identify the gene responsible for a desired trait in a particular species–such as insects, fish and animals–copy it and forcibly insert it into the DNA of the target plant. Because this is an unnatural process, however, the foreign genes must be smuggled into the new organism and need an artificial boost in order to express themselves within their new environment.[iv] Therefore, scientists have to create a "cassette" of genetic material, which may include antibiotic resistance marker genes, viral and bacterial promoters and vectors and terminators,[v] that has been specifically designed to breach species boundaries.[vi] This cassette of foreign material disturbs the function of the region of native DNA into which it has been spliced in order to successfully confer the desired trait.[vii]

However, genetic modification is not a precise operation. Scientists cannot control with any precision the location where the trait is inserted and, because the effect of a gene on an organism is significantly governed by its location, this is a significant cause of unexpected effects.[viii] Nor can scientists guarantee stable expression of the transgene.[ix] More than one copy of a gene may be inserted,[x] other genes may get switched off,[xi] or the genes vary in how they work.[xii] Therefore, these genes operate in an unprecedented way in plant foods and can lead to deleterious imbalances, because the genes act in virtual independence from the host plant's regulatory system. As a result, scientists cannot reliably predict the effect of the introduction of new genetic material just by knowing the biology of the introduced species.[xiii]

The unpredictable disruptions in normal DNA functioning caused by genetic engineering may produce unanticipated and unknown side effects for human health but, to date, there have been no long-term studies conducted to determine the effects of genetically engineered foods on human health.[xiv]

A. The FDA's 1992 Policy on Genetically Engineered Foods.

On May 29, 1992, the Food and Drug Administration published a "policy statement" establishing a regulatory framework for foods created through genetic engineering technology.[xv] The 1992 Policy allows genetically engineered foods to be marketed without mandatory premarket safety testing and labeling. The 1992 Policy was based on the FDA's determination that genetically engineered foods are substantially equivalent to foods produced through conventional methods:

"The agency is not aware of any information showing that foods derived by these new methods differ from other foods in any meaningful or uniform way, or that, as a class, foods developed by the new techniques present any different or greater safety concern than foods developed by traditional plant breeding."[xvi]

The FDA received nearly 7,000 comments on its 1992 Policy.[xvii] An agency analysis of these comments concluded that more than 98% of the public commenters opposed the policy. Moreover, about 80% of the commenters demanded mandatory labeling of genetically engineered foods, and a significant number questioned the safety (testing and allergies) and environmental effects of these novel foods.[xviii] Despite the vehement public outcry, the FDA never issued a response to those comments. Nor did the agency complete or release any documentation which assessed the human health, environmental and socio-economic impacts of the commercialization of unlabeled and potentially untested genetically engineered foods, although FDA staff recommended that such an analysis be performed.[xix]

In 1994, the FDA held a conference for scientists to discuss the problem of allergenicity, but never modified its policy as a result. In 1999, the FDA held three public hearings to entertain public comment on its 1992 Policy,[xx] but no response has been issued to date.

B. Genetically Engineered Food Is Radically Different From Conventionally Produced Food.

The 1992 Policy contained no scientific studies or data to support the assumption that gene altered foods were substantially equivalent to conventional foods.[xxi] And, in fact, scientists within the FDA and outside of the agency agree that there are profound differences between genetically engineered foods and those produced by traditional breeding.[xxii]

As a general rule, conventional breeding develops new plant varieties by the process of ***selection*** and seeks to achieve expression of genetic material which is already present within a species. Conventional breeding employs processes that occur in nature, such as sexual and asexual reproduction. The product of conventional breeding emphasizes certain characteristics; however, these characteristics are not new for the species. These characteristics have been present for millennia within the genetic potential of the species.[xxiii]

Genetic engineering, by contrast, works primarily through ***insertion*** of genetic material, followed up by selection. Gene transfer occurs by artificial means–through a gene "gun," a bacterial "truck" or a chemical or electrical treatment inserts--without regard to natural boundaries. Biotechnicians use vectors, derived from genetic parasites, that have been designed to breach species barriers, as well as promoters to ensure that the right amount of the desired gene product will be produced at the right time. Neither vectors nor promoters are needed in traditional breeding.[xxiv] As FDA scientists explain, genetic engineering allows "for the possibility of transfering (sic) to any organism a gene from any other organism or from a synthetic source (i.e., an enzyme composed of several domains of unrelated proteins). This potential is beyond the realm of possibility of standard breeding practice. The food safety of organisms derived from recombinant DNA technologies do not have the history of the safe use that has come to be associated with organisms derived by standard breeding practices."[xxv] In fact, scientists may even insert custom-designed genes that do not exist in nature, producing a synthetic life form.[xxvi] One FDA expert summed up the novel nature of these foods, "We should also keep in mind that plant genetic engineering is an entirely new adventure with potentially new effects."[xxvii]

FDA scientists also warn that the artificial insertion of DNA into plants, a technique unique to genetic engineering, could cause a variety of significant problems with plant foods including an increase in levels of known toxicants, the appearance of new toxicants, loss of nutrients, poor growth and higher concentrations of herbicides and pesticides.[xxviii] Scientists also caution that genetically engineered foods can be allergenic and may cause antibiotic resistance.[xxix]

C. Genetically Engineered Food Can Cause Toxic Effects.

Agency scientists have evidence that desirable and undesirable pleiotropic effects have been shown to occur at frequencies up to 30% in genetically engineered plants.[xxx] The resulting undesirable phenotypes may include, *inter alia*, increased levels of naturaltoxicants, the appearance of new, not previously identified toxicants, increased capability of concentrating toxic substances from the environment (e.g. pesticides or heavy metals), and undesirable alterations in the levels of nutrients which may escape a breeder's attention unless genetically engineered plants are evaluated specifically for these changes.[xxxi]

FDA scientists caution that genetically modified plants might contain unexpectedly high concentrations of plant toxicants. This can occur by two mechanisms. One could be the amplification of normal levels of existing toxicants into higher levels.[xxxii] For example, since biotechnicians must use promoters to ensure that the inserted genes are expressed, those promoters also may induce hyperexpression of existing plant toxins.[xxxiii] Also, the imprecise location of an inserted gene may explain why a scientific study found a 40-fold to 200-fold increase in the toxic substance methyglyoxal in genetically engineered yeast.[xxxiv]

Second, normally inactive plant toxins could become activated and create unexpected toxicants.[xxxv] The finding by FDA scientists that genetic engineering can create new toxicants in foods is of particular concern in that the genetic engineering of a food supplement, the amino acid L-tryptophan, may have led to it becoming toxic. The non-genetically engineered version of this supplement was not associated with any human health impacts. The genetically engineered version manufactured in 1988 caused the deaths of 37 people and the permanent disability of at least 1500 others. The FDA did not rule out the possibility that the genetic engineering of the supplement was responsible for it becoming toxic.[xxxvi]

D. Genetically Engineered Food Can Cause Allergic Reactions.

Virtually every genetically engineered transfer results in some protein production, and proteins are what cause allergic reactions in humans. Genetic engineering will bring proteins into food crops not just from known allergens, like peanuts, shellfish, and dairy, but from plants of all kinds, bacteria and viruses, whose potential allergencity is uncommon or unknown. FDA scientists warn that "[s]ince a number of proteins have been shown to cause allergic responses in man, the possibility exists that the new proteins in novel plant foods could be allergic in humans."[xxxvii]

Agency scientists explain: "Antigenic plant proteins (i.e. allergens) could become concentrated in novel plant foods by two different mechanisms. First, novel food contains new DNA that could constitutively produce a new protein allergen which was not present in the wild type plant. Alternatively, the process of insertion of the new DNA in the novel plant may cause positional mutagenesis (i.e. pleiotropy) that could enhance the synthesis of existing plant food allergens."[xxxviii] The scientists further caution that "DNA transferred to plants usually contains a gene

or genes of interest, a selectable marker gene, and regulatory DNA sequences such as promoters and terminators. It may also contain a scorable marker gene." These marker genes "produce proteins that are new with respect to plants. Because the background exposure to these proteins, e.g., from microorganisms present in the environment, would be negligible (see Chemistry memoranda), they should be considered to be new proteins in the human diet."[xxxix] Thus, these new proteins should be subject to safety evaluation for allergenicity.

E. Genetically Engineered Food Can Create Antibiotic Resistance.

Most genetically engineered plant foods are created with fully functioning antibiotic resistance genes,[xl] a practice that the British Medical Association (BMA), the Royal Society and the House of Lords Select Committee on the European Communities have criticized.[xli]

Antibiotic resistance genes are used early in the engineering process, to help select cells that have taken up foreign genes. Although they have no further use, the genes continue to be expressed in plant tissues.[xlii] The most frequently used selectable marker genes code for proteins that inactivate kanamycin, neomycin and other antibiotics.[xliii]

The presence of antibiotic resistance genes in foods could have several harmful effects. The BMA warns that the risk that antibiotic resistance may be passed on to bacteria affecting human beings cannot presently be ruled out.[xliv]

FDA scientists share similar concerns. First, these inserted antibiotic resistance genes may impact human health by possibly interfering with the oral therapeutic usage of antibiotics in humans.[xlv] Antibiotic-resistance genes produce enzymes that can degrade antibiotics. If a tomato with an antibiotic-resistance gene is eaten at the same time as an antibiotic, it could destroy the antibiotic in the stomach.[xlvi] Second, agency scientists warn, the inserted antibiotic resistance genes may create resistance in consumers to important antibiotics.[xlvii] In addition, the widespread presence of antibiotic-resistance genes in engineered food suggests that as the number of genetically engineered products grows, the effects of antibiotic resistance should be analyzed cumulatively across the food supply.[xlviii]

The BMA has demanded a ban on the use of antibiotic resistance marker genes because "the risk to human health from antibiotic resistance developing in micro-organisms is one of the major public health threats that will be faced in the 21st Century."[xlix]

F. Genetically Engineered Food Can Have Altered Nutritional Value.

As explained above, FDA scientists have evidence that desirable and undesirable pleiotropic effects have been shown to occur at frequencies up to 30% in genetically engineered plants and this may include "undesirable alterations in the levels of nutrients which may escape a breeder's attention unless genetically engineered plants are evaluated specifically for these changes.[l]

G. Consumers Have A Right to Know If Food Is Genetically Engineered.

There is overwhelming public support for the labeling of genetically engineered foods. A January 1999 poll in Time magazine poll showed that 81% of American consumers want bioengineered foods to be labeled.[li] Even a 1997 survey by the biotechnology company Novartis echoed this result, finding that 93% of Americans want FDA to require labeling of genetically engineered foods.[lii]

When the policy was first issued in 1992, the public clearly demanded the labeling of genetically engineered foods. According to the agency, approximately 80% of the comments received by the agency requested labeling of "genetically engineered" foods. Almost 25% of the commenters demanded labeling so that allergenic food consumers have the material facts necessary to distinguish genetically engineered foods.[liii] As the agency summed up, "A great deal of fear was expressed by consumers that they would not know whether they were eating foods to which they might be allergic." In addition, approximately 15% of the comments received by the agency mentioned concerns related to vegetarian, religious or ethical beliefs." The agency also states, "many consumers who avoid certain types of food for health, religious, or moral reasons expressed concern that they would not know what they were eating when eating genetically engineered foods."[liv]

Additional analysis of the 1992 comments by the FDA states: "Not surprisingly, most consumers believed that genetically engineered foods should be labeled. Almost every comment reflected this sentiment. Many also said that labels should be clear, prominent, and not restricted to fine print."[lv] And a United States Department of Agriculture poll, taken the same year, found that 85% of consumers thought that the labeling of products of genetic engineering "very important."[lvi]

Obviously, an overwhelming number of consumers are concerned about these foods and want to know if the foods that they are eating contain GMO's. (And more than likely they do. Testing conducted by Genetic ID on foods purchased from supermarket shelves found that many of them were genetically engineered, including: Kellogg's Corn Flakes, General Mills Total Corn Flakes Cereal, Quaker Chewy Granola Bars, Ball Park Franks, Duncan Hines Cake Mix, Ultra Slim Fast, Quaker Yellow Corn Meal, Aunt Jemima Pancake Mix, Alpo Dry Pet Food, Gardenburger, Boca Burger Chef Max's Favorite, McDonald's McVeggie Burgers, Ovaltine Malt Powdered Beverage Mix, Old El Paso Taco Shells, and Jiffy Corn Muffin Mix. Testing conducted by Consumers' Union found similar results.[lvii]) Consumers want to know if the food they eat contains or was produced with genetically engineered organisms for a variety of reasons, including religious and ethical considerations and concerns about the environmental, economic and health implications of bioengineered foods.

III. Argument

A. The Federal Food Drug and Cosmetic Act Requires That All Transferred Genetic Material and Expression Products Thereof in Genetically Engineered Foods Go Through Food Additive Petition Process.

Petitioners request that all genetically engineered food additives including all transferred genetic material (including but not limited to vectors, promoters and markers) and expression products thereof used in a genetically engineered food must complete the food additive petition process prior to their commercialization and allowance on the market. This request is consistent with the existing provisions of the Food Additive Amendments and, as such, is legally required by the FFDCA.[lviii]

Under the FFDCA, the FDA must regulate all food additives to ensure their safety of use prior to their appearance on the market. Rather than complying with this mandate, the FDA's current 1992 Policy excludes virtually all transferred genetic material and expression products used in genetically engineered foods on the grounds that these substances are "generally recognized as safe" (GRAS). The FDA's exclusion of these genetically engineered food additives does not comply with the plain meaning of the FFDCA nor give effect to Congress' intent.[lix] Therefore, the FDA must rescind its 1992 Policy and implement new regulations that subject all genetically engineered foods to the food additive petition process.

1. The FFDCA Requires All Transferred Genetic Materials and Their Expression Products Used in Genetically Engineered Foods To Complete The Food Additive Petition Pre-Market Review Process.

The FFDCA, as amended by the Food Additive Act of 1958, defines a "food additive" as follows:

> any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, *in its becoming a component or otherwise affecting the characteristics of any food* (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use . . ." (emphasis added)[lx]

Thus, the FFDCA excludes from the definition of "food additive" only substances that are GRAS either: (1) because they were used in foods before January 12, 1958; or (2) because they have been proven GRAS through scientific procedures. The agency has already conceded that, but for the GRAS exclusion, the transferred genetic material and intended expression products used in genetically engineered foods meet the statutory definition of "food additive."[lxi] The FDA's attempts to exempt genetically engineered foods from the definition of food additives and the requirements of the food additive petition process are illegal for the following reasons:

(a). Genetic Engineering Was Not Used in Foods Before 1958 And Cannot Be GRAS.

In its 1992 Policy the FDA erroneously misapplied the GRAS exclusions. First, because genetic engineering (including rDNA) technology was not "in use before 1958," substances used and expressed through this technology cannot be exempted from the definition of food additive on the grounds of "prior safe use."

(b). Genetically Engineered Foods Have Not Been Proven To Be Safe (GRAS) Through Scientific Procedures.

Additionally, the genetic materials and their expression products used in genetic engineering cannot be exempted from the definition of food additive because they have not been proven to be safe (GRAS) through scientific procedures. The GRAS exemption to the food additive process can only apply to a substance that has been "generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures . . . to be safe under the conditions of its intended use."[lxii] For reasons set out below, the agency cannot make such a finding.

In particular, the use of untested (and potentially unsafe) substances as food additives is precisely the situation that the Food Additive Amendments of 1958 were enacted to prevent:

> Nonetheless, existing law permits any processor who chooses to pay no heed either to the public's health or to his continuance in one particular line of business to unfairly compete with responsible processors, to defy the FDA and to endanger the health of millions by using an untested additive for as long a time as it may take for the Government to suspect the deleteriousness of his additives, schedule research into its properties and effects, and, finally - perhaps years later - to begin the years-long experiments needed to prove the particular additive safe or unsafe.[lxiii]

While Congress did not want to unnecessarily stifle technological advances, it nevertheless intended that additives created through new technologies[lxiv] be proven safe before they go to market.[lxv]

Unfortunately, the FDA has clearly violated the express intent of Congress and exposed consumers to the unique risks of genetically engineered food by applying the GRAS exclusion to the genetic materials and intended expression products from genetically engineered foods without the necessary expert consensus of such a determination based in scientific procedures. Specifically, the agency has improperly (1) chosen to treat genetically engineered crops as if they were the same as, and entail no different risk than, crops developed through traditional breeding and (2) determined that genetically engineered foods were generally recognized as safe, even though they knew that -- (a) such general recognition did not, in fact, exist and (b) they could not have been based upon scientific procedures as required by law.

(i). Genetic Engineering Is Not Equivalent to Traditional Cross-Breeding.

The FDA 1992 Policy on genetically engineered foods asserted that genetic engineering is just a "more advanced" form of traditional plant breeding and therefore need not be regulated any more stringently.[lxvi] "The agency is not aware of any information showing that foods derived by these new methods differ from other foods in any meaningful or uniform way, or that, as a class, foods developed by the new techniques present any different or greater safety concern than foods developed by traditional plant breeding."[lxvii]

However, the agency made the above assertion despite substantial and repeated warnings from its own scientists about the extent to which genetic engineering differs from conventional

practices and entails a unique set of risks. For example, Dr. Louis J. Pribyl of the FDA's Microbiology Group critiqued a draft of the Policy Statement by saying:

> The unintended effects cannot be written off so easily by just implying that they too occur in traditional breeding. There is a *profound difference* between the types of unexpected effects from traditional breeding and genetic engineering which is just glanced over in this document. This is not to say that they are more dangerous, just quite different, and this difference should be and is not addressed (emphasis added).

Dr. Pribyl added that several aspects of gene insertion ". . . may be more hazardous . . ." than traditional crossbreeding. Regarding the possible activation of "cryptic" pathways to generate unexpected toxins, Dr. Pribyl stated: "This situation IS different than that experienced by traditional breeding techniques." (emphasis in original)[lxviii]

In the same vein, Dr. Linda Kahl, an FDA compliance officer, objected that a draft of the Statement of Policy was " . . . trying to fit a square peg into a round hole . . . [by] trying to force an ultimate conclusion that there is no difference between foods modified by genetic engineering and foods modified by traditional breeding practices." She declared: "The processes of genetic engineering and traditional breeding are different, and according to the technical experts in the agency, they lead to different risks."[lxix] Thus, the record shows that FDA's own scientists consistently informed the agency that genetically engineered crops significantly differ from their conventionally produced counterparts and entail a different set of risks.

More recently, this FDA position of "substantial equivalence" has been rejected on an international level with the establishment of an international protocol on biosafety that recognizes the unique nature of organisms modified by biotechnology.[lxx] It has also been further criticized in major scientific journals.[lxxi]

(ii). There Is Not A General Recognition That Genetically Engineered Foods Are Safe.

The FDA has also ignored a substantial number of its own scientists that did not regard genetically engineered foods as safe. This clear evidence of scientific dispute within the FDA itself shows that the agency cannot exempt genetically engineered foods from the food additive petition requirements because there is no general recognition of safety within the scientific community.

In particular, the FDA's own Division of Food Chemistry and Technology cautioned, "it would . . . be necessary to demonstrate that edible seed and oils produced from genetically engineered plants do not contain unintended potentially harmful substances at levels that would cause concern." Concerning marker genes, the division warned that because they " . . . produce proteins that are new with respect to plants . . . they should be considered to be new proteins in the human diet and be subjected to safety evaluation." Regarding unintended changes, the division concluded that although most of these effects can be managed by subsequent procedures, "[n]evertheless, some undesirable effects such as increased levels of known naturally occurring toxicants, appearance of new, not previously identified toxicants, increased capability of concentrating toxic substances from the environment (e.g., pesticides or heavy metals), and undesirable alterations in the levels of nutrients may escape breeders' attention unless genetically engineered plants are evaluated specifically for these changes. Such evaluations should be performed on a case-by-case basis, i.e., every transformant should be evaluated before it enters the marketplace. (A similar approach was recommended by the International Food Biotechnology

Council . . .)." The same division added that in order to adequately address the potential of unexpected toxins, " . . . toxicological evaluation of the edible plant tissue may be more appropriate than using chemical identification and quantitation procedures."[lxxii]

FDA scientists also have pointed out that in addition to the risks posed by unintended products of rDNA technology, even those substances intentionally introduced could pose problems. For example, one scientist stated that a protein " . . . while acting on one specific, intended substrate to produce a desired effect, will also affect other cellular molecules, either as substrates, or by swamping the plant's regulatory/metabolic system and depriving the plant of resources needed for other things."[lxxiii]

Not only was the agency aware of uncertainties within its own ranks, it also knew that there was a lack of consensus about the safety of genetically engineered foods in the scientific community at large. For instance, FDA's Biotechnology Coordinator acknowledged in a letter to the Chairman of Canada's Food Directorate, Working Group on Biotechnology, dated Oct. 23, 1991, commenting on a document that working group produced: "As I know you are aware, there are a number of specific issues addressed in the document for which a scientific consensus does not exist currently, especially the need for specific toxicology tests. Also, the quantity and quality of data that would be required is not addressed and is difficult to specify at this time. I think the question of the potential for some substances to cause allergenic reactions is particularly difficult to predict."[lxxiv]

Finally, the agency recognized that there was a lack of proper scientific evidence on which to base any general recognition of safety. One FDA scientist has acknowledged that "(t)he paucity of data on recombination results with, but not exclusively on food plants, results in a difficulty in analyzing the data."[lxxv]Others have also emphasized the lack of adequate scientific data: " . . . (A)re we asking the scientific experts to generate the basis for this policy statement in the absence of any data? It's no wonder that there are so many different opinions - it is an exercise in hypotheses forced on individuals whose jobs and training ordinarily deal with facts." The FDA official continued, " . . . there is no data that could quantify risk" and acknowledged that " . . . the scientific issues section of the document [i.e., the Policy Statement] deals totally in hypotheses about 'possibilities' . . . ."[lxxvi]

Since the FDA's policy on genetically engineered foods is inconsistent with the FFDCA, as amended by the Food Additive Amendments, as well as the FFDCA's legislative history, the FDA should immediately rescind its 1992 Policy.

For the reasons stated above and to facilitate compliance with the Food Additive Petition process with regard to genetically engineered foods, petitioners request the agency to take the following action:

1. Pursuant to the procedures outlined in 21 C.F.R. § 170.38, the Commissioner shall issue a notice in the Federal Register determining that all genetically engineered food additives are not GRAS and are food additives subject to section 409 of the FFDCA;

2. Amend 21 C.F.R. §170.3 to include the following:

21 C.F.R. §170.3. Definitions.

(p) <u>Genetically engineered food</u> means food that contains or was produced with a genetically engineered material.

(1) Genetically engineered material means material derived from any part of a genetically engineered organism, without regard to whether the altered molecular or cellular characteristics of the organism are detectable in the material.

(2) Genetically engineered organism means -

(A) an organism that has been altered at the molecular or cellular level by means that are not possible under natural conditions or processes (including, but not limited to, recombinant DNA and RNA techniques, cell fusion, microencapsulation, macroencapsulation, gene deletion and doubling, introducing a foreign gene, and changing the positions of genes), other than a means consisting exclusively of breeding, conjugation, fermentation, hybridization, in vitro fertilization, or tissue culture, and

(B) an organism made through sexual or asexual reproduction (or both) involving an organism described in(A), if possessing any of the altered molecular or cellular characteristics of the organism so described."

(3) Genetically engineered food additive means a genetic construct, its protein or expression product, vector, promoter, or marker system that are used or created individually or together as a result of a genetically engineered food.

B. The Unique Characteristics of Genetically Engineered Foods and Genetically Engineered Food Additives Require Additional Safety Assessment Protocols Beyond Those Traditionally Used In The Food Additive Review Process.

The FDA's current "Guidance on Consultation Procedures Foods Derived From New Plant Varieties" is inadequate to assess the safety of genetically engineered food additives. First, the guidance is wholly voluntary and "does not operate to bind the FDA or public." Such a voluntary policy creates a legal loophole in which any genetically engineered food or genetically engineered food additive could come on the market without any safety assessment or even notification to the FDA. Second, even if made mandatory, the consultation process provides no legal basis for adequate testing and insufficient scientific direction on the types of testing and protocols that are necessary to assess the safety of a genetically engineered food or a genetically engineered food additive prior to its use in commerce.

In contrast, the FDA's food additive regulations define "safety" as "a reasonable certainty in the minds of competent scientists that the substance is not harmful[lxxvii] under the intended conditions of use" and set out certain factors that shall be considered including: "Any other safety factors that qualified experts generally recognize as appropriate."[lxxviii] Accordingly, the food additive petition assessment procedures requested in this petition also should include a finding under 21 C.F.R. § 170.3(i) that the mandatory assessment of the following risks prior to any determination of "safety" can be made as contained in the existing regulations.

1. Petitioners Demand the Establishment of Testing Protocols for Known and Unknown Allergens.

In the United States, about a quarter of all people say they have an adverse reaction to some food.[lxxix] Studies have shown that 2 percent of adults and 8 percent of children have true food allergies, mediated by immunoglobin E (IgE).[lxxx] People with IgE mediated allergies have an immediate reaction to certain proteins that ranges from itching to potentially fatal anaphylactic shock. The most common allergies are to peanuts, other nuts and shellfish.

Allergens can be transferred from foods to which people know they are allergic, to foods that they think are safe, via genetic engineering. In March 1996, researchers at the University of Nebraska confirmed that an allergen from Brazil nuts had been transferred into soybeans. The Pioneer Hi-Bred International seed company had put a Brazil nut gene that codes for a seed protein into soybeans to improve their protein content for animal feed. In an in-vitro and a skin prick test, the engineered soybeans reacted with the IgE of individuals with a Brazil nut allergy in a way that indicated that the individuals would have had an adverse, potentially fatal reaction to the soybeans.

This case was resolved successfully. As Marion Nestle, the head of the Nutrition Department at New York University summarized in an editorial in the respected *New England Journal of Medicine*, "In the special case of transgenic soybeans, the donor species was known to be allergenic, serum samples from persons allergic to the donor species were available for testing and the product was withdrawn."[lxxxi] Proteins are what cause allergic reactions, and virtually every gene transfer in crops results in some protein production. Genetic engineering will bring proteins into food crops not just from known sources of common allergens, like peanuts, shellfish and dairy, but from plants of all kinds, bacteria and viruses, whose potential allergenicity is largely uncommon or unknown. Most biotechnology companies increasingly use microorganisms rather then food plants as gene donors, or are designing proteins themselves, even though the allergenic potential of these proteins is unpredictable and untested. Consequently, Nestle continues, "The next case could be less ideal, and the public less fortunate. It is in everyone's best interest to develop regulatory policies for transgenic foods that include premarketing notification and labeling."[lxxxii]

In April 1994, the EPA, FDA and USDA hosted a "Conference on Scientific Issues Related to Potential Allergenicity in Transgenic Food Crops." The conference revealed how little is actually known about the topic. Indeed, two conclusions/observations noted by the scientists at the meeting were that there are: (i) no direct methods to assess potential allergenicity of proteins from sources that are not known to produce food allergy, and (ii) although some assurance can be provided to minimize the likelihood that a new protein will cause an allergic reaction by evaluating its similarity with characteristics of known food allergens (i.e., whether the new protein has a similar protein sequence, is prevalent in food, is resistant to enzymatic and acid degradation, is heat stable, and is of the appropriate molecular size), no single factor is predictive. Since this meeting, FDA has appeared to have taken no significant steps to increase the scientific understanding of allergenicity or to develop a truly predictive methodology for assessing allergenicity of transgenic crops.

Petitioners now request that the FDA conduct scientific research that will result in the development of a truly predictive test for allergenicity. Furthermore, at present, companies voluntarily evaluate allergenicity by looking only at the similarity of the engineered proteins with characteristics of known food allergens. As pointed out at the April, 1994 Interagency Conference, such a rudimentary approach is not completely predictive. Petitioners believe that the voluntary nature of such a review is negligent and that this type of analysis is insufficient. *Therefore, petitioners request that the FDA develop a stringent protocol for testing for allergenicity and to publish such a protocol for comment.*[lxxxiii]

In sum, the FDA is aware of this new and potentially massive allergenicity problem and the concerns regarding this class of health risks have been expressed within the health community and to the agency.[lxxxiv] The agency's scientists have repeatedly warned that genetic engineering could "produce a new protein allergen." Indeed, the agency's own scientists urged long-term testing.[lxxxv] Despite these clear warning, the FDA has failed to act.

Therefore, petitioners also request that the FDA mandate specific testing protocols for the assessment of allergenicity for all genetically engineered food additives. In instituting these new mandatory pre-market regulations, the agency should include requirements that all food additives be subject to allergenicity screening that includes, but is not limited to:

(a). Prick-puncture skin testing to determine whether the food additive triggers a specific IgE antibody response;

(b) In vitro testing screening for specific IgE (radioallergosorbent tests [RAST]) responses to a genetically engineered food additive;

(c) Use of T Cell marker assays[lxxxvi]**;**

(d) Complete molecular characterization of known allergens; and

(e) Consistent with regulatory requirements concerning informed consent, pursuant to 21 C.F.R. part 50 and 45 C.F.R. part 46, subpart A and part 690 (as applicable), an assessment of the ethical and reasonable outcomes of conducting limited double-blind placebo controlled food challenges.[lxxxvii]

2. Petitioners Demand the Establishment of Testing Protocols for Toxicity and Other Unexpected Effects.

Information has appeared in the scientific literature related to the safety of foods derived from genetically engineered plants which collectively indicates that the FDA's voluntary approach to oversight is not only not in compliance with the requirements of FFDCA, but also grossly insufficient to ensure that bioengineered foods will not pose health risks to those who consume them.[lxxxviii] This information relates to unexpected and unpredicted effects of gene insertions, and instability of the genetic characteristics that are introduced. This information further indicates that the FDA must scrutinize genetically engineered foods in a mandatory manner and more closely than it has so far, and in particular should require long-term (one- to two-year) feeding studies of the whole engineered food.[lxxxix] Requiring a complete molecular characterization for each separate transgenic line will also help FDA evaluate the potential for risk and may provide a means for FDA to decide how much additional testing is needed.

The studies which lead to greater concern about unexpected effects can be put into two categories: unpredictability of the location and expression of transgenic DNA inserts; and differences resulting from post-translational processing (e.g. proteins from the same gene are not identical in differing organisms).

(a). Unpredictability of the location and expression of transgenic DNA underlines need for long-term toxicity tests of engineered food.

The FDA maintains that genetic engineering is more precise than traditional breeding because *just* the desired gene(s) can be transferred without extra unwanted genetic material and that this increased precision "increase[s] the potential for safe, better characterized, and more predictable foods"[xc] Petitioners disagree. Although rDNA techniques may be more precise than traditional plant breeding in terms of the identity of genetic material transferred, they are less precise in terms of where the material is transferred. Conventional plant breeding shifts aberrent versions (alleles) of the same genes, which basically are fixed in the chromosomal locations as a result of evolution. With genetic engineering (or rDNA techniques), one inserts genes on essentially a random basis, using a gene "gun" or other techniques (e.g. use of Ti-plasmid, chemoporation, electroporation, etc.)

into a plant's pre-existing chromosomes. Frequently, the genetic material comes from living things with which the host organism(s) would never cross in nature.

The process of insertion of genetic material via genetic modification is unpredictable with regard to a number of parameters, including: the number of inserts of transgenic DNA, their location (chromosome, chloroplast, mitochondria), their precise position (i.e. where and on which chromosome), their structure, and their functional and structural stability. While all of these parameters can have consequences, perhaps the most important is the random or semi-random nature of the physical location of the genetic insert. The inability to control where the insertion happens is of key importance. This means that each transformation event is unique and cannot be replicated because the precise location of the insertion of genetic material always will be different.

The variable insertion site can have a number of unpredictable, and potentially negative, consequences.[xci] The insertion site can affect expression of the inserted transgene itself as well as the expression of host genes (i.e., genes in the recipient organisms). The former is known as the "position effect." A classic example involved attempting to suppress the color of tobacco and petunia flowers via the transfer of a synthetically created gene designed to turn off (via anti-sense technology) a host pigment gene.[xcii] The expected outcome was that all the transformed plants would have the same color flowers. However, the transformed plants varied in terms of the amount of color (or pigmentation) in their flowers as well as the pattern of color in the individual flowers. Not only that, but as the season changed (i.e., in different environments), some of the flowers also changed their color or color pattern. The factors contributing to the position effect are not fully understood.

The expression of host genes can be influenced by the location of the genetic insertion as well. If the material inserts itself into "the middle" of an important gene, that gene would functionally be turned off. In one experiment, insertion of viral genetic material into a mouse chromosome lead to disruption of a gene which resulted in the death of the mouse embryos.[xciii] If the "turned off" gene happened to code for a regulatory protein which prevented the expression of some toxin, the net result of the insertion would be to increase the level of that toxin.

The genetic background of the host plant can also affect the level of expression of the transferred gene, which explains the common observation that varieties of the same plant species varied widely in the ease with which they can be genetically engineered.[xciv] In some varieties, the trait can be expressed at high enough levels to have the desired impact. In others, the expression level is too low to have the desired impact. In general though, scientists do not really understand why some plant varieties yield more successful results in GE than other varieties.

To get around the common problem of an insufficient level of expression of a desired gene product, powerful regulatory elements—particularly promoters/enhancers—are inserted along with the desired transgene and used to maximize gene expression. The promoter has numerous elements that enable it to respond to signals from other genes and from the environment which tell it when and where to switch on, by how much and for how long. When inserted into another organism as part of a "genetic construct," it may also change the gene expression patterns in the recipient chromosome(s) over long distances up- and down-stream from the insertion site. If the promoter (plus associated transgenes) is inserted at very different places on a given chromosome or on different chromosomes, the effects may be very different; it will depend on the nature of the genes that are near the insertion site. This uncertainty of insertion site, along with the promoter means that for all transgenic plants, there will be a fundamental unpredictability with regard to: expression level of the inserted foreign gene(s); expression of a vast number of the recipient organism's own

genes; influence of geographical, climate, chemical (i.e., xenobiotics) and ecological changes in the environment; and transfer of foreign genetic sequences within the chromosomes of the host organism, and vertical and/or horizontal gene transfer to other organisms. Such unpredictability explains the common observations that different insertion events in the same variety can vary greatly in terms of the level of expression of the desired transgene and that the majority of transformation events do not yield useful results (i.e., the transgenic plant is defective in one way or another).

The unpredictable influence of the environment may explain what went wrong in Mississippi and Texas with thousands of acres of Monsanto's glyphosate tolerant (Roundup Ready®) cotton and Bt cotton. In the first year of commercial planting in Mississippi, approximately 30,000 acres of the glyphosate-tolerant cotton malfunctioned, causing up to $500,000 in damage. Large numbers of the plants dropped their cotton bolls before harvest, in others the tolerance genes were not properly expressed, so that the GE plants were killed by the herbicide. Inspectors from the state agriculture department found "extensive problems of aborted and deformed bolls."[xcv] Monsanto maintained that the malfunctioning was due to "extreme climatic conditions." A number of farmers sued and Monsanto ended up paying millions of dollars in out-of-court settlements.[xcvi]

Similarly, in Texas, a number of farmers had problems with Monsanto's Bt cotton in the first year of planting. In up to 50% of the acreage, the Bt cotton failed to provide complete control (a so-called "high dose") to the cotton bollworm (*Helicoverpa zea*). In addition, numerous farmers had problems with germination, uneven growth, lower yield and other problems. The problems were widespread enough that the farmers filed a class action against Monsanto. Just a few months ago, Monsanto settled the case out of court, again by paying the farmers a significant sum.[xcvii] If there could be this unexpected effect on the growing characteristics of the cotton, it is theoretically possible that their could be changes in the plant itself which affect the nutritional or safety characteristics of the plant (used as cattle feed) or the seed (the oil from which is used in a number of food products). *Thus, petitioners request that the FDA should immediately establish regulatory procedures for assuring long term safety.*

The unpredictability associated with the process of genetic engineering itself could lead to unexpected effects such as the production of a toxin that does not normally occur in a plant or the increase in a level of a naturally occurring toxin. An example of the former occurred in an experiment with tobacco plants engineered to produce gamma-linolenic acid. Although the plants did produce this compound, another metabolic pathway ended up producing higher quantities of a toxic compound, octadecatetraenic acid, which does not exist in non-engineered plants.[xcviii]

An example of an increase in a naturally occurring toxin occurred in an experiment involving yeast where genes from the yeast were duplicated and then reintroduced via genetic engineering. The scientists found that a three-fold increase in an enzyme in the glycolytic pathway, phoshofructokinase, resulted in a 40-fold to 200-fold increase of methylglyoxal (MG), a toxic substance which is known to be mutagenic (i.e., tests positive in an Ames test). This unexpected effect occurred even though the inserted genetic material came from the yeast itself. As the scientists themselves concluded, "Although, except for the case of microbes, we have no information as to the toxic effect of MG in foods on human beings, the results presented here indicate that, in genetically engineered yeast cells, the metabolism is significantly disturbed by the introduced genes or their gene products and the disturbance brings about the accumulation of the unwanted toxic compound MG in cells. Such accumulation of highly reactive MG may cause a damage in DNA, thus suggesting that the scientific concept of "substantially equivalent" for the

safety assessment of genetically engineered food is not always applied to genetically engineered microbes, at least in the case of recombinant yeast cells. . . . Thus, the results presented may raise some questions regarding the safety and acceptability of genetically engineered food, and give some credence to the many consumers who are not yet prepared to accept food produced using gene engineering techniques."[xcix]

A controversial study is that of Ewen and Pusztai published in *Lancet* in late 1999.[c] That study used potatoes that were genetically engineered to contain a chemical from the snow drop plant (a lectin, *Galanthus nivalis* agglutinin [GNA]) to increase resistance to insects and nematodes. Feeding experiments with rats demonstrated a number of potentially negative effects. The study found variable effects on the gastrointestinal tract, including proliferation of the gastric mucosa. Interestingly, the potent proliferative effect on the jejunum was seen only in the rats fed GE potatoes with contained the GNA gene but not in rats fed non-transgenic potatoes to which GNA had been added. Indeed, the authors explain, a previous feeding study utilizing GNA with a 1,000-fold higher concentration than the level expressed in the GE potatoes had found no proliferative effect. The authors proposed "that the unexpected proliferative effect was caused by either the expression of other genes of the construct or by some form of positioning effect in the potato genome caused by GNA gene insertion."[ci] Such a fine-grained feeding study, which involved utilizing young rats which were still growing and involved weighing various organs and looking very carefully for effects on various organ systems and the immune system is far more detailed than the general feeding studies done utilizing GE plants. While many criticisms have been leveled at this study, petitioners believe it raises important questions that merit further research.

The most commonly used promoter in plant genetic engineering is one from the cauliflower mosaic virus (CaMV); all GE crops on the market contain it.[cii] A promoter has numerous elements that enable it to respond to signals from other genes and from the environment which tell it when and where to switch on, by how much and for how long. A CaMV promoter is used for a number of reasons: because it is a very powerful promoter, because it is active in all plants—monocots, dicots, algae—and in *E. Coli* because it is not greatly influenced by environmental conditions or tissue types. CaMV has two promoters, 19S and 35S, but the 35S is the one most frequently used because it is the most powerful. The powerful nature of the CaMV 35S promoter means that it is not readily controlled by the host genes that surround it and often yields a high expression level of the transgene next to it. This is not unexpected as CaMV is a virus that is designed to hijack a plant cell's genetic machinery and make many copies of itself. This also means that it is designed to overcome a plant cell's defensive devices that are intended to prevent foreign DNA from being expressed. In the case of transgenic crops, however, the CaMV promoter is used to put the transgenes outside the normal regulatory circuits of the host organism and have them expressed a very high levels. Being placed outside of normal regulatory circuits may be one of the reasons why genetically engineered foods are known to be so unstable.[ciii] The questions raised by the extensive use of the CaMV 35S promoter in engineered crops should be investigated with further research.[civ]

(b) Post-translational processing underlines need for long-term toxicity tests of engineered foods.

Another area of study that raises serious questions about the safety of transgenic traits is the phenomenon of post-translational processing, which consists of the modification of a protein after it has been translated from the genetic message. In addition, such post-translational processing can have a significant impact on the structure and function of a gene. Furthermore, post-translational processing can differ between organisms, so that the same gene expressed in different genetic

backgrounds may have the same amino acid sequence but may differ in structure and function. Examples of such processing includes glycosylation, methylation and acetylation.

Glycosylation consists of the addition of sugar groups (usually oligosaccharides) and can dramatically affect the three-dimensional structure and thus function of a protein. Indeed, glycosylation is thought to be connected to allergenic and immunogenic responses.[cv] Different proteins produced from the same gene are called glycoforms. Research with recombinant human tissue plasminogen activator (rt-PA) revealed that different glycoforms were created depending on whether the rt-PA gene was expressed in human, Chinese hamster ovary, or mouse cells.[cvi] Different glycoforms were even produced when different human cell lines were used.[cvii] The activity (or behavior) of these glycoforms differed. Further work demonstrated that when the rt-PA gene was inserted into tobacco, although it was expressed and the protein had the normal amino acid sequence, it had no physiological activity whatsoever.[cviii] Scientists argue that recombinant glycoproteins produced in plants could be allergenic as it is known that many allergens are glycoproteins.[cix]

But perhaps the most dramatic example of how glycosylation can affect the structure and function of proteins and have negative results occurs with the prion protein, which is thought to be the causative agent for transmissible spongiform encephalopathies [cx] Prion proteins are a normally found attached to the surface of cells in the nerve and immune system. Research has demonstrated that the prion proteins in people suffering nvCJD—a particularly severe form of Creutzfeldt-Jakob disease (CJD) that recently has been strongly linked to bovine spongiform encephalopathy (BSE)—have a glycosylation pattern that differs significantly from that of prion proteins from people suffering other forms of CJD and is identical to the glycosylation patterns of prion proteins from cows with BSE.[cxi] This occurs despite the fact that the amino acid sequence from normal prion proteins and those suffering nvCJD is identical. In this case, the altered glycosylation pattern has had a catastrophic effect on the behavior of the prion protein.

Given that glycosylation patterns can dramatically change the structure and function of proteins and may affect antigenicity and allergenicity, petitioners request that FDA's regulatory implementation of testing for toxicity and unexpected effects must require information on the glycosylation patterns of all transgenes expressed in GE foods.

Acetylation of proteins consists of the addition of acetyl groups to certain amino acids, thereby modifying their behavior. Although incompletely understood, acetylation of the amino acid lysine has been most studied in certain groups of proteins that bind with DNA—histones and high-mobility group proteins—and such acetylation appears to be involved with the regulation of interaction of these proteins with negatively charged DNA molecules.[cxii] However, it has been discovered that some of the lysine residues in recombinant Bovine Growth Hormone (rBGH) are acetylated, to form epsilon-*N*-acetyllysine when it is produced in *E. coli* . Harbour et al. (1992) found this to occur at lysine residues 157, 167, 171 and 180 or rBGH, while Violand et al. (1994) found it at residues 144, 157, and 167.[cxiii] The creation of this mutant amino acid may be overlooked because "(T)he identification of this amino acid cannot be determined by simple amino acid analysis because the acetyl group is labile to the acidic or basic conditions normally used for hydrolysis."[cxiv] The effect this has on the safety, structure and function of rBGH is not known as it has not been actively studied.

The differences in glycosylation and acetylation that can happen when transgenes are expressed in plants or bacteria can possibly affect toxicity and therefore lend further support to the need for toxicity testing using the whole engineered food. At present, to test for acute toxicity of a given transgene, the companies invariably do not use the protein that is produced in the plant itself.

Rather, in order to obtain large enough quantities of the protein for testing, the companies will put the transgene into a bacteria (invariably, *E. coli*), isolate the expression product (i.e. the protein) and use that for the acute toxicity testing. However, the protein produced in the bacteria may be glycosylated differently than the same protein produced in the plant. Even if there are no differences in glycosylation, acetylation of lysine residue(s) could cause differences. The presence of such mutant lysine residues could easily be missed as routine amino acid analysis will remove the acetyl group; to find if there are mutant lysine residues, one must specifically look to the transgene of interest (gene for herbicide tolerance or Bt endotoxin, for example).[cxv] *Thus, petitioners request that FDA require the companies to use material derived from the transgenic plants themselves in toxicity studies rather than bacterially-derived proteins.*

Methylation is the process of putting methyl groups on a molecule. Methylation of DNA, which occurs with the nucleotide bases cytosine and adenosine, is important as this appears to prevent that piece of DNA from being expressed (or "turned on"). Methylation is one of the mechanisms behind the phenomenon of "gene silencing," whereby a cell "turns off" a gene. Transgenic work has found that if you try to insert multiple copies of a gene into a plant, the plant will frequently turn off all, or all but one, of the copies of the transgene.[cxvi] Indeed, some scientists now think that gene silencing is an important defense mechanism that plants use to prevent foreign DNA from being expressed (other mechanisms exist to try to degrade the foreign DNA before it can enter the nucleus of the cell).[cxvii] This should be combined with the recent finding that tobacco plants may contain large numbers of copies of pararetroviral-like sequences, in some cases reaching copy numbers of about 10,000.[cxviii] This study is quite striking as it was previously thought that plant viruses rarely integrate, if at all, into host genomes. Furthermore, such integrated viral genetic material is normally silenced via methylation, so that there could be a lot of dormant viral sequences in plants. Interestingly, the cauliflower mosaic virus promoter (CaMV 35) used in virtually all transgenic plants on the market is a pararetrovirus-derived sequence (i.e. CaMV is a pararetrovirus).

With methylation, the danger exists that the CaMV 35S promoter, being a very powerful "on switch" that can have effects thousands of base pairs upstream and downstream from an insertion point, could inadvertently "turn on" a foreign gene that has previously been silent. Recent studies have suggested that horizontal gene transfer may be more common than previously thought and that most such foreign DNA, if it survives and is able to incorporate itself in the host genome, is frequently "silenced" via methylation. Thus, there is a potential risk that some harmful dormant genetic material will be inadvertently turned on due to the presence of the CaMV promoter. Therefore, it becomes important to know the exact insertion site of any and all genetic construct. It also becomes critical to know what the genetic sequence is for thousands of base pairs upstream and downstream from the insertions site and to do long term toxicity tests with the whole engineered food.[cxix]

For all of the reasons stated above, and because of the random nature of the genetic transformation process, each random insertion of transgenic DNA will differ in location and in structure from all other inserts.[cxx] It will be accompanied by a different pattern of unintended positional and pleiotropic effects due, respectively, to the location of the insert and the functional interaction of the insert with host genes. Thus, each transgenic line resulting from the same process, despite using the same vector system and plant materials under the same conditions, will be distinct, and must be treated as such.[cxxi] *Consequently, petitioners request that the FDA require the companies to submit data for each separate transgenic line. For every line, petitioners request that FDA should require a complete molecular characterization of each line with respect to the identity, stability and unintended positional and pleiotropic*

effects. And based on the results of such characterization, the agency could decide on how much toxicity data to require.

The components of a complete molecular characterization for molecular identity should include, for each transgenic or transformed line:

(a). Total number of inserts of transgenic DNA;

(b). Location of each insert (organelle [chloroplast, mitochondria, etc.] or chromosomal);

(c.) Exact chromosomal position of each insert;

(d) Structure of each insert (whether duplicated, deleted, rearranged, etc.);

(e) Complete genetic map of each insert including all elements (coding region, noncoding regions, marker gene, promoters, enhancers, introns, leader sequences, terminators, T-DNA borders, plasmid sequences, linkers, etc., including any truncated, incomplete sequences);

(f). Complete (nucleotide) base sequence of each insert; and

(g). (Nucleotide) base sequence of at least 10kbp (10,000 base pairs) of flanking host genome DNA on either side of the insert, including changes in methylation patterns.

To determine stability, the FDA needs data on both functional stability (level of expression remains constant over time and over successive generations) and structural stability (location in the genome and structural arrangement of the insert). For functional stability, FDA would need data on the level of expression of the transgene over time—throughout the lifetime of the plant as well as over a number of generations.[cxxii] For structural stability, the FDA would need data on the physical location of the insert in the genome as well as the structure of the insert—throughout the lifetime of the plant as well as over successive generations. In addition, the FDA would require appropriate molecular probes for each insert with flanking host genome (organelle sequence) sequences in order to monitor the structural stability of the insert.

To test for unintended positional effects, the FDA should look carefully at the methylation patterns of the genes in the flanking host genome DNA (data we suggest be required under molecular identity characterization). To look for pleiotropic (as well as positional effects), each transformed line must be identified in terms of total protein profile and metabolic profiles. The total protein profiles would help to monitor for unintended changes in the pattern of gene expression while the metabolic profile would help to monitor for unintended changes in metabolism. The use of mRNA fingerprinting and protein fingerprinting as part of the protein profiles would represent a better, finer screen for detecting novel biochemical, immunological or toxicological hazards. Some such tests have been suggested by a Dutch government team and should be more carefully considered by the FDA[cxxiii] If any of these tests found differences, there would be more reasons to ask for more comprehensive toxicity testing.

In sum, the FDA has been well aware of the "genetic instability" problem prior to establishing their voluntary compliance, no-testing policy. FDA scientists have warned that this problem could create dangerous toxins in food and is a significant health risk. The agency's scientists specifically warned that the genetic engineering of foods could result in "increased levels of known naturally occurring toxicants, appearance of new, not previously identified toxicants,

increased capability of concentrating toxic substances from the environment (e.g., pesticides or heavy metals). . . ."[cxxiv] These same FDA scientists recommended that long term toxicological tests be required prior to the marketing of GE foods.[cxxv]

Consistent with the precautionary approach suggested by the FDA's own scientists, petitioners request that the agency also require the use of chemical/biochemical and/or toxicological bioassays necessary to assess the creation of novel toxins or the elevation of existing toxins as a result of the use of genetic engineering and the use of genetically engineered food additives. *Accordingly, petitioners request that the agency require that all food additive reviews for genetically engineered food additives include tests to determine the potential for unexpected effects using molecular characterization (as outlined above), biochemical characterization, mRNA profiling or other techniques, long-term feeding studies or, as appropriate, a combination of such techniques.*

C. Petitioners Demand the Elimination of Antibiotic Resistance Markers Systems.

In 1991-1992, when FDA was developing its policy of GE plants, the conventional wisdom in the scientific community was that DNA was a very fragile molecule that would be readily broken down in the environment and would not survive digestion in the gut. We now know that both assumptions may not always be valid.[cxxvi] Even though DNases (molecules that break down DNA) are widely distributed in the environment, free DNA has been found in all ecosystems (marine, fresh water, sediments) studied.[cxxvii] Indeed, pooled data suggest that free DNA is present in significant amounts in the environment. Larger amounts of DNA are extracted from soil than can be extracted from the cells in the soil.[cxxviii] Further studies have shown that this free DNA in the soil comes from microorganisms that no longer occur in that habitat thus demonstrating that DNA can out-survive the organism it came from and still be capable of being taken up and expressed by microorganisms. Finally, yet other studies have found that pollution (i.e., xenobiotics) can affect the survivability of DNA and the possibility of its transfer to other organisms.[cxxix]

These data lead to serious concerns about the antibiotic resistance marker genes that are present in virtually all engineered plants presently on the market. These genes code for proteins that confer resistance to a given antibiotic. The possibility therefore exists that these genes for antibiotic resistance could be taken up by bacteria, thus exacerbating the already very serious problem of antibiotic resistance in disease causing organisms.

In mammalian systems, the question is whether foreign DNA can survive digestion, be taken up through the epithelial surfaces of the gastrointestinal or respiratory tract, or be excreted in feces. Studies in the 1970s[cxxx] and 1980s[cxxxi] in rats and ruminants, respectively, suggested that DNA was readily digested. However, the methods used to detect DNA in these studies were not very sensitive. In the mid-1990s, researchers in Germany, using far more sensitive methods, had different results.[cxxxii] Mice were fed DNA from the M13 bacteriophage either by pipette or by adding it to the feed pellets. Using sensitive hybridization methods and PCR (polymerase chain reaction) the authors found 2-4% of the M13 DNA in feces and 0.01-0.1% in the blood—both in serum and cell fraction. Sizeable DNA fragments (almost a quarter of the M13 genome) could be found up to 7 hours after uptake.[cxxxiii]

If free DNA is not immediately digested in the gastrointestinal tract, the possibility also exists that it can be transferred to bacteria that live there. A recent study utilizing a simulated human gut demonstrated that naked DNA had a half-life of 6 minutes, more than enough time for such DNA to transform bacteria.[cxxxiv]

In another experiment, a genetically engineered plasmid was found to survive (6 to 25%) up to an hour of exposure to human saliva.[cxxxv] Partially degraded plasmid DNA also successfully transformed *Streptococcus gordonii* (a bacteria that normally lives in the human mouth and pharynx), although the frequency of transformation dropped exponentially with time. Transformation occurred with either filter-sterilized human saliva or unfiltered saliva. The study also found that human saliva contains factors that increase the ability of resident bacteria to become transformed by "naked" DNA. Since transgenic DNA from food is highly unlikely to be completely broken down in the mouth, it may be able to transform resident bacteria. Of particular concern would be the uptake of transgenic DNA containing antibiotic resistance marker genes, which are found in the majority of GE crops presently on the market.[cxxxvi] It should be pointed out that the antibiotic marker gene present in Novartis' B.t. corn, which codes for resistance to ampicillin, is under the control of a bacterial promoter rather than a plant promoter which would further increase the possibility of expression of the ampicillin resistance gene if it were taken up by bacteria.

In September, 1998, the British Royal Society put out a report on genetic engineering that called for ending the use of antibiotic resistance marker genes in engineered food products.[cxxxvii] In May, 1999, the British Medical Association released a report calling for a prohibition on the use of antibiotic resistance mark genes in genetically engineered plants.[cxxxviii] The BMA's announcement is consistent with recommendations made by the FDA's own scientists in 1992. In particular, an entire division within FDA stated, "It would be a serious health hazard to introduce a gene that codes for antibiotic resistance into the normal flora of the general population."[cxxxix]

Therefore, petitioners urge FDA to prohibit use of antibiotic resistance marker genes as there is no consumer benefit for the presence of such genes in engineered foods and a significant potential risk. Included in this request is that the agency immediately rescind regulations established for the use of kanamycin resistance marker systems including 21 C.F.R. § 173.170 and 21 C.F.R. § 573.130.

D. The National Environmental Policy Act Requires The FDA To Complete a Programmatic Environmental Impact Statement Analyzing Its Approval of the Commercialization of Genetically Engineered Foods.

Petitioners request that the agency complete a programmatic environmental impact statement (PEIS) on the commercialization of the class of genetically engineered foods[cxl] because, in addition to the human health threats of allergenicity, toxicity and antibiotic resistance explained above, the FDA's actions have other significant impacts on the human environment. These impacts include adverse effects on Monarch butterfly populations, endangered species and other non-target organisms, as well as the threat of resistance leading to the increased use of pesticides. The warnings about potential adverse environmental effects come from scientists inside the agency and outside as well, and more and more scientific studies are showing a panoply of significant environmental risks posed by the commercialization of genetically engineered foods.

(1) Both NEPA and CEQ Regulations Require The FDA To Prepare a PEIS on Genetically Engineered Foods.

NEPA is the "basic national charter for protection for the environment"and applies to all federal agencies.[cxli] Its purposes are to "promote efforts which will prevent or eliminate damage to the environment and biosphere and stimulate the health and welfare of man,"[cxlii] and to "insure that environmental information is available to public officials and citizens before decisions are made and before actions are taken."[cxliii]

To that end, NEPA specifically states:

> The Congress authorizes and directs that, to the fullest extent possible: ... (2) all agencies of the Federal Government shall- (C) include in every recommendation or report on proposals for legislation and other major Federal actions significantly affecting the quality of the human environment, a detailed statement by the responsible official on -- (i) the environmental impact of the proposed action, (ii) any adverse environmental effects which cannot be avoided should the proposal be implemented, (iii) alternatives to the proposed action, (iv) the relationship between local short-term uses of man's environment and the maintenance and enhancement of long-term productivity, and (v) any irreversible and irretrievable commitments of resources which would be involved in the proposed action should it be implemented.[cxliv]

NEPA has a dual purpose. First, it "places upon the agency the obligation to consider every significant aspect of environmental impact of a proposed action."[cxlv] Second, it "ensures that the agency will inform the public that it has considered environmental concerns before going forward with a proposed action."[cxlvi] The statute is designed to inject environmental considerations into federal agency decisionmaking and "to inform the public that the [federal] agency has considered environmental concerns in its decision making process."[cxlvii]

To accomplish these purposes, NEPA requires all federal agencies to prepare a "detailed statement" regarding all "major federal actions significantly affecting the quality of the human environment . . ."[cxlviii] This statement - known as an Environmental Impact Statement ("EIS") - requires a federal agency to review, *inter alia*, the adverse environmental effects which cannot be avoided should its proposal be implemented.[cxlix] The possible effects from a proposed action that must be reviewed include not only ecological impacts, but also direct, indirect, or cumulative impacts affecting public health.[cl] The duties under this section of NEPA are not "inherently flexible."[cli] In fact, "[c]onsideration of administrative difficulty, delay or economic cost will not suffice to strip the section of its fundamental importance."

In this case, by not preparing an EIS, the FDA not only failed to take the requisite "hard look" at the environmental consequences of its actions, but took no look whatsoever at the potential impacts caused by genetically engineered foods on the human environment. This procedural abdication occurred in direct contravention of recommendations from within the FDA. In a memo to FDA's Task Group on Food Biotechnology, the Environmental Sciences Staff stated "[i]t is our opinion that the full integration of environmental safety, as mandated by NEPA, into the decision-making process for the evaluation of transgenic plants and microorganisms is required for the promulgation of this policy."[clii]

Consistent with FDA's obligations under NEPA, the environmental staffs from the Center for Food Safety and Applied Nutrition and the Center for Veterinary Medicine developed a point by point 11-page framework for the FDA to use in assessing the environmental impacts associated with the commercial applications of plant biotechnology. This assessment framework laid out a host of specific environmental impacts associated with genetically engineered foods including, but not limited to, the impacts directly associated with the expression of the modified genome of the subject plant, with the transfer of genetic sequences to other plants and with the production of modified plant varieties. The framework also noted the need to review the numerous indirect impacts

associated with changes in agricultural and processing practices that result from the commercial use of these genetically engineered plants.[cliii] Despite the framework's acknowledgment of such impacts, agency review of the Policy under the framework was terminated because it was too detailed and could have provided "a possible basis for later legal challenges."[cliv]

Coinciding with the completion and subsequent dismissal of its review framework, the FDA specifically admitted several new environmental concerns resulting from genetically engineered food including: "FDA is concerned with the potential environmental impacts associated with changes in current agricultural practices that may arise during the commercialization of a modified food crop;" "FDA is concerned that some commercial applications of genetically modified food crops may involve changes in processing methods;" and "FDA is concerned with the potential release, movement, and establishment of transforming vectors in the environment."[clv] The agency even concluded that an umbrella regulation concerning genetically engineered foods "would require that FDA develop an environmental assessment under NEPA and possibly an Environmental Impact Statement."[clvi] The FDA's failure to complete a programmatic analysis of the potential environmental impacts of its 1992 Policy Statement on genetically engineered foods violates this statutory mandate.

In addition, the failure of the FDA to perform a programmatic analysis for its genetically engineered foods program arbitrarily and capriciously ignores federal regulations promulgated by the Council on Environmental Quality (CEQ) requiring agencies to undertake a NEPA analysis.[clvii] These regulations specifically address the need for the FDA to prepare an EIS for all major federal actions including:

> Adoption of programs, such as a group of concerted actions to implement a specific policy or plan; systematic and connected agency decisions allocating agency resources to implement specific statutory program or executive directive.[clviii]

The CEQ regulations also require programmatic EISs for "broad" federal actions such as the agency's 1992 Policy allowing the commercialization of genetically engineered foods.[clix] The regulations also specify when broad federal actions are to be evaluated including "actions which have relevant similarities, such as common timing, impacts, alternatives, methods of implementation, media, or subject matter."[clx] The successive conclusion of 45 genetically engineered food consultations is such a federal action.[clxi]

The FDA's policy allowing the large-scale commercialization of genetically engineered foods represents a broad federal action that will have adverse environmental impacts. As stated previously, the commercialization of several transgenic foods will result in adverse impacts on the human environment including, but not limited to, toxicity, allergic reactions and antibiotic resistance in humans; harm to Monarch butterflies, endangered species and other non-target organisms; and increased pesticide usage. The commercialization of genetically engineered crops also threatens to eliminate the effectiveness of many organic agricultural practices, such as the use of naturally occurring *Bacillus thuringiensis* (B.t.) and non-target organisms such as lacewings. At a minimum, the commercialization of genetically engineered foods marks a series of related actions that will have a cumulative environmental impact. As when several proposals for related actions that will have a cumulative or synergistic environmental impact upon a region, the successive consultations and commercialization of genetically engineered foods by an agency means that their environmental consequences must be considered together.[clxii]

The CEQ regulations defining "scope" also provide guidance by advising the preparation of a programmatic impact statement on "cumulative actions, which when viewed with other proposed actions have cumulatively significant impacts and should therefore be discussed in the same impact statement."[clxiii] The relevant CEQ regulation defines cumulative environmental impacts that should be assessed:

> "Cumulative impact" is the impact on the environment which results from the incremental impact of the action when added to other past, present, and reasonably foreseeable future actions regardless of what agency (Federal or non-Federal) or person undertakes such other actions. Cumulative impacts can result from individually minor but collectively significant actions taking place over a period of time.[clxiv]

The possible effects from a proposed action that must be reviewed include not only ecological impacts, but also direct, indirect, or cumulative impacts affecting public health.[clxv] "NEPA requires an EIS to disclose the significant health, socioeconomic, and cumulative consequences of the environmental impact of a proposed action."[clxvi] These duties under this section of NEPA are not "inherently flexible."[clxvii] In fact, "[c]onsideration of administrative difficulty, delay or economic cost will not suffice to strip the section of its fundamental importance."[clxviii]

For the reasons stated above, petitioners request that the agency complete a programmatic environmental impact statement (PEIS) analyzing the agency's major federal action of approving food additive petitions for genetically engineered foods and genetically engineered food additives.

(2) The FDA May Not Categorically Exclude Its Genetically Engineered Foods Program From NEPA Review.

Petitioners request that the FDA find that genetically engineered food additive petitions are not categorically excluded from NEPA review pursuant to 21 C.F.R. §§ 25.30, 25.32.

An agency may "categorically exclude" a proposed action from NEPA review only if the project falls squarely in a category of agency decisions that do not "individually or cumulatively have a significant effect on the human environment."[clxix] The Council on Environmental Quality ("CEQ"), an agency within the Executive Office of the President, has promulgated regulations implementing NEPA that set forth specific factors that agencies must consider when determining whether to prepare an EIS, including whether an action will "significantly" affect the environment.[clxx] These factors for determining the "significance" of an action include: (1) the degree to which the effects on the quality of the human environment are likely to be highly controversial; (2) the degree to which the possible effects on the human environment are highly uncertain or involve unique or unknown risks; or (3) the degree to which the action may establish a precedent for future actions with significant effects or represents a decision in principle about a future consideration."[clxxi] The "presence of one or more of these factors should result in an agency decision to prepare an EIS."[clxxii]

Clearly the evidence before the agency shows that, by allowing unlabeled and untested genetically engineered foods on the market, all three CEQ factors of "significance" are present, thereby triggering full NEPA review.

(a) The Effect of Genetically Engineered Foods on the Human Environment Is Highly Controversial.

The commercialization of genetically engineered foods has been "highly controversial," in that a "substantial dispute" exists as to the "size, nature, or effect" of the agency's action.[clxxiii] The agency's action has sparked a substantial public outcry and is contrary to the evidence before the agency showing that these novel foods present many unknown safety and environmental effects.

The controversial nature of the commercialization of genetically engineered foods is immediately apparent by reviewing the large number of comments sent to the FDA by outraged consumers protesting the marketing of these novel foods.[clxxiv] Only 2% of commenters supported FDA's action whereas a significant number questioned the safety (testing and allergies) and environmental effects posed by these novel foods.[clxxv] Many commenters challenged the safety of the "changes in the soil where bioengineered plants are grown, in animals that eat the bioengineered plants, and in the plants themselves."[clxxvi] Other commenters were concerned that novel plants genetically engineered to be herbicide tolerant will result in the indiscriminant and greater use of pesticides.[clxxvii]

Beyond the immediate comments, the public has consistently responded that the presence of genetically engineered foods in the human environment is controversial. A September 1999 poll for the Grocery Manufacturers of America found that 92% of all Americans support the labeling of all genetically engineered foods. This echoed the results of a 1997 poll conducted by the biotechnology firm Novartis, which found that 93% of the citizens responding to its poll wanted transgenic foods to be labeled. In addition, in January 2000, 89% of those citizens responding to an MSNBC live vote demanded that the government require premarket safety testing of genetically engineered foods.[clxxviii] Also, new studies indicating that some genetically engineered crops could be contributing to declining populations of Monarch butterflies have triggered significant public outcry.[clxxix] The New York Times Sunday Magazine recently ran a cover story detailing both consumer and farmer concerns about the use of genetically engineered food.[clxxx]

Furthermore, the commercialization of transgenic foods is extremely controversial among the agency's own scientific experts because, among other things, "[t]here is no data that addresses the relative magnitude of the risks" connected with genetically engineered food."[clxxxi] In a memo to the Toxicology Section of the Biotechnology Workgroup, an FDA official expressed two warnings regarding the safety of genetically engineered foods by stating: (1)"it is possible that all of the recommended test methods could miss an unexpected toxicological effect of novel foods that is only detected in a heterogeneous human population" and (2) "some proteins in genetically modified plant foods (*i.e.* novel foods) might induce allergic reactions in people, because certain proteins from normal plant foods have been documented to cause food allergies."[clxxxii] Despite these warnings from the FDA' own scientific experts about the potential safety hazards with genetically engineered foods, FDA allowed these novel foods to enter the market without considering any impacts on human health or the environment as required under NEPA.

Accordingly, there can be no legitimate question that the effects of decision to allow the commercialization of transgenic foods is "highly controversial" within the meaning of the CEQ regulations. Therefore, the agency cannot use a categorical exclusion to avoid preparing an EA or an EIS.

(b) The Possible Effect of Genetically Engineered Foods on the Human Environment is Highly Uncertain.

The FDA's decisions on the commercialization of genetically engineered foods are also "significant" because the effect on human health and the environment involves "highly uncertain" and "unique or unknown risks." FDA even admits that "unlike classical breeding methods, the theoretical possibility exists that pleiotropic and other related unintentional effects may occur through the use of DNA insertion techniques now available, and that these could cause a detrimental change in the level of natural nutrients or toxins in a transformed plant."[clxxxiii] These pleiotropic effects or unintentional effects include "poor growth, reduced levels of nutrients, increased levels of natural toxicants, etc." and are expected to occur as much as 30% of the time in genetically engineered plants.[clxxxiv] Furthermore, FDA's own molecular biologists caution that "the interactions between the host and inserted gene's DNA, RNA, and expressed product are still not predictable."[clxxxv]

Evidence of "unique" environmental impacts is also demonstrated by the FDA' scientific experts who conclude that "animal feeds derived from genetically modified plants present some unique safety concerns."[clxxxvi] It is precisely these kind of "uncertain" and "unique" environmental impacts that must be analyzed under NEPA before an agency implements its action. The very purpose of the EIS requirement, as the Supreme Court has emphasized, is to ensure that an "agency will not act on incomplete information only to regret its decision after it is too late to correct."[clxxxvii] In light of the incomplete information showing that genetically engineered foods are safe, FDA's action in allowing genetically engineered foods to enter the market is clearly "significant" agency action.

(c) The FDA's Action Sets A Precedent Concerning the Regulation of Genetically Engineered Foods.

FDA's action is also "significant" in that it establishes a precedent for the future regulation of all genetically engineered foods. For the first time, manufactures of genetically engineered foods are now able to market these novel foods without seeking FDA approval. The FDA has recognized the unprecedented nature of this action. James Maryanski, FDA's coordinator for the 1992 Policy, describes the agency's rule as an "unprecedented step" because it was the first time the agency specifically stated "the safety issues that should be taken into account in developing new varieties of fruits and vegetables."[clxxxviii]

The precedent setting nature of the FDA' action is also demonstrated by the number of genetically engineered foods on the market. Forty-five different genetically engineered foods are known to be commercially viable or currently available to consumers.[clxxxix] Despite opening the door to these unique foods with uncertain effects, FDA has never considered any environmental or human health impacts resulting from this agency action. Without question, the unprecedented nature of the FDA's action is "significant" within the meaning of the CEQ regulations.

Thus, the FDA's decisions on the commercialization of genetically engineered foods has all the characteristics that the CEQ regulations equate with "significant" effects on the environment. The Policy is a controversial, precedent setting legislative rule that has unique and uncertain health and environmental impacts. As such, the FDA cannot apply categorical exclusions to the its decisionmaking in this regard.[cxc]

Therefore, petitioners request that the FDA prepare a PEIS of its genetically engineered foods program and find that 21 C.F.R. §§ 25.30, 25.32 are not applicable to all genetically engineered food additive petitions.

E. Genetically Engineered Foods Must Be Labeled As Required By the FFDCA.

Petitioners request that the FDA, under FFDCA §§ 321(n) and 343(a)(1), require the labeling of genetically engineered foods because of the reasonable expectations of consumers, admitted performance and organoleptic changes in such foods, and the widespread public desire for labeling (including for purposes of religious conviction and allergenic sensitivity).

The purpose of food labeling is "to make it possible that the consumer should know that an article purchased was what it purported to be; that it might be bought for what it really was, and not upon misrepresentations as to character and quality."[cxci] Under the FFDCA food is deemed misbranded if its labeling is "false or misleading in any particular."[cxcii] Further, in accordance with Section 201(n), the FFDCA provides that:

> If an article is alleged to be misbranded because the labeling or advertising is misleading, then in determining whether the labeling or advertising is misleading there shall be taken into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, <u>but also the extent to which the labeling or advertising fails to reveal facts material in the light of such representations</u> or material with respect to consequences which may result from the use of the article to which labeling or advertising relates under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary. (emphasis added)[cxciii]

These sections of the FFDCA have been interpreted broadly to mandate food labeling in favor of consumer interests. [cxciv] As the Supreme Court has stated, "Remedial legislation such as the Food, Drug and Cosmetic Act is to be given liberal construction consistent with the Act's overriding purpose to protect the public health."[cxcv] To this end, the courts "have construed Section 343 broadly, since the test is not the effect of the label on a reasonable consumer, but upon 'the ignorant, the unthinking and credulous consumer.'"[cxcvi] Therefore, in considering whether the omission of a material fact from a food label renders that food misbranded under § 343 the agency must examine what is "material" in the light most favorable to the consumer, even a less than reasonable, credulous consumer. In order to meet this standard, the FDA must require the labeling of genetically engineered foods.

<u>(1). Consumers Reasonably Expect Genetically Engineered Foods To Be Labeled.</u>

Consumers reasonably expect that changes in their food of the magnitude created by genetic engineering will trigger labeling, as evidenced by the over 80% requesting labeling in response to the agency's 1992 Policy Statement.[cxcvii] Such reasonable expectations are further borne out in 1992 a USDA poll which found that 85% of consumers thought that the labeling of products of genetic engineering "very important."[cxcviii]

(a) Genetically Engineered Foods Are Not "Substantially Equivalent" to Conventionally Produced Foods.

In the past, the FDA has justified its failure to require labeling by claiming that genetically engineered foods are "substantially equivalent" to conventionally produced foods and thus need not be labeled. Specifically, in the 1992 Policy and subsequent regulatory actions, the FDA claims that the genetic engineering of food does not differ in principle from older plant breeding techniques and

thus that the food products of genetic engineering do not have traits that distinguish them from products of older techniques.[cxcix] The agency further asserts that genetic engineering is an extension of traditional plant breeding at a molecular level and, as such, the novel genes, antibiotic markers, promoters and vectors added to these foods are not "material" and do not require labeling.[cc]

The FDA's own scientific experts have contradicted this finding of "substantial equivalence." As Linda Kahl of FDA's Office of Compliance relays to the 1992 Policy coordinator James Marayanski concerning the 1992 Policy, cited supra:

> I believe that there are at least two situations relative to this document in which it is trying to fit a square peg into a round hole. The first square peg into a round hole is that the document is trying to force an ultimate conclusion that there is no difference between foods modified by genetic engineering and foods modified by traditional breeding practices. This is because of the mandate to regulate the product, not the process.
>
> a. *The processes of genetic engineering **are** different and according to the technical experts in the agency, they lead to different risks (emphasis in original).*[cci]

As the agency experts further concede, genetic engineering allows "for the possibility of transfering (sic) to any organism a gene from any other organism or from a synthetic source (i.e., an enzyme composed of several domains of unrelated proteins). This potential is beyond the realm of possibility of standard breeding practice. The food safety of organisms derived from recombinant DNA technologies do not have the history of the safe use that has come to be associated with organisms derived by standard breeding practices."[ccii]

The FDA has, in similar circumstances, required labeling. In addressing the issue of irradiation, for example, the agency stated, "in the absence of a statement that a food has been irradiated, the implied representation to consumers is that the food has not been processed."[cciii] Genetic engineering presents consumers with a similar implied representation. In the absence of labeling a person who walks into the supermarket to purchase a tomato does not have a reasonable expectation that the tomato they may purchase contains novel proteins never before present in food and genetic material from a flounder. Similarly, the reasonable consumer, much less the credulous consumer, does not go into the supermarket and purchase a tomato with a reasonable expectation that they may be consuming proteins that could ultimately impact the efficacy of antibiotics they are currently taking.

Since genetically engineered foods are not "substantially equivalent" to conventionally produced foods, the FFDCA demands labeling so that consumers have "material" facts about these foods.

(b) Genetically Engineered Foods Have Performance and Organoleptic Changes That Trigger Labeling Requirements.

Labeling is required **either** (1) where it is found that where there are changes in a performance characteristic of a food; **or** (2) where it is found that there are organoleptic changes to the food.[cciv] For example, in addressing regulatory changes for food nutrient content claims, the agency has stated:

> Under section 201(n) (21 U.S.C. § 321(n)) and 403 (a) of the act, the label or labeling of food must disclose to consumers what they are buying when they purchase these

> modified foods. Information disclosing differences in performance characteristics (e.g. physical properties, flavor characteristics, functional properties and shelf life) is a material fact under section 201(n) of the act because it bears on the consequence of the use of the article. Accordingly, this information must be communicated to the consumer on the product label, or the labeling would be misleading and the product would be misbranded under section 403(a) of the act.[ccv]

Thus, the interpretation of § 321(n) adopted by the FDA and recognized by the courts establishes that performance changes such as alterations in food characteristics such as physical properties, flavor characteristics, functional properties and changes in shelf life must be communicated to the consumer via labeling; otherwise, such food is misleading and misbranded under § 343(a).[ccvi] At a minimum, this agency interpretation of § 321(n) must be implemented and applied consistently and predictably.[ccvii]

Performance Changes. The FDA concedes that genetically engineered foods contain performance changes. Indeed, the agency has even provided a compendium on how genetic engineering is leading to performance changes such as herbicide-tolerance, new possibilities for improving food composition (protein modification, oil modification, carbohydrate modification) and modifying processing and other characteristics.[ccviii] For example, the Flavr Savr tomato is genetically engineered to control the expression of the enzyme polygalacturonase (PG) thereby slowing ripening and increasing shelf-life.[ccix] The resulting tomatoes also have an altered molecular weight as result of increased pectin content.[ccx] Use of Flavr Savr tomatoes in juice and tomato paste showed an increase in serum viscosity.[ccxi] Thus, the Flavr Savr exemplifies the performance changes such as new physical properties (increased pectin) functional qualities (increased viscosity) and longer shelf-life initiated by genetic engineering.

Similarly, DNA Plant Technology's Improved Ripening Tomato is genetically engineered to suppress ethylene enzyme production thereby leading to a performance change of delayed ripening.[ccxii] Zeneca Plant Science's Delayed Softening Tomato is genetically engineered to alter ripening enzymes so the tomato's performance is changed by softening less quickly.[ccxiii] Agritope Inc.'s Modified Fruit Ripening Tomato is genetically engineered to lower enzyme levels in tomatoes affecting ripening performance.[ccxiv] These tomatoes are all genetically engineered to, *inter alia*, have improved production dynamics and reduced losses in distribution because of longer shelf life.[ccxv]

Other plants provide examples of the clear intention of genetic engineering to alter performance characteristics as it relates to a crop's physical properties. Numerous plants are engineered to be resistant to indiscriminant herbicide application. For example, AgrEvo's glufinosinate tolerant corn was genetically engineered to alter the performance characteristics of corn to be resistant to the application of the herbicide Liberty®.[ccxvi] Similarly, Monsanto's Gylphosate Tolerant Corn is genetically engineered to be similarly tolerant to the application of the herbicide Roundup®.[ccxvii]

Other examples abound. Dupont's High Oleic Acid Soybean has performance changes including the characteristics of the derived soybean oil during cooking.[ccxviii] The soybean oil is compositionally different from conventional soybean oil and will be used in, *inter alia*, food frying and baking operations because of its enhanced natural stability and favorable fatty acid profile.[ccxix]

While by no means exhaustive, the examples cited provide undisputed fact that genetic engineering directly alters the performance characteristics of food including, *inter alia*, its physical and functional properties and shelf-life. Such evidence is material fact under § 201(n) and mandates labeling.

Organoleptic Changes. Additionally, genetically engineered foods are organoleptically (taste, color, smell, texture, etc . . .) altered.[ccxx] Calgene's Laurate Canola is genetically engineered to produce high levels of lauric acid and modest amounts of myristic acid in canola seed oil.[ccxxi] It has been specifically genetically altered to change the fatty acid composition of canola oil.[ccxxii] Similarly, Dupont's High Oleic Acid Soybean is genetically engineered to produce soybean oil "with a dramatically modified fatty acid spectrum."[ccxxiii] The modified soybean oil has oleic acid content of at least 55% greater than conventional soybean oil.[ccxxiv] Also, Dupont's Sulfonylurea Tolerant Cotton is genetically engineered to be tolerant to sulfonylurea herbicides and Staple® herbicide use.[ccxxv] Differences in cottonseed oil from this cotton were significant for the level of three fatty acids myristic, linoleic, and linolenic acids.[ccxxvi]

Other genetically engineered foods have organoleptic alterations. Flavr Savr tomatoes have increased solids as a result of greater pectin content.[ccxxvii] And the FDA approved voluntary labeling language in which the tomato's maker, Calgene, states "Flavor you can see. And feel. And smell. And taste."[ccxxviii] These engineered tomatoes are also significantly firmer than non-genetically engineered tomatoes.[ccxxix] Monsanto's Improved Ripening Tomato has the explicit goal to produce a better tasting tomato through genetic engineering.[ccxxx] Zeneca Plant Science's Delayed Softening Tomato is genetically engineered to intentionally alter its structure, composition and level of carbohydrates.[ccxxxi] These tomatoes have less breakdown in pectin and improved thickness.[ccxxxii] The FDA further admits that alterations of fruit ripening enzymes in tomatoes will yield organoleptic changes stating, "For example, genetic modifications of plant enzymes involved in fruit ripening may yield tomatoes with improved ripening characteristics, texture and flavor."[ccxxxiii]

Again, while by no means exhaustive, these examples cited provide clear evidence that genetic engineering directly alters the organoleptic characteristics of food including, *inter alia*, sensory conditions such as increased or decreased solid content, direct attempts to change taste and potential nutrient content such as fatty acid content levels.

In addition to these specific foods, there are potential organoleptic changes which could occur in any genetically engineered plant food because insertion of DNA by genetic engineering into a host plant can produce phenotypic [observable constitution of an organism] changes (desirable and undesirable) referred to as pleiotropic effects.[ccxxxiv] Pleiotropic effects have been shown to occur at frequencies up to 30% in genetically engineered plants.[ccxxxv] The resulting undesirable phenotypes may include, *inter alia*, increased levels of natural toxicants, the appearance of new, not previously identified toxicants, increased capability of concentrating toxic substances from the environment (e.g. pesticides or heavy metals), and undesirable alterations in the levels of nutrients which may escape a breeder's attention unless genetically engineered plants are evaluated specifically for these changes.[ccxxxvi] As the agency further concedes, genetically modified plants might contain unexpectedly high concentrations of plant toxicants. This can occur by at least two mechanisms. One could be the amplification of normal levels of existing toxicants into higher levels. Second, normally inactive plant toxins could become activated.[ccxxxvii] As one of the FDA's scientists suggests about the 1992 Policy, "the unintended effects cannot be written off so easily by just implying that they occur too in traditional breeding. There is a profound difference between the types of unexpected effects from traditional breeding and genetic engineering which is just glanced at in this document."[ccxxxviii]

Both the intended and unintended changes in the physical and organolepetic properties of genetically engineered plants mandate labeling under § 201(n).

(c) Genetically Engineered Foods Have Potential Allergenicity That Triggers Labeling Requirements.

The FDA has consistently required potentially allergenic foods to be labeled. For example, when regulating foods named by a nutrient content claim (such as "fat free") in conjunction with a traditional standardized name (for example "reduced fat sour cream"), the agency stated:

> The highlighting of ingredients that are not part of the traditional standard of identity, or that are added in excess of what is permitted by that standard, is appropriate to ensure continued consumer confidence in standardized foods. FDA believes under section 201(n) and 403(d) of the act, consumers are entitled to know how the new standardized food differs from traditional standardized food. In some case, consumers may have allergies to certain ingredients that may not be normally encountered in the standardized food. Therefore, FDA finds that these ingredients must be highlighted (emphasis added).[ccxxxix]

Similarly, in the case of sulfiting agents the FDA has stated:

> Because, as stated above, sulfiting agents can cause allergic-type responses of unpredictable severity, the presence of a detectable amount of sulfites . . . in a food is a material fact. Therefore the absence on the label of a food of the material fact that the food contains sulfiting agents renders that label misleading and the food misbranded under sections 403(a) and 201(n) of the act.[ccxl]

In the case of genetically engineered foods, food labeling is of particular interest to those with food sensitivity and allergies. The FDA admits that:

> Since certain proteins from normal plants have caused documented allergic reactions in people, it is possible that the edible portion of genetically modified plants (i.e. novel plants) may cause food allergies. Antigenic plant proteins (i.e. allergens) could become concentrated in novel plant foods by two different mechanisms. First, the novel food contains new DNA that could constitutively produce a new protein allergen which was not present in the wild type plant. Alternatively, the process of insertion of the new DNA in the novel plant may cause positional mutagenesis (i.e. pleiotropy) that could enhance the synthesis of existing plant food allergens.[ccxli]

Genetic engineering will bring proteins into food crops not just from known allergens, like peanuts, shellfish, and dairy, but from plants of all kinds, bacteria and viruses, whose potential allergencity is uncommon or unknown. As to those "new" proteins, FDA scientists warn that because the background exposure to these proteins would be negligible, they should be considered to be new proteins in the human diet and be subjected to safety evaluation.[ccxlii]

Potential allergenic responses in consumers resulting from novel proteins raise serious health concerns. Such concerns are not trivial. In 1996, the New England Journal of Medicine reported that a soybean genetically engineered with a gene from a Brazil nut could cause a significant adverse or potentially fatal reaction to the soybeans in consumers allergic to the Brazil nut.[ccxliii]

Almost 25% of all members of the public who commented on the 1992 Food Policy requested the FDA to adequately protect consumer health from the effects of unrecognized or uncommon allergens. As the agency summed up, "A great deal of fear was expressed by consumers that they would not know whether they were eating foods to which they might be allergic."[ccxliv]

The need for labeling is particularly material since one of the potential consequences is sudden death, and the most affected population will be children.(2). Consumers Are Demanding The Labeling of Genetically Engineered Foods.

Consumer demand for the labeling of genetically engineered foods bolsters a finding of "material fact." As the FDA has stated previously, "whether information is material depends not on the abstract worth of the information but on whether consumers view such information as important and whether the omission of label information may mislead a consumer."[ccxlv] More specifically, in addressing consumer interest in labeling the agency has stated:

> [T]he large number of consumer comments requesting retail labeling attest to the significance placed upon such information by consumers. Moreover, several comments argued irradiation of food altered the organoleptic properties of food thereby reducing its nutritional value. These changes in the food, the comments asserted, make the irradiation of the food a material fact that must be disclosed under section 403(a) and 201(n) of the act.[ccxlvi]

In addressing the role of public concern as it relates to labeling, the agency has further elaborated that:

> In determining whether labeling is misleading, the agency must take into account the extent to which labeling fails to reveal material facts in light of representations made about the food or consequences that many result from the use of such food [section 201(n) of the act]. Therefore, the agency must decide whether the changes in the organoleptic properties of irradiated foods constitute a material fact or whether the information that a food has been irradiated constitutes information that is material to a consumer even if the organoleptic changes were not significant.[ccxlvii]

The public is clearly interested in demanding the labeling of genetically engineered foods. Approximately 80% of the comments sent to the FDA in response to its 1992 Policy Statement requested labeling of "genetically engineered" foods.[ccxlviii] The FDA has conceded: "Not surprisingly, most consumers believed that genetically engineered foods should be labeled. Almost every comment reflected this sentiment. Many also said that labels should be clear, prominent, and not restricted to fine print."[ccxlix] As one FDA employee notes: "It is immaterial that the FDA doesn't believe methods of genetic modifications are material information important to consumers if regulations do indeed indicate that the former will be a material fact when consumers view such information as important."[ccl] At a minimum, when combined with the performance and organoleptic changes in genetically engineered food, the consumers' high level of interest in labeling renders such characteristics "material" under § 201(n).

(3). Consumers Have Religious Demands for Mandatory Labeling.

Religious interest also contributes to a finding of material fact which triggers the FDA's labeling requirements. In addressing the labeling issues involving protein hydrolysates used as food flavors or flavor enhancers the agency has stated:

> The agency tentatively finds that food source of a protein hydrolysate is information of material importance for a person who desires to avoid certain foods for religious or cultural reasons. This information

> is necessary for such an individual to determine whether the food is acceptable or non-acceptable for inclusion in their diet. If such information is not included in the declaration of a protein hydrolysate, a consumer would have no way of knowing that he/she was consuming a food prohibited or discouraged by his/her personal convictions. The agency thus tentatively concludes that the food source of a protein hydrolysate is a material fact under 21 U.S.C. 321(n), and that the failure to identify the food source in the declaration of a protein hydrolysate would cause the food to be misbranded.[ccli]

Approximately 15% of the comments received by the agency in response to its 1992 Policy Statement mentioned concerns related to vegetarian, religious or ethical beliefs.[cclii] The agency also states, "many consumers who avoid certain types of food for health, religious, or moral reasons expressed concern that they would not know what they were eating when eating genetically engineered foods."[ccliii] Thus, when combined with the performance and organoleptic changes in genetically engineered food and the consumers high level of interest in general labeling, the concerns of religious consumers renders a failure to label "material" under § 201(n).

In sum, the reasonable expectations of consumers, admitted performance and organoleptic changes, potential allergenicity of genetically engineered foods, and the widespread public desire for labeling (including for purposes of religious conviction) demand that the FDA require labeling of genetically engineered foods pursuant to FFDCA §§ 321(n) and 343(a)(1).

Therefore, petitioners respectfully request that the FDA enact new labeling regulations under 21 C.F.R. part 101, to require as follows:

> *(A). "If the food contains a genetically engineered material, or was produced with a genetically engineered material, unless it bears a label (or labeling, in the case of a raw agricultural commodity, other than the sale of such a commodity at retail) that provides notices in accordance with the following:*
>
> > *(1) "A notice as follows: 'GENETICALLY ENGINEERED'.*
> >
> > *(2) "A notice as follows: 'UNITED STATES GOVERNMENT NOTICE: THIS PRODUCT CONTAINS A GENETICALLY ENGINEERED MATERIAL, OR WAS PRODUCED WIT H A GENETICALLY ENGINEERED MATERIAL'.*
> >
> > *(3) "The notice required in clause (1) immediately precedes the notice required in clause (2) and is not less than twice the size of the notice required in clause (2).*
>
> *(4) "The notice required in clause (3) is of the same size as would apply if the notice provided nutrition information."*

ENVIRONMENTAL IMPACT

The enforcement actions here requested will not cause the release of any substance into the environment. They are categorically excluded from the requirement of environmental documentation under 21 C.F.R. § 25.30(h).

CERTIFICATION

The undersigned certify that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data known to the petitioner which are unfavorable to the petition.

CONCLUSION

Wherefore the reasons contained herein, the petitioners respectfully request that the Commissioner undertake the following actions:

(1). Rescind its 1992 Statement of Policy: Foods Derived From New Plant Varieties and implement new regulations that comply with the legal requirements by subjecting all genetically engineered foods and/or genetically engineered food additives to the food additive petition process. Such a process should include:

> (A). Pursuant to the procedures outlined in 21 C.F.R. § 170.38, the Commissioner shall issue a notice in the Federal Register determining that all genetically engineered food additives are not Generally Recognized As Safe (GRAS) and are food additives subject to section 409 of the FFDCA;
>
> (B). Amend 21 C.F.R. §170.3 to include the following:
>
> > (p) *Genetically engineered food* means food that contains or was produced with a genetically engineered material.
> >
> > > (1) *Genetically engineered material* means material derived from any part of a genetically engineered organism, without regard to whether the altered molecular or cellular characteristics of the organism are detectable in the material.
> > >
> > > (2) *Genetically engineered organism* means (A) an organism that has been altered at the molecular or cellular level by means that are not possible under natural conditions or processes (including, but not limited to, recombinant DNA and RNA techniques, cell fusion, microencapsulation, macroencapsulation, gene deletion and doubling, introducing a foreign gene, and changing the positions of genes), other than a means consisting exclusively of breeding, conjugation, fermentation, hybridization, in vitro fertilization, or tissue culture, *and* (B) an organism made through sexual or asexual reproduction (or both) involving an organism described in(A), if possessing any of the altered molecular or cellular characteristics of the organism so described.
> > >
> > > (3) *Genetically engineered food additive* means a genetic construct, its protein or expression product, vector, promoter, or marker system that are used or created individually or together as a result of a genetically engineered food.

(2). Enact additional regulatory protocols within the food additive petition review process for genetically engineered foods or genetically engineered food additives that assess potential allergencity, toxicity and unintended effects. Such protocols should include, but not be limited to the following:

> (A). Allergenicity. The FDA must develop and mandate specific testing protocols for the assessment of allergenicity for all genetically engineered food additives. In instituting these new mandatory pre-market regulations, the agency should include requirements that all food additives be subject to allergenicity screening that includes, but is not limited to:
>
> > (i). Prick-puncture skin testing to determine whether the food additive triggers a specific IgE antibody response;

(ii). In vitro testing screening for specific IgE (radioallergosorbent tests [RAST]) responses to a genetically engineered food additive;

(iii). Use of T Cell marker assays;

(iv). Complete molecular characterization of known allergens; and

(v). Consistent with regulatory requirements concerning informed consent, pursuant to 21 C.F.R. part 50 and 45 C.F.R. part 46, subpart A and part 690 (as applicable), an assessment of the ethical and reasonable outcomes of conducting limited double-blind placebo controlled food challenges.

(B). Toxicity and Unintended Effects. The FDA must develop and mandate specific testing protocols for the assessment of toxicity and other unintended effects for all genetically engineered food additives. In instituting these new mandatory pre-market regulations, the agency should include requirements that all food additives be subject to toxicity and other screening that includes, but is not limited to:

(i). Determination of the potential for unexpected effects using molecular characterization biochemical characterization, mRNA profiling or other techniques, long-term feeding studies or as appropriate a combination of such techniques;

(ii). Review of required information on the glycosylation patterns of all transgenes expressed in GE foods;

(iii). Use of material derived from the transgenic plants themselves in all required toxicity studies rather than bacterially-derived proteins;

(iv). Submission of data for each separate transgenic line. Specifically for every line, the FDA should require a complete molecular characterization of each line with respect to the identity, stability and unintended positional and pleiotropic effects;

(v). Complete molecular characterization for molecular identity for each transgenic or transformed line, to include the following components:

(a). Total number of inserts of transgenic DNA;

(b). Location of each insert (organelle [chloroplast, mitochondria, etc.] or chromosomal);

(c). Exact chromosomal position of each insert;

(d). Structure of each insert (whether duplicated, deleted, rearranged, etc.);

(e). Complete genetic map of each insert including all elements (coding region, noncoding regions, marker gene, promoters, enhancers, introns, leader sequences, terminators, T-DNA borders, plasmid sequences, linkers, etc. including any truncated, incomplete sequences);

(f). Complete (nucleotide) base sequence of each insert; *and*

(g). (Nucleotide) base sequence of at least 10kbp (10,000 base pairs) of flanking host genome DNA on either side of the insert, including changes in methylation patterns

(3). Immediately comply with the NEPA including undertaking the following actions:

(A). Pursuant to 42 U.S.C. § 4332(c), complete a programmatic environmental impact statement assessing the agency's program on genetically engineered foods and genetically engineered food additives under the food additive petition process; and

(B). Find that 21 C.F.R. §§ 25.30, 25.32 are not applicable to all genetically engineered food additive petitions, and therefore, such petitions are not categorically excluded from NEPA review.

(4). Enact new labeling regulations under 21 C.F.R. part 101, to require as follows: "If the food contains a genetically engineered material, or was produced with a genetically engineered material, unless it bears a label (or labeling, in the case of a raw agricultural commodity, other than the sale of such a commodity at retail) that provides notices in accordance with the following:

(A) "A notice as follows: 'GENETICALLY ENGINEERED'.

(B) "A notice as follows: 'UNITED STATES GOVERNMENT NOTICE: THIS PRODUCT CONTAINS A GENETICALLY ENGINEERED MATERIAL, OR WAS PRODUCED WITH A GENETICALLY ENGINEERED MATERIAL'.

(C) "The notice required in clause (A) immediately precedes the notice required in clause (B) and is not less than twice the size of the notice required in clause (B).

(D) "The notice required in clause (C) is of the same size as would apply if the notice provided nutrition information."

As established in 21 C.F.R. § 10.30(e)(2), petitioners request that the agency provide an answer to this citizen petition within 180 days.

Respectfully submitted,

Andrew Kimbrell

Executive Director

Joseph Mendelson, III
Legal Director

Charlotte Arnold Christin
Policy Director
Center for Food Safety
666 Pennsylvania Ave., SE
Suite 302
Washington, DC 20003

[i] **Jean Halloran & Michael K. Hansen, Why We Need Labeling of Genetically Engineered Food, Consumers International (April 1998).**

[ii] **Id.**

[iii] **Michael K. Hansen,Consumer Policy Institute/Consumers Union, Genetic Engineering Is Not An Extension of Conventional Plant Breeding: How Genetic Engineering Differs From Conventional Breeding, Hybridization, Wide Crosses and Horizontal Gene Transfer (1999).**

[iv] **Id. at 7.**

[v] **Memorandum from FDA Divisions of Food Chemistry & Technology and Contaminants Chemistry to FDA Office of Compliance and James Maryanski, Biotechnology Coordinator, Scientific Considerations in the Safety Evaluation of Foods Derived from Genetically Modified Plants (Nov. 25, 1991).**

[vi] **Hansen, supra note 6, at 7.**

[vii] **Stokely Webster, Genetically Modified Crops and Animal Feed, Address Before the Friends of the Earth Animal Feed Briefing (Sept. 27, 1999).**

[viii] **Hansen, supra note 6, at 5.**

[ix] **Id. at 4. By contrast, since conventional breeding occurs between organisms that share an evolutionary background, it only involves shuffling around of different versions of the same gene. Furthermore, these genes are usually fixed in their location on the chromosome by evolution. Id. at 5.**

[x] **S.C. Deroles & R.C. Gardner, Expression and inheritance of kanamycin resistance in a large number transgenic petunias generated by Agrobacterium-mediated transformation, 11 Plant Molecular Biology 355-64 (1988).**

[xi] **Hansen, supra note 6, at 6.**

[xii] **M. Mannerlof & P. Tenning, Variability of gene expression in transgenic tobacco, 98 Euphytica 133-39 (1997).**

[xiii] **Hansen, supra note 6, at 3.**

[xiv] **Id. .**

[xv] **Statement of Policy: Foods Derived From New Plant Varieties, 57 Fed. Reg. 22984 (May 29, 1992) (hereinafter "1992 Policy").**

[xvi] **Id. at 22991.**

[xvii] **There were 6,486 comments submitted. Telephone call with FDA Dockets Mgt. Branch (Mar. 10, 2000).**

[xviii] **Preliminary Analysis of Comments: FDA Statement of Policy: Food From New Plant Varieties (undated).**

[xix] **Environmental Points to Consider for Plant Biotechnology.**

[xx] **64 Fed. Reg. 57470 (Oct. 25, 1999).**

[xxi] **57 Fed. Reg. at 22991.**

[xxii] **Memorandum from Linda Kahl, FDA Compliance Officer to James Maryanski, FDA Biotechnology Coordinator (Jan. 8, 1992); Memorandum from Louis Pribyl, Comments on Biotechnology Draft Document, 2/27/92 (Mar. 6, 1992); See also, e.g., supra note 6 and infra.**

[xxiii] **Hansen, supra note 6, at 1 (noting that there are limited exceptions for species hybridization (with a wild relative within the same genus), wide crosses (only between fairly closely related plants) and horizontal gene transfer).**

[xxiv] **Id. at 1, 7. The Cauliflower mosaic virus gene (CaMV35S)is used because it leads to hyperexpression of the foreign genes, at perhaps 2-3 orders of magnitude higher than the organism's own genes. The CaMV35S promoter effectively puts the transgene(s) outside of virtually any regulatory control by the recipient plant. Id.**

[xxv] **FDA Memorandum on the use of microorganisms and plants as whole foods (notation dated Nov. 4, 1991).**

[xxvi] **Hansen, supra note 6, at 1.**

[xxvii] **FDA Document, Comments on proposed approach to unknown and unexpected toxicants (undated).**

[xxviii] **Memorandum from the FDA Divisions of Food Chemistry & Technology and Contaminants Chemistry to James Maryanski, FDA Biotechnology Coordinator (Nov. 1, 1991).**

[xxix] **FDA Draft Appendix: Specific Considerations in the Safety Assessment of Foods and Feeds Derived from Genetically Modified Plants (Dec. 12,**

1991); Jan-Peter Nap *et al.*, Biosafety of kanamycin-resistant transgenic plants: an overview (undated); Letter from Nick Tomlinson, Ministry of Agriculture, Fisheries and Food, U.K. to Dr. W.D. Beversdorf, Ciba-Geigy, Ltd. (Apr. 29, 1996).

[xxx] **FDA Divisions of Food Chemistry & Technology and Contaminants Chemistry, supra note 8.**

[xxxi] **FDA Divisions of Food Chemistry & Technology and Contaminants Chemistry, supra note 31.**

[xxxii] **FDA Memorandum, Draft Supplementary Information: The Safety of Whole Food Plants Transformed by Biotechnology Methods (Nov. 13, 1991).**

[xxxiii] **Hansen, supra note 6, at 6.**

[xxxiv] **T. Inose & K. Murata, Enhanced accumulation of toxic compound in yeast cells having high glycolytic activity: A case study on the safety of genetically engineered yeast, 30 International Journal of Food Science and Technology 141-46 (1995). The scientists concluded that "the results presented here indicate that, in genetically engineered yeast cells, the metabolism is significantly disturbed by the introduced genes or their gene products and the disturbance brings about the accumulation of the unwanted toxic compound MG in cells. Such accumulation of highly reactive MG may cause a damage in DNA." Id.**

[xxxv] **FDA Memorandum, supra note 35.**

[xxxvi] **Memorandum of Meeting between James Maryanski, FDA, and Bill Layden & Michelle Bernard, Industry (Sept. 27, 1991).**

[xxxvii] **FDA Draft Appendix, supra note 32.**

[xxxviii] **Memorandum from Dr. Edwin J. Matthews to the Toxicology Section of the Biotechnology Working Group (Nov. 8 1991).**

[xxxix] **FDA Divisions of Food Chemistry & Technology and Contaminants Chemistry, supra note 8.**

[xl] **Id.**

[xli] **British Medical Association, The Impact of Genetic Modification on Agriculture, Food and Health: An Interim Statement 10 (May 1999).**

[xlii] **Hansen, supra note 6.**

[xliii] **FDA Divisions of Food Chemistry & Technology and Contaminants Chemistry, supra note 8.**

[xliv] **British Medical Association, supra note 44, at 13.**

[xlv] **Nap, supra note 32; Tomlinson, supra note 32.**

[xlvi] **Hansen, supra note 6.**

[xlvii] **Nap, supra note 32; Tomlinson, supra note 32.**

[xlviii] **Hansen, supra note 6.**

[xlix] **British Medical Association, supra note 44, at 13.**

[l] **See supra note 31.**

[li] **James Walsh, Brave New Farm, Time 86, 87 (Jan. 11, 1999).**

[lii] **B.J. Feder, Biotech Firm to Advocate Labels on genetically altered products, New York Times (Feb. 24, 1997).**

[liii] **Preliminary Analysis, supra note 21.**

[liv] **Memorandum from Alan Heaton to James Maryanski (Nov. 3, 1993).**

[lv] **Id.**

[lvi] **T.J. Hoban & P.A. Kendall, Report to Extension Service, USDA, Consumer Attitudes About the Uses of Biotechnology in Agriculture and Food Production (1992).**

[lvii] **Seeds of Change, Consumer Reports, Sept. 1999.**

[lviii] **21 U.S.C. § 301, *et seq.***

[lix] **See Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc., 467 U.S. 837, 842-3 (1984).**

[lx] **21 U.S.C. § 321(s)(emphasis added).**

[lxi] **57 Fed. Reg. at 22990 ("Thus, in the case of foods derived from new plant varieties, it is the transferred genetic material and the intended expression product or products that could be subject to food additive regulation, if such material or expression products are not GRAS.") See also, A.R. at 18130.FDA scientist Eric Flamm argued that applying the Food Additives Amendment would *be "consistent with the original intent behind the passage of the f.a.a.*: to assure that FDA was reviewing the safety of those**

new ingredients entering the food supply *whose safety was unknown.*" (emphasis added). Id.

[lxii] **21 U.S.C. § 321(s).**

[lxiii] **S. Rep. 2422, 85th Cong., 2d Session, 1958 U.S.C.C.A.N. 5300, 5301.**

[lxiv] **The FDA has stated that the Food Additive Amendments were limited only to new chemicals, this is incorrect because (1) the substances used in genetically engineered foods are chemicals and (2) had the Congress intended to regulate only chemicals as food additives, it would have done so–just as it exempted "pesticide chemicals" from the definition of food additive. FAA § 201(s)(1),(2), codified at 21 U.S.C. § 321(s)(1),(2).**

[lxv] **S. Rep. 2422, 1958 U.S.C.C.A.N. 5301-2.**

[lxvi] **57 Fed. Reg. at 22985-86.**

[lxvii] **Id. at 22991.**

[lxviii] **Pribyl, supra note 25.**

[lxix] **Kahl, supra note 25.**

[lxx] **Draft Cartegena Protocol on Biosafety, UNEP/CBD/ExCOP/1/L.5 (Jan. 28, 2000).**

[lxxi] **See, e.g., Eric Millston, *et al*. Beyond "Substantial Equivalence," 401 Nature 525-26 (Oct. 7, 1999).**

[lxxii] **See supra note 31.**

[lxxiii] **Pribyl, supra note 25.**

[lxxiv] **Letter from James Maryanski to Dr. Bill Murray, Chairman, Food Directorate, Canada (Oct. 23, 1991).**

[lxxv] **FDA Draft Memorandum, Points to Consider in the Development of Human Foods and Animal Feeds Derived From Plants (Nov. 14, 1991).**

[lxxvi] **See supra note 22.**

[lxxvii] **The definition concedes the impossibility of proving, with complete certainty, absolute harmlessness. 21 C.F.R. § 170.3(i).**

[lxxviii] **21 C.F.R. § 170.30(i).**

[lxxix] **A. Wesley Burks & J. Steven Stanley, Food Allergy, 10 Current Opinions in Pediatrics 588-93 (1998). "Food allergy can be defined as the**

clinical symptoms resulting from an inappropriate immune response to specific food proteins or food additives. The broader term, food intolerance, describes any adverse reaction to a food that is nonimmune in nature." Id.

[lxxx] **S.A. Bock, Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life, 79 Pediatrics 683-88 (1987); H.A. Sampson, *et al.*, Fatal and near-fatal anaphylactic reactions to food in children and adolescents, 327 New England Journal of Medicine 380-84 (1992).**

[lxxxi] **M. Nestle, Allergies to transgenic foods—Questions of policy, 334 New England Journal of Medicine 726-28 (1996).**

[lxxxii] **Id. at 727.**

[lxxxiii] **Furthermore, since there is no foolproof predictive methodology for testing for allergenicity, FDA must require labeling of all genetically engineered foods to facilitate the ability to detect the appearance of new allergies.**

[lxxxiv] **Nestle, supra note 86; FDA, EPA, USDA. Conference on scientific issues related to potential allergenicity in transgenic food crops (Docket No. 94N-0053), Annapolis, MD (April 18-19, 1994).**

[lxxxv] **See supra note 31.**

[lxxxvi] **Burks and Stanley, supra note 82.**

[lxxxvii] **Any use of human subjects is required to comply with the existing regulations for protecting human subjects in research found at 21 C.F.R. part 50 and 45 C.F.R. part 46, subpart A & part 690 (as applicable).**

[lxxxviii] **See, e.g., Hansen, supra note 6 and the studies cited there. See also, Consumers Union, Consumers Union's comments on Docket No. 99N-4282, Biotechnology in the Year 2000 and Beyond Public Meetings and the studies cited there.**

[lxxxix] **Prior to the implementation of any animal-based feeding studies, the agency must ensure that testing requirements must comply with the Animal Welfare Act (AWA). In particular, 7 U.S.C. § 2143(a)(3) requires that any animal be afforded humane treatment and care *and that alternatives to procedures using animals be fully assessed*. See also, ARDF v. Glickman, Docket No. 99-581(ESH) (filed March 9, 1999) (arguing that birds, rats and mice are animals covered under the purview of the AWA).**

[xc] **57 Fed. Reg. 22986.**

[xci] **W. Doerfler, *et al.,* Integration of foreign DNA and its consequences in mammalian systems, 15 Trends in Biotechnology 297-301 (1997).**

[xcii] **A. Van der Krol *et al.*, An anti-sense chalcone synthase gene in transgenic plants inhibits flower pigmentation, 333 Nature 866-69 (1988).**

[xciii] **A. Schnieke *et al.*, Embryonic lethal mutation in mice induced by retrovirus insertion into the alpha-1(I) collagen gene, 304 Nature 315-20 (1983).**

[xciv] **Doerfler, supra note 94; See also Consumers Union, supra note 91, citing T. Traavik, Too early may be too late: Ecological risks associated with the use of naked DNA as a tool for research, production and therapy, Directorate for Nature Research. Trondheim, Norway (1998) and M.W. Ho *et al.*, Unregulated Hazards: 'Naked' and 'Free' Nucleic Acids, ISIS (2000).**

[xcv] **J.L. Fox,Farmers say Monsanto's engineered cotton drops bolls , 15 Nature Biotechnology 1233 (1997).**

[xcvi] **Consumers Union, supra note 91.**

[xcvii] **Id., citing personal communication with Shanks [plaintiffs attorney].**

[xcviii] **A.S. Reddy & T.L. Thomas, Expression of a cyanobacterial delta 6-desaturase gene results in gamma-linolenic acid production in transgenic plants, 14 Nature Biotechnology 639-42 (1996).**

[xcix] **Inose, supra note 37.**

[c] **S.W.B. Ewen & A. Pusztai, Effect of diets containing genetically modified potatoes expressing *Galanthus nivalis* lectin on rat small intestine, 354 The Lancet 1353-54 (1999).**

[ci] **Id. at 1354.**

[cii] **Consumers Union, supra note 91.**

[ciii] **J. Finnegan and D. McElroy, Transgene Inactivation: Plants Fight Back!, 12 Bio/Technology 883-88 (1994).**

[civ] **M.W. Ho, Genetic Engineering: Dream or Nightmare?, (Gateway Books: Bath, U.K. (1998).**

[cv] **Consumers Union, supra note 91.**

[cvi] **R.B. Parekh, *et al.*, Cell-Type-Specific and Site-Specific N-Glycosylation of Type I and Type II Human Tissue Plasminogen Activator, 28**

Biochemistry 7644-62 (1989); R.B. Parekh *et al.*, N-Glycosylation and in Vitro Enzymatic Activity of Human Recombinant Tissue Plasminogen Activator Expressed in Chinese Hamster Ovary Cells and a Murine Cell Line, 28 Biochemistry 7670-79 (1989) .

[cvii] **Parekh, Cell-Type-Specific, supra note 109.**

[cviii] **Consumers Union, supra note 91, citing a reference to come.**

[cix] **Parekh, N-Glycosylation, supra note 109.**

[cx] **M.R. Scott *et al.*, Compelling transgenetic evidence for transmission of bovine spongiform encephalopathy prions to humans 96 Proceedings of the National Academy of Sciences 15137-42 (1999).**

[cxi] **M.E. Bruce *et al.*, Transmissions to mice indicate that 'new variant' CJD is caused by the BSE agent, 389 Nature 498-501 (1997).**

[cxii] **A. Csordas, On the biological role of histone acetylation, 265 Biochemistry Journal 23-38 (1990).**

[cxiii] **G.C. Harbour *et al.*, N-'-acetylation can occur at lysine residues 157, 167, 171 and 180 of recombinant bovine somatotropin, *Techniques in Protein Chemistry III* 487-95 (1992); B.N. Violand, *et al.*, Isolation of *Escherichia coli* synthesize recombinant eukaryotic proteins that contain e-N-acetyllysine, 3 Protein Science 1089-97 (1994).**

[cxiv] **Violand, supra note 116, at 1089.**

[cxv] **Consumers Union, supra note 91, at 6.**

[cxvi] **Finnegan, supra note 106.**

[cxvii] **Ho, supra note 107; Traavik, supra note 97.**

[cxviii] **J. Jakowitsch *et al.*, Integrated pararetroviral sequences define a unique class of dispersed repetitive DNA in plants, 96 Proceedings of the National Academy of Sciences 13241-46 (1999).**

[cxix] **Consumers Union, supra note 91.**

[cxx] **Id.**

[cxxi] **Id.**

[cxxii] **Id. (suggesting 3 to 5 generations).**

[cxxiii] **Id., citing H.A. Kuiper *et al.*, Ministry of Economic Affairs, The Hague, Netherlands, Food Safety Evaluation of Genetically Modified Foods as a Basis for Market Introduction (1998).**

[cxxiv] **See supra note 31.**

[cxxv] **Id.**

[cxxvi] **Consumers Union, supra note 91, at 8.**

[cxxvii] **M.G. Lorenz and W. Wackernagel, Bacterial gene transfer by natural genetic transformation in the environment, 58 Microbial Reviews 563-602 (1994).**

[cxxviii] **R.J. Steffan *et al.*, Recovery of DNA from soils and sediments, 54 Applied and Environmental Microbiology 2908-15 (1988).**

[cxxix] **Consumers Union, supra note 91, at 8.**

[cxxx] **L. Maturin and R. Curtiss, Degradation of DNA by nucleases in intestinal tract of rats, 196 Science 216-18 (1977).**

[cxxxi] **A.B. McAllen, The fate of nucleic acids in ruminants, 41 Proc. Nutr. Soc. 309-17 (1982).**

[cxxxii] **R. Schubbert *et al.*, Ingested foreign (phage M13) DNA survives transiently in the gastrointestinal tract and enters the bloodstream of mice, 242 Molecules, Genes and Genetics 495-504 (1994).**

[cxxxiii] **Id.**

[cxxxiv] **Consumers Union, supra note 91, citing a reference to come.**

[cxxxv] **D.K. Mercer *et al.*, Fate of free DNA and transformation of the oral bacterium Streptococcus gordonii DL1 by plasmid DNA in human saliva, 65 Applied and Environmental Microbiology 6-10 (1999).**

[cxxxvi] **Consumers Union, supra note 91, at 9.**

[cxxxvii] **E. Masood, Call for UK genetic watchdog, 395 Nature 5 (Sept. 3, 1998).**

[cxxxviii] **BMA, supra note 44.**

[cxxxix] **Memo from Murray M. Lumpkin, M.D., Director of FDA Division of Anti-Infective Drug Products to Bruce Burlington, M.D. December 17, 1992.**

[cxl] **In conjunction with their request that the FDA rescind its 1992 Policy, petitioners request that the FDA analyze the agency's major federal action**

of approving food additive petitions for genetically engineered foods and genetically engineered food additives. In addition, petitioners request that the FDA find that genetically engineered food additive petitions are not categorically excluded from NEPA review pursuant to 21 C.F.R. §§ 25.30, 25.32.

[cxli] **40 C.F.R. § 1500.1**.

[cxlii] **42 U.S.C. § 4321.**

[cxliii] **40 C.F.R. § 1500.1(b).**

[cxliv] **42 U.S.C. 4332(c).**

[cxlv] **Baltimore Gas & Electric Co. v. NRDC, 462 U.S. at 97.**

[cxlvi] **Id.**

[cxlvii] **Weinberger v. Catholic Action of Hawaii/Peace Education Project, 454 U.S. 139, 143 (1981)**

[cxlviii] **42 U.S.C. § 4332 (C).**

[cxlix] **Id.**

[cl] **40 C.F.R. § 1508.8(b); Baltimore Gas & Electric Co. v. NRDC, 462 U.S. 87, 106 (1983) (explaining that "NEPA requires an EIS to disclose the significant health, socioeconomic, and cumulative consequences of the environmental impact of a proposed action").**

[cli] **Calvert Cliffs Coordinating Comm. Inc. v. U.S. Atomic Energy Comm'n, 449 F.2d 1109 (D.C. Cir. 1971).**

[clii] **Memorandum from Raanan A. Bloom to James Maryanski (Aug. 19, 1991) (emphasis added).**

[cliii] **Environmental Points to Consider, supra note 22.**

[cliv] **Note from Eric Katz to John Gallivan, Food Biotechnology Policy Statement (Mar. 27, 1992).**

[clv] **Environmental Points to Consider, supra note 22.**

[clvi] **Recommendations by the FDA Task Group on Food Biotechnology: FDA Policy for Human Foods and Animal Feeds Derived From Plants, Animals and Microorganisms With Modified Hereditary Traits (Oct. 9, 1991).**

[clvii] **40 C.F.R. §§ 1500-1508 (1996). As the agency is well aware, the CEQ regulations are, by their terms and by court precedent, to be given substantial deference by all federal agencies. C.E.Q. issued its regulations implementing NEPA in response to President Carter's Executive Order 11991 (1977). *See*, Andrus v. Sierra Club, 442 U.S. 347, 357 (1979). The Executive Order directed federal agencies to "comply with the regulations issued by the Council." See id., *quoting* Executive Order No. 11991. The E.P.A. has adopted the C.E.Q. NEPA regulations. 40 C.F.R. § 6.100, *et seq*. (July 1, 1996); The Supreme Court has held that the regulations are entitled to substantial deference by the courts. Andrus v. Sierra Club at 358;**

[clviii] **40 C.F.R. § 1508.18(b)(3) (1996).**

[clix] **40 C.F.R. § 1502.4(b) (1996).**

[clx] **40 C.F.R. § 1502.4(c)(2) (1996).**

[clxi] **"To date, FDA has completed 45 consultations on foods derived from genetically engineered plants." Letter from F. Edward Scarbrough, Ph. D., U.S. Manager for Codex, Office of the Administrator, Food Safety Inspection Service, to Dr. Shunsaku Minami, Director for International Food Safety Programme, Ministry of Health and Welfare, Japan 10 (February 10, 2000).**

[clxii] **Kleppe v. Sierra Club, 427 U.S. 390, 409 (1976).**

[clxiii] **40 C.F.R. § 1508.25 (a)(2) (1996).**

[clxiv] **40 C.F.R. § 1508.7 (1996).**

[clxv] **40 C.F.R. § 1508.8(b) (1996).**

[clxvi] **Baltimore Gas & Electric Co. v. NRDC, 462 U.S. 87, 106 (1983).**

[clxvii] **Calvert Cliffs Coordinating Comm. Inc. v. U.S. Atomic Energy Comm'n, 449 F.2d 1109 (D.C. Cir. 1971).**

[clxviii] **Id.**

[clxix] **40 C.F.R. § 1508.4. While the FDA has promulgated a regulation allowing for the categorical exclusion of the approval of food additive petitions, GRAS affirmation, the granting of a request for exemption from regulation as a food additive, and the approval of a food additive petition for the intended expression product(s) present in food derived from new plant varieties, these categorical exclusions only apply to individual approvals of petitions, affirmations and requests, and not to programmatic agency decisions. 21 C.F.R. § 25.32(i), (o). Even then, there are some**

circumstances where even an individual petition, affirmation or request would require an EA or EIS. 21 C.F.R. § 25.32 (stating that "ordinarily" an EA or EIS need not be prepared).

[clxx] **See 40 C.F.R. §§ 1500-1508.CEQ issued its regulations implementing NEPA in response to President Carter's Executive Order 11991 (1977). See Andrus v. Sierra Club, 442 U.S. 347, 357 (1979). The Executive Order directed federal agencies to "comply with the regulations issued by the Council." Id. quoting Executive Order 11991. The Supreme Court has held that the regulations are entitled to substantial deference by the courts. Id. at 358; Marsh v. Oregon Natural Resources Council, 490 U.S. 360, 372 (1989).**

[clxxi] **40 C.F.R. § 1508.27(b)(4),(5),(6).**
[clxxii] **Public Service Co. of Colo. v. Andrus, 825 F. Supp. 1483, 1495 (D. Idaho 1993).**
[clxxiii] **Foundation for North American Wild Sheep v. U.S. Dep't of Agric., 681 F.2d 1172, 1182 (9th Cir. 1982)**
[clxxiv] **FDA Public Docket No. 92N-0139.**
[clxxv] **See supra note 21.**
[clxxvi] **Id.; see also A.R. at 29700("[w]e object to FDA's redefinition of GRAS, because FDA "presents no valid scientific evidence").**
[clxxvii] **Id.**
[clxxviii] **MSNBC Live Vote Results (January 2000).**
[clxxix] **Rick Weiss, "Biotech vs. Bambi of Insects?" Washington Post, (May 20, 1999).**
[clxxx] **Michael Pollan, "Fried, Mashed or Zapped with DNA?" New York Times Sunday Magazine (October 25, 1998).**
[clxxxi] **See supra note 21.**
[clxxxii] **Memorandum from Dr. Edwin J. Matthews to the Toxicology Section of the Biotechnology Working Group, Comments on food allergies for Toxicology Section document entitled, "THE SAFETY OF WHOLE FOOD PLANTS TRANSFORMED BY BIOTECHNOLOGY" (Nov. 14, 1991).**
[clxxxiii] **Id. (emphasis added).**
[clxxxiv] **See supra note 8.**
[clxxxv] **See supra note 28.**
[clxxxvi] **Memorandum from Deputy Director, Division of Animal Feeds to Director, Center for Veterinary Medicine (Feb. 5, 1992) (emphasis added).**
[clxxxvii] **Marsh v. Oregon Natural Resources Council, 490 U.S. 360, 371 (1990) (emphasis added)**
[clxxxviii] **Transcript of Proceedings, FDA Food Advisory Committee Meeting, Vol. I (Apr. 6, 1994).**
[clxxxix] **See supra note 164.**
[cxc] **See Motor Vehicle Manufacturers' Ass'n., 463 U.S. at 43 (explaining that an agency's decision is arbitrary and capricious if the agency "offered an**

explanation for its decision that runs counter to evidence before the agency").

[cxci] **United States v. Lexington Mill & Elevator Co., 232 U.S. 399, 409 (1914).**

[cxcii] **21 U.S.C. § 343(a)(1) (1992 & Supp. 1997).**

[cxciii] **21 U.S.C. § 321(n) (emphasis added).**

[cxciv] **The legislative history of the FFDCA suggests, at a minimum, that a material fact would be an omission on a food label that a reasonable person would view as important and would thus trigger a finding of misbranding under 21 U.S.C. § 343(a). Although the FFDCA legislative history is quiet as to what type of fact is "material" stating only the "purpose is obvious," H.R. Conf. Rep. No. 2139 at 3, the drafters explicitly connected the language of § 201(n) with the Wheeler-Lea Act language regarding false advertising. S.5, H.R. Conf. Rep. No. 2139, 75th Cong., 3rd Sess. 3 (April 14, 1938) *reprinted in* FDA, A Legislative History of the Food, Drug & Cosmetic Act, Vol. 6 at 302 (1979); See also, S.1077, H.R. Conf. Rep. No. 1774, 75th Cong. 3d Sess. § 15 (February 8, 1938) *reprinted in* Charles Wesley Dunn, Wheeler-Lea Act: A Statement of Legislative History (1938) at 163. In that context the language has been traced back to the 1938 Restatement of Torts §538 which defined a fact to be material "if its existence or nonexistence is a matter to which a reasonable man would attach importance in determining his choice of action in a transaction in question." (See also, 1977 Restatement of Torts 2d. § 538(2)(a), retaining identical language.) Milton Handler, "The Control of False Advertising under the Wheeler-Lea Act," 6 Law & Contemp. Probs. 91, 97-98 (1939).**

[cxcv] **United States v. An Article of Drug . . . Bacto-Unidisk, 394 U.S. 784, 798 (1969); United States v. 25 Cases More or Less, 942 F.2d 1179, 1182 (7th Cir. 1991).**

[cxcvi] **United States v. Strauss, 999 F.2d 692, 696 (2d Cir.1993) (quoting United States v. An Article . . . Sudden Change, 409 F.2d 734, 740 (2d Cir. 1969).**

[cxcvii] **Preliminary Analysis, supra note 21.**

[cxcviii] **T.J. Hoban and P.A. Kendall. Report to Extension Service, USDA. Consumer Attitudes About the Uses of Biotechnology in Agriculture and Food Production (1992).**

[cxcix] **Memo from Eric Flamm to Jim Maryanski, Draft Response to EDF Proposal (Nov. 4, 1991).**

[cc] **57 Fed. Reg. at 22991; See also id.**

[cci] **See supra note 25.**

[ccii] **See supra note 28.**

[cciii] **51 Fed. Reg. 1375, 13390 (April 18, 1986).**

[cciv] **Stauber v. Shalala, 895 F.Supp. 1178, 1193 (W.D. Wis. 1995).**

[ccv] **58 Fed. Reg. 2431, 2437 (June 6, 1993) (emphasis added)**

[ccvi] **If the agency now claims to depart from this existing interpretation, it must set forth a reasoned explanation from its departure of prior norms. Western States Petroleum Assoc. v. EPA, 87 F.3d 280, 284-285 (9th Cir.**

1996); Telecommunications Research and Action Center v. FCC, 800 F.2d 1181, 1184 (D.C. Cir. 1986).

[ccvii] **See Morton v. Ruiz, 415 U.S. 199, 232, 39 L.Ed.2d 270, 94 S.Ct. 1055 (1974).**

[ccviii] **See supra note 8.**

[ccix] **Calgene, Inc., Request for Advisory Opinion on FLAVR SAVR tomato 000011 (Aug. 12, 1991); Regulatory Toxicology & Pharmacology Ch. 3, S111-12 (Dec. 1990).**

[ccx] **Calgene, supra note 212 at 000016.**

[ccxi] **Id. at 000234.**

[ccxii] **DNA Plant Technology Corp., Safety Assessment of a New Fresh Market Tomato Variety (Sept. 16, 1994).**

[ccxiii] **Zeneca Plant Science, A Safety Assessment of New Varieties of Processing Tomatoes: Safety Assessment–The Donor (Aug. 1994).**

[ccxiv] **Letter from Matthew G. Kramer, Agritope, to Dr. Nega Beru, FDA (Nov. 23, 1994).**

[ccxv] **Agritope, Summary of Agritope Low Ethylene Technology (Jan. 23, 1995).**

[ccxvi] **Letter from Sally L. Van Wert, AgrEvo, to Dennis Keefe and William Price, FDA (Aug. 29, 1995).**

[ccxvii] **Monsanto Co., Safety, Compositional and Nutritional Aspects of Roundup Ready Corn Line GA21 (Aug. 19, 1997).**

[ccxviii] **See 56 Fed. Reg. 60421 (Nov. 27, 1991) (changes in functional properties for cooking are performance changes).**

[ccxix] **DuPont Agricultural Products, Safety Assessment of High Oleic Acid Transgenic Soybeans (Aug. 1996).**

[ccxx] **See generally, 62 Fed. Reg. 8248, 8249 (Feb. 24, 1997).**

[ccxxi] **Letter from Keith Redenbaugh, Calgene, to Dr. Laura Tarantino, FDA, Laurate Canola, Confirmation of Compliance with the FDA Policy of May 29, 1992 (Feb. 24, 1995).**

[ccxxii] **Id.**

[ccxxiii] **Letter from Edward W. Raleigh, DuPont Agricultural Products, to Dr. Laura M. Tarantino, FDA (Aug. 28, 1996).**

[ccxxiv] **Id.**

[ccxxv] **Letter from Edward W. Raleigh, DuPont, to Dr. Nega Beru, FDA (Sept. 26, 1995).**

[ccxxvi] **DuPont Agricultural Products, U.S. Dept. of Agriculture, Animal Plant Health Inspection Service Exemption Petition (Sept. 11, 1995).**

[ccxxvii] **Calgene, supra note 212 at 000016.**

[ccxxviii] **Letter from Keith Redenbaugh, Calgene, to James Maryanski, FDA, Labeling for FLAVR SAVR Tomato (Sept. 17, 1992).**

[ccxxix] **Calgene, supra note 212 at 000235, 000277.**

[ccxxx] **Memorandum of Conference between Monsanto and FDA re: Delayed Ripening Tomato (Sept. 19, 1994).**

[ccxxxi] **See supra note 216 at Safety Assessment: New or Modified Carbohydrates.**
[ccxxxii] **See supra note 216 at Executive Summary.**
[ccxxxiii] **57 Fed. Reg. at 22986.**
[ccxxxiv] **See supra note 8 (bracketed explanation added).**
[ccxxxv] **Id.**
[ccxxxvi] **See supra note 31.**
[ccxxxvii] **See supra note 41.**
[ccxxxviii] **Pribyl, supra note 25.**
[ccxxxix] **58 Fed. Reg. 2431, 2443 (Jan. 6, 1993) (emphasis added).**
[ccxl] **53 Fed. Reg. 51062, 51063 (Dec. 19, 1988).**
[ccxli] **Matthews, supra note 41.**
[ccxlii] **See supra note 8.**
[ccxliii] **J.A. Nordlee *et al.*, Identification of a Brazil nut Allergen in Transgenic Soybeans, 334 New England Journal of Medicine 688-92 (1996).**
[ccxliv] **FDA Memorandum, Public Comments on Labeling of Bioengineered Foods (undated).**
[ccxlv] **See supra note 195.**
[ccxlvi] **51 Fed. Reg. 13376, 13388 (April 18, 1986).**
[ccxlvii] **Id. at 13390 (emphasis added).**
[ccxlviii] **Preliminary Analysis, supra note 21.**
[ccxlix] **See supra note 57.**
[ccl] **Memorandum from Mitchell J. Smith to James Maryanski, Comments on Draft Federal Register Notice on Biotechnology (Jan. 8, 1992) .**
[ccli] **56 Fed. Reg 28592, 28600 (June 21, 1991).**
[cclii] **Preliminary Analysis, supra note 21.**
[ccliii] **See supra note 57.**