Allergies à la Carte
Is There a Problem with Genetically Modified Foods?

What's in a name? Ask genetically modified (GM) foods. They go by many names, ranging from the sinister ("Frankenfoods") to the adoring ("super crops"), depending on who's doing the naming. Although there are clear benefits to the use of this technology—for example, genetic modification could reduce the amount of allergenic substances in foods such as peanuts, the most common food allergen—there is also growing concern among the general public about whether foods modified by recombining DNA from widely different organisms are safe.

A conference titled "Assessment of the Allergenic Potential of Genetically Modified Foods," organized and sponsored by the National Toxicology Program, the U.S. Environmental Protection Agency, the U.S. Food and Drug Administration (FDA), and the NIH, was held 10–12 December 2001 in Chapel Hill, North Carolina, to address this question. Clinicians, bench scientists, government regulators, industry personnel, and policy analysts summarized the current state of the knowledge, examined the issues, and made recommendations for setting research priorities to improve risk assessment.

GM foods are products of plants engineered by biotechnology (no GM animal products are currently approved for the U.S. market). GM crops contain either genes from other plant, animal, or bacterial species, or modified genes constructed in the laboratory and not found in nature. These "borrowed" genes confer some advantage such as pest resistance, herbicide tolerance, longer shelf life in the supermarket, or increased nutritional value.

One unanswered human health question concerns allergenicity. GM foods often contain proteins that humans may not have ingested before or that they may have encountered in a different context (for example, as a glycosylated protein in the original plant but as a nonglycosylated protein in a GM food). Might such novel proteins cause allergic reactions in genetically predisposed people?

Matt Ray/EHP

Reason for Concern?

In his keynote address, Dean Metcalfe, chief of the Laboratory of Allergic Diseases at the National Institute of Allergy and Infectious Diseases, explained that an allergic reaction is a complex immune system response to an antigen—a protein or piece of a protein that is recognized by the immune system as a potential allergen. Antigens come from foreign proteins found in substances such as food, fungi, bacteria, viruses, pollen, and cells from transplanted tissues. They trigger the production of antibodies, which protect the body by neutralizing the "invader."

The immune response generally provides protection against foreign substances. In genetically predisposed individuals, however, exposure to certain proteins may cause an overreaction to an ordinarily innocuous substance. A later reaction between the antigen and the antibody releases chemicals that affect many different tissues, causing symptoms ranging from minor skin rashes, headaches, vomiting, and diarrhea, to, in rare instances, anaphylaxis and death.

Metcalfe emphasized that the mechanisms involved in allergic reactions are highly complex because of their interdependency on other molecular conditions in both the body and the environment. For example, a person may have an allergic response to a food only when there is also some kind of infection present. People can also develop tolerance or sensitivity to different allergens depending on their exposure and stage of physical development. Babies and children are more prone to allergies because of their immature immune systems. Children are not born with the ability to tolerate food proteins; as they are weaned and begin to eat food, they gradually develop tolerance to food proteins. Approximately 80% of children with allergies outgrow them at some point.

In the United States, around 7 million people have documented food allergies. A Mayo Clinic study published in the August 1999 (part 1) issue of the *Journal of Allergy and Clinical Immunology* showed that a third of the cases of anaphylaxis in the United States were due to food allergies, whereas a

British study published in the December 1996 issue of *Clinical and Experimental Allergy* showed 50% of the cases in England were caused by food allergies (a discrepancy that may be due to study design). There are 150–175 deaths per year from food allergy reactions in the United States. The majority of people who die from food allergies also have asthma.

The only treatment for food allergies is dietary avoidance, which depends upon being able to identify the source of exposure and treat reactions should they occur. This defines the central problem in regard to the safety of GM foods: because GM foods are not currently labeled, it is impossible to know whether the produce one buys at the supermarket contains possibly allergenic transgenic proteins.

Many scientists believe GM food safety could be well characterized by clinical trials using double-blind food challenge tests in which subjects sample foods under immediate medical supervision. However, such tests are not routinely conducted on GM foods.

Introducing an itch? Speakers at a recent conference on genetically modified foods debated whether transgenic crops might result in allergic reactions in susceptible populations.

Steve McCaw

Determining Allergenicity

Three criteria are currently used to determine if a transgenic protein is safe for human consumption. First, a sequence comparison to food proteins known to elicit allergic reactions is conducted to see whether the novel protein has a linear sequence of amino acids similar to known allergens. Scientists then test the reaction of antibodies to known food antigens in the new food. Finally, they run test tube assays to determine how well a protein withstands digestion. These same criteria can be useful for crops produced by more conventional agricultural crossbreeding as well. But questions remain as to the effectiveness of these methods for assessing the safety of foods with novel proteins.

The bioinformatic tools and databases available to compare sequence homology were developed to look at evolutionary relationships between different organisms. In predicting allergenicity, the critical questions involve much more subtle differences within organisms that are not necessarily revealed by available computer programs and search engines. One issue is that there is no standardization of how many amino acids should be looked for in a sequence. The fewer the number of amino acids in the sequence search, the more possible matches, and many of those matches may not be valid indicators of allergenicity. On the other hand, the greater the number of amino acids in the sequence search, the higher the likelihood of missing a sequence that may cause a problem. The question is determining the optimal number of search sequences.

Robert Hamilton, director of the Johns Hopkins Dermatology, Allergy, and Clinical Immunology Reference Laboratory, pointed out that another problem with the comparison of the primary amino acid structure to proteins already in databases is that allergic reactions often arise while or after proteins are metabolized. In such cases, this technique could not reveal allergenic potential.

Research scientist Tong-Jen Fu of the FDA's National Center for Food Safety and Technology discussed the reliability of digestion assays for determining food safety. This concept assumes that all or most food allergens resist digestion more than other foods. This is not necessarily a safe assumption to make; although many food allergens are indeed stable during digestion, many other major allergens are broken down by gastric enzymes, and these cannot be detected in the digestion stability assays. Also, due to a lack of standardization, there is considerable variability in results from different laboratories that use different ratios of enzymes to test proteins in their digestion assays. Furthermore, because *in vitro* tests use much higher amounts of enzymes than what is found in the human digestive tract, these assays do not simulate what actually occurs in human digestion.

The Future of GM Foods

Although GM foods may offer great benefits, certain concerns must be assuaged before these foods can be accepted as a net gain. Current methods for assessment have not been validated as robust indicators of safety; alternative strategies including animal models and immunoassays need to be developed. The clear identification and articulation of the challenges posed by widespread deployment of novel proteins in our food supply is a vital step toward improving risk assessment and preventing adverse health effects that could arise from eating GM foods.

In an upcoming issue, *EHP* will publish a mini-monograph resulting from research presented at this meeting.

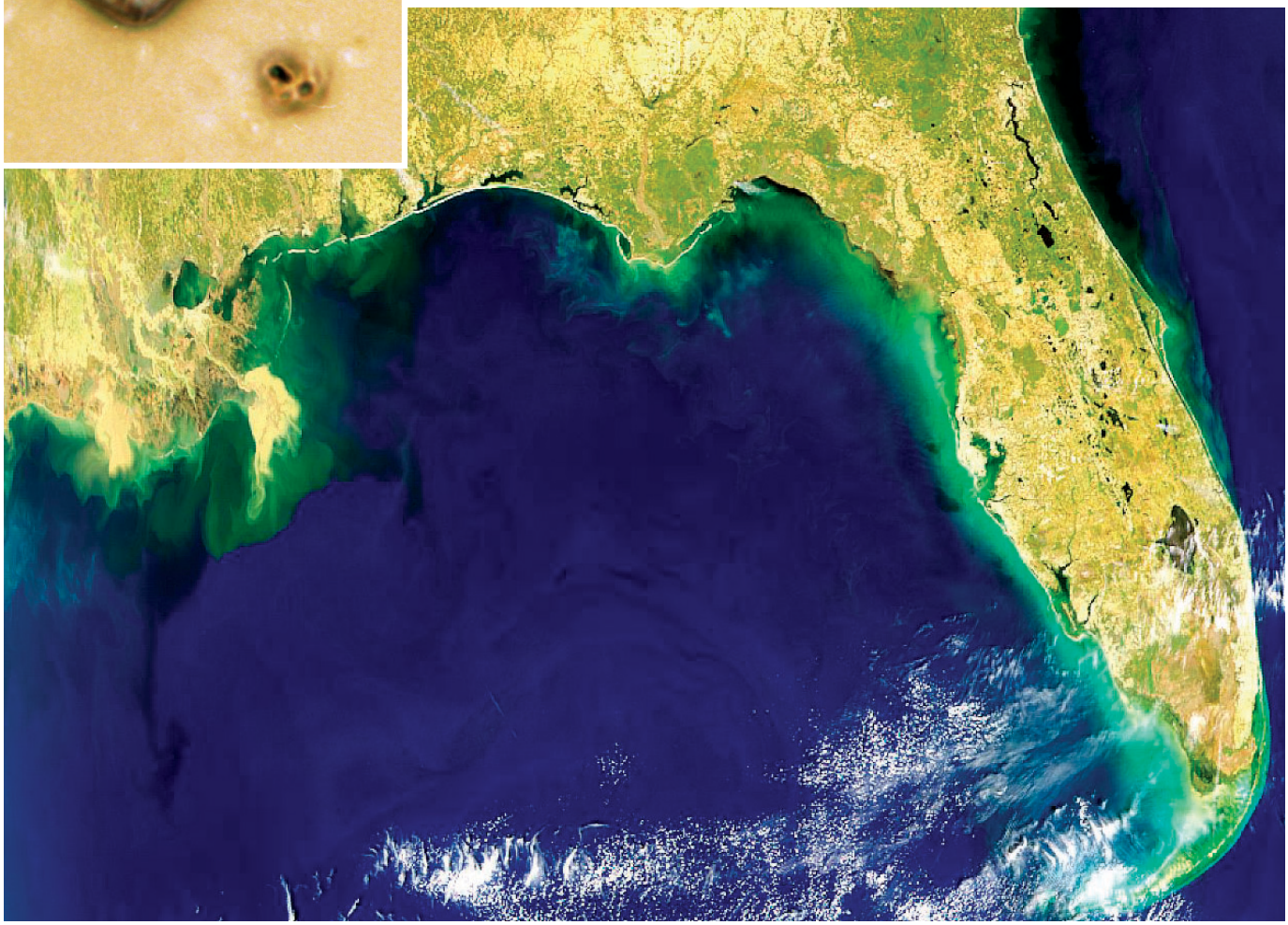
–Mary Eubanks

The Current of Red Tide Research

An interdisciplinary group of scientists from federal and state government, academic, and research institutions have completed the first phase of data collection for human exposure to aerosolized brevetoxins during red tide events. Brevetoxins are potent neurotoxins produced by the dinoflagellate *Karenia brevis* (previously classified as *Gymnodinium breve*), a marine microalga found in the Gulf of Mexico and the western North Atlantic. The first portion of this study, known as the 2001 Occupational Red Tide Survey, is being funded by the Florida Department of Health, the Centers for Disease Control and Prevention (CDC), the Florida Harmful Algal Bloom Taskforce, and the NIEHS. The group is being led by Daniel Baden, director of the Center for Marine Science at the University of North Carolina at Wilmington, and Lorrie Backer, leader of the CDC's Emerging Environmental Threats Team.

Measuring mammals. Researchers perform spirometry on red tide–afflicted manatees to detect respiratory effects.

On an almost annual basis, *K. brevis* forms large toxic blooms, known as red tides, particularly along the west coast of Florida. An extensive bloom of *K. brevis* red tide such as the one present in Florida since late in the summer of



Overstaying its welcome. A *K. brevis* red tide has plagued the Gulf of Mexico since August 2001—the dark, cloudy areas near the shoreline show where the bloom lingers. The dinoflagellate *K. brevis* (inset) is implicated in health problems in humans as well as marine mammals and birds, including respiratory and neurotoxic effects.

clockwise from top right: Red Tide Research Group; NASA; Carmelo Tomas

Barb Kirkpatrick

On the lookout for trouble. A member of the 2001 Occupational Red Tide Survey team collects lung function and respiratory effect data from a lifeguard who worked on beaches affected by *K. brevis* red tides.

2001 can kill tons of fish. Marine mammals (such as the highly endangered West Indian manatee) and birds also succumb to the respiratory paralysis and other neurotoxic effects caused by exposure to brevetoxins.

One recognized human health effect from exposure to *K. brevis* and its toxins is neurotoxic shellfish poisoning (NSP), which can occur when people eat shellfish that have been contaminated through filter-feeding activities. NSP can be prevented by monitoring waters for *K. brevis* and rapidly closing shellfish beds when blooms approach; in the United States, the only reported cases of NSP in about 30 years have been from the consumption of shellfish collected illegally from closed beds.

In addition to NSP, people have reported a number of symptoms, including respiratory complaints, after being on or near the beach during a red tide event. Although a link has not been scientifically and medically demonstrated, scientists believe these symptoms are caused by exposure to aerosolized brevetoxins and perhaps airborne *K. brevis* cellular debris generated during red tide events.

During the *K. brevis* bloom that formed in August 2001 in the Gulf of Mexico, the research team collected water for *K. brevis* cell enumeration and for brevetoxin concentrations, collected air samples for brevetoxin concentrations, and monitored meteorologic conditions. The team also monitored the incidence of human health effects associated with red tide events. Specifically, pre- and postexposure information on pulmonary function and inflammatory response as well as respiratory symptoms was collected from a group of lifeguards stationed at the affected beaches and from some of the scientists collecting environmental samples. Preliminary results will be presented at the 2002 annual meeting of the Society of Toxicology to be held this month.

In the future, scientist collaborators will return to this area to collect similar human health and environmental data on the same individuals during a time when there is no red tide event. The scientists also plan to evaluate the health effects from exposure to red tide in people visiting beaches, particularly sensitive populations such as those with asthma and older people with chronic respiratory problems. In addition, ongoing studies are using experimental animals to evaluate both mechanisms and possible prevention of exposure to and health effects of the aerosolized brevetoxins associated with *K. brevis* red tides. **–Red Tide Research Group**

Harmful Algal Bloom Web Sites

National Oceanic and Atmospheric Administration
http://state-of coast.noaa.gov/bulletins/html/hab_14/hab.html

Woods Hole Oceanographic Institution
http://www.agu.org/revgephys/anders01/anders01.html

International Society for the Study of Harmful Algae
http://www.cbr.nrc.ca/issha/

Florida Marine Research Institute
http://www.floridamarine.org/

Mote Marine Laboratory
http://www.mote.org/

Northwest Fisheries Science Center
http://www.nwfsc.noaa.gov/hab/

University of Miami NIEHS Marine and Freshwater Biomedical Sciences Center
http://www.rsmas.miami.edu/groups/niehs/

National Marine Fisheries Service
http://www.sh.nmfs.gov/EAquaBpg.htm