

New Centers for Oceans and Human Health

One in twenty: that's the percentage of people who develop rashes, nausea, or other symptoms after swimming in marine waters with levels of pollution deemed acceptable by the European Union and the U.S. Environmental Protection Agency, according to the World Health Organization. Most people infected by pathogens in the water generally will recover quickly, as will those exposed to harmful algal blooms (HABs), sometimes known as red tides. But in rare cases, especially among the young or the elderly, illnesses can be severe, resulting in life-threatening infections or—in the case of exposure to algal toxins—paralysis, neurological disorders, and death.

With the aim of reducing disease and death among people who eat seafood and swim in oceans and bays, scientists at four new research centers will study the ecology, oceanography, genetics, and health effects of marine pathogens. Center scientists will also search for new marine sources of antibiotics and other drugs. The National Science Foundation (NSF) and the NIEHS announced funding for the four joint Centers for Oceans and Human Health on 22 April 2004. The two agencies will invest about \$5 million annually for a total of \$25 million to support the centers, which are located at the University of Washington, the University of Hawaii, Woods Hole Oceanographic Institution, and the University of Miami.

“Oceans have become conduits for a number of environmental threats to human health,” said NIEHS director Kenneth Olden at the time of the centers’ announcement. “At the same time, oceans harbor a diverse array of organisms that show great promise for providing new drugs to combat cancer and fight infectious diseases. In order to guard against health threats and to take advantage of medicinal benefits that oceans might provide, the impact of oceans on human health must be more fully explored.”

“The NIEHS has recognized the linkage between oceans and human health for a number of years, as evidenced by its support of marine-related research projects on the effects of toxins from HABs and contaminated seafood consumption, and a set of Freshwater and Marine Biological Research Centers,” says center program administrator Fred Tyson. “Moreover, the NIEHS has embraced the concept of using multi- and interdisciplinary approaches to address complex environmental health issues with programs such as its Centers for Children’s Environmental Health and Disease Prevention Research and Centers for Population Health and Health Disparities.”

“I’m glad to see the NSF and the NIEHS involved in this,” says Walter McLeod, president of the Clean Beaches Council, a nonprofit group that sponsors the Blue Wave Campaign certification program for environmentally conscious beaches. “It’s a long overdue area of research, and the right kind of project for the beach-going public.” Adds David Helvarg, president of the Blue Frontier Campaign, an

education and activism group, “We’ve looked at the positive health impacts of going to the beach without looking at the impacts of using the oceans as our toilet and our wastebasket.”

Senator Ernest F. Hollings (D–SC) stated before the U.S. Senate on 24 March 2004 that the centers “show tremendous promise.” Hollings, a sponsor of the Oceans and Human Health Act, which passed the Senate in March, has said, “Because oceans act as a route of exposure for human disease through ingestion of contaminated seafood or direct contact with saltwater containing toxins and disease-causing organisms, it is vital that we learn more about how public health is affected by the marine environment.”

Harmful Algal Blooms

No one is sure why algae rapidly increase in abundance, or “bloom,” and why some blooms produce toxins and others do not. Gaining a better understanding of the factors that cause HABs is a primary research focus of all four centers. Each center will study conditions, such as currents, salinity, water temperature, and nutrient loading, that may trigger blooms and the release of toxins. Center researchers will also study blooms at the microscopic level, using genetic analysis to identify the different species and subspecies that bloom under various conditions. The ultimate goal of such research is to find better ways to predict blooms and detect the toxins they produce, thus reducing human exposure and disease. For example, the results of genetic studies could be used to develop molecular probes to detect toxic species and prevent exposure.

Once toxins accumulate in the water during certain blooms, swimmers and beachgoers can be affected through skin contact or by swallowing water or inhaling aerosolized spray. However, eating seafood is the most common route of exposure. Algal toxins work their way up the food chain by accumulating in the digestive tracts, and sometimes the muscle tissue, of fish and shellfish. In the United States, few people eat tainted shellfish, thanks to monitoring programs that close commercial and recreational shellfish beds if toxins are detected. However, there are serious gaps in toxin protection programs for tropical and subtropical areas.

One reason is a lack of programs that regularly test for the ciguatera toxins found in tropical reef fish. Another is the high cost of most existing testing programs for all types of HABs. “We need to develop low-cost, effective monitoring protocols affordable by poor populations in tropical and



Ocean of possibilities. New research centers will investigate human health issues related to the ocean, such as conditions caused by marine toxins and the use of marine microorganisms to treat diseases.

PhotoDisc

subtropical regions,” says Lora Fleming, director of the University of Miami’s Center for Subtropical and Tropical Oceans and Human Health. “HAB poisoning is a problem in these areas because poverty precludes expensive monitoring.” For example, in a case in Guatemala, 187 people contracted paralytic shellfish poisoning, and 26 died, including half of the children who were exposed. Further, says Fleming, organisms and their associated toxins and diseases can turn up in new geographic locations and new transvectors. While this can happen in developed nations, too, those countries can better afford to evaluate the outbreaks that result and sometimes even prevent them.

Many existing tests for algal toxins use mouse bioassays, which are costly and time-consuming. “We are hoping to develop more efficient ways to detect toxins,” says Edward Laws, director of the University of Hawaii’s Pacific Research Center for Marine Biomedicine.

Another issue with current testing is that existing monitoring programs are designed to detect relatively high toxin levels that cause noticeable illness. Don Anderson, a senior scientist at Woods Hole, says harvesting closures typically occur only after toxins reach certain threshold concentrations, such as 80 micrograms of saxitoxin per 100 grams of meat, or 20 micrograms of domoic acid per gram of meat. “It is therefore possible for products to be sold and consumed that contain low levels of toxins that are detectable, but below these thresholds,” he says. “We do not know the effects of long-term exposure to these low levels, especially in sensitive segments of the population, such as the elderly and children.”

The interdisciplinary center teams will study several types of algal toxins that cause human illness. Researchers at the Woods Hole Center for Oceans and Human Health will focus on saxitoxins, a group of more than 20 neurotoxins that cause paralytic shellfish poisoning. Saxitoxins attack the nervous system, causing numbness, dizziness, headache, and in the worst cases, respiratory failure. In the oceans, they are produced by dinoflagellates, single-celled organisms distinguished by dual flagella, or hair-like structures, that propel them through the water.

The Woods Hole team will focus on two species of algae: *Alexandrium fundyense*, which produces saxitoxins, and *A. ostenfeldii*, which also generates spirolides, a type of neurotoxin first detected off Nova Scotia in 1995. Spirolides kill mice quickly. However, “there is as yet no [human] poisoning syndrome linked to spirolides, and thus far, no monitoring for spirolides anywhere in the United States,” says Anderson.

Centers for Oceans and Human Health

Center	Director	Areas of Study
Pacific Northwest Center for Human Health and Ocean Sciences University of Washington	Elaine Faustman	Researchers will study toxic algae and how toxic domoic acid accumulates in Puget Sound shellfish. Researchers will also study how domoic acid affects human health through the consumption of contaminated seafood, especially in sensitive populations such as children.
Pacific Research Center for Marine Biomedicine University of Hawaii	Edward Laws	Researchers will study ciguatoxin-producing organisms and develop improved methods for detecting these toxins in fish and humans. Researchers will also study pathogens in tropical coastal waters to learn more about their sources, survival, and ecology, and explore extracts from tropical microorganisms and their potential application in the treatment of cancer and infectious diseases.
Woods Hole Center for Oceans and Human Health Woods Hole Oceanographic Institution	John Stegeman	Researchers will study populations of the toxic plankton <i>Alexandrium</i> in the Gulf of Maine and the relationship of its various genotypes to its toxicity. Researchers will also study human pathogens in Mount Hope Bay.
Center for Subtropical and Tropical Oceans and Human Health University of Miami	Lora Fleming	Researchers will study harmful algal blooms in subtropical ecosystems and develop probes to identify new species and toxins. Algal genomics will be studied to see if different genotypes are more successful during algal blooms. Researchers will also investigate microbes in coastal waters and their effects on human health in recreational waters.

“Efforts to predict or forecast toxicity in the future will have to recognize that we are not just dealing with a single species but rather a complex of strains or subpopulations that will respond differently to the environment,” continues Anderson. For example, in the Woods Hole researchers’ study area off the coast of Maine, Anderson predicts that researchers will find multiple varieties of *Alexandrium* that vary significantly in toxicity, physiology, and behavior—for example, some will grow faster, others will swim faster, still others may migrate vertically in different patterns. “Our objective is to develop genetic markers that will distinguish among the different genotypes, and then to map out their distributions,” Anderson says.

Researchers at the University of Miami will study a subtropical species of dinoflagellate (*Karenia brevis*, formerly *Gymnodinium breve*) that produces brevetoxins, the cause of neurotoxic shellfish poisoning. Neurotoxic shellfish poisoning is similar to paralytic shellfish poisoning, but with somewhat milder symptoms. “With [neurotoxic shellfish poisoning], the primary concern used to be eating seafood. But now we have concerns about skin contact and drinking water,” says Fleming. There is also evidence that the toxins can be aerosolized, because people have developed asthma-like symptoms while simply walking on the beach and, presumably, inhaling minute amounts of sea spray.

Researchers at the University of Hawaii are studying another warm-water dinoflagellate (*Gambierdiscus toxicus*) that produces the ciguatoxins that cause ciguatera fish poisoning. People are most often exposed by eating reef fish such as barracuda and grouper. Symptoms—which can include gastrointestinal distress, blurred vision, irregular heartbeat, depression, and the reversal of temperature sensations (hot things feel cold and vice versa)—can last months after exposure. Like other diseases caused by algal toxins, ciguatera fish poisoning is underreported. According to the Centers for Disease Control and Prevention, perhaps 50,000 people worldwide suffer from ciguatera, but only 2–10% of U.S. cases are reported.

The Hawaii team will work on molecular probes and markers with the goal of eventually developing monitoring systems that could be used throughout Pacific and Caribbean waters. Reef fish usually are not migratory, so specific reefs could be monitored and marked the same way shellfish beds are to reduce exposures, says Fleming: “Fishermen tell us they don’t fish certain reefs because there’s ciguatera there.” An added benefit to ciguatera reef closures, she adds, is that they could protect reef fish from overharvest.

Domoic acid caught the attention of medical and oceanographic researchers when it was found in mussels that sickened more than 100 people and killed 3 in a 1987 outbreak in Canada’s Prince Edward Island. Once a test for domoic acid was developed, it was detected in razor clams in Washington State and Dungeness crabs in Alaska. Domoic acid causes amnesic shellfish poisoning, a neurological illness with symptoms ranging from gastrointestinal distress to permanent loss of short-term memory. Birds and mammals can also be affected. Researchers now suspect that a 1961 incident in Capitola, California, in which nonviolent seabirds attacked people and dive-bombed windows (later inspiring the Alfred Hitchcock thriller *The Birds*) was caused when the birds ate fish tainted with domoic acid. Many recent seabird and marine mammal mortalities on the East and West coasts have been linked to domoic acid moving through the food web, even to whales.

Researchers at the University of Washington Pacific Northwest Center for Human Health and Ocean Sciences, directed by Elaine Faustman, will study environmental factors associated with blooms of single-celled plankton called diatoms (*Pseudo-nitzschia* spp.) that produce domoic acid. Studies will compare conditions in the open Pacific with the more enclosed, estuarine waters of Puget Sound, where

domoic acid was detected in 2003. The researchers will also analyze the molecular mechanisms by which domoic acid kills nerve cells, as well as examine possible reasons why some shellfish, such as razor clams, retain domoic acid for weeks or months, while other species eliminate the toxin quickly.

Of particular concern to these researchers is determining who is at greatest risk of neurological damage from exposure to domoic acid. Susceptible individuals may include members of Native American tribes and Asian/Pacific Islander groups, who tend to eat much more seafood than other groups and who sometimes eat parts of shellfish where the toxin accumulates, such as the hepatopancreas. In addition, children and the elderly are potentially more vulnerable to the effects of domoic acid and other algal toxins.

Parasitic Protists and Bacteria

In addition to algal toxins, which cannot be passed from one person to the next, center researchers will also study infectious agents of disease. Researchers at Woods Hole will study the prevalence and ecology of a range of bacteria and parasitic protists including amoebae in temperate waters, while the centers at Miami and Hawaii will focus on developing better indicators for infectious pathogens in warmer waters.

The Woods Hole researchers will study Mount Hope Bay in Massachusetts, where warm water discharged from a power plant may encourage the growth of pathogens that would not normally be found there. According to center director John Stegeman, many pathogens enter marine waters, especially through sewage, but “whether they survive marine conditions or accumulate in concentrations that could be vectored back to humans is a question.”

The group will study the ecology of several types of bacteria in the same genus (*Vibrio*) as the species that causes cholera. They will also hunt for rarer organisms, including amoebae that harbor the bacterium that causes Legionnaire disease (*Legionella pneumophila*) and a parasitic amoeba (*Naegleria fowleri*) that thrives in warm water and travels up the noses of swimmers and divers to cause rare, but often fatal, infections of the nervous system and brain.

Researchers at the Hawaii and Miami centers will search for microorganisms that can serve as better indicators of marine pathogens. “A problem is that a lot of the indicators commonly in use have nonfecal sources, or they aren’t appropriate for tropical or subtropical waters,” says Laws. He adds that recent studies have shown that

Enterococcus species—the standard indicator recommended by the U.S. Environmental Protection Agency—grow naturally in the soil of Hawaii, and probably other tropical areas, and so don’t necessarily signal fecal pollution.

Pharmaceuticals from the Sea

At the same time as the center researchers study marine organisms that harm, they will also prospect for those that heal. “Scientists believe the oceans represent a promising source of novel compounds with therapeutic and/or disease-fighting capabilities,” Hollings said in his 24 March 2004 address to the U.S. Senate. “At present, there are only three marine compounds in clinical use—and these were developed in the 1950s. While there are some new compounds in the pipeline, we need to speed research efforts to ensure we get more products approved.”

In their search for pharmaceuticals, center researchers at the University of Hawaii will focus on marine microbes. “The fact is that there are more microbes in the ocean than there are stars in the sky,” says Helvarg. “It’s reasonable to assume that some have devised biochemical defenses to protect themselves from potential enemies, and that some of those biochemical defenses may involve compounds of interest to humans.”

The Hawaii team will screen microbe extracts for tumor-fighting and antibiotic properties, working in collaboration with the University of Hawaii Cancer Research Center and private laboratories. Given recent results from other laboratories, it’s possible that center researchers may find compounds in both categories. Researchers affiliated with the National Cancer Institute and other groups have extracted compounds from marine sponges and corals that inhibit the growth of tumor cells, and a group from the Scripps Institution of Oceanography has isolated marine bacteria closely related to the terrestrial organisms from which antimycin antibiotics were originally derived.

Helvarg’s enthusiasm for such research is tempered by concerns about continuing degradation of the marine environment. The discovery of new marine pharmaceuticals is possible only “if we can explore these marine environments before we destroy them,” he says. McLeod anticipates that research by the centers and other groups could support efforts to protect and restore marine habitats by creating “a groundswell of data for decision makers.” According to Helvarg, the key message for citizens and government is simply that “when we dump into the ocean, we put our own lives at risk.” —Kris Freeman



Toxin Talk in Miami

Summertime in the United States means crowds of people flocking to the coast to enjoy the beaches and oceans. For many people—with no small credit to Steven Spielberg—their biggest fear associated with the oceans is sharks. But a much more realistic and just as dangerous hazard may lurk beneath the waves. Marine and freshwater toxins such as ciguatoxins, saxitoxins, domoic acid, and brevetoxins are becoming



more widespread around the world. These toxins may be eaten in seafood, ingested in ocean water, or breathed in the air, resulting in a wide range of effects including respiratory illness and paralytic, neurotoxic, amnesic, and diarrhetic shellfish poisoning. For people concerned about exposure to these toxins, help is just a phone call away.

The toll-free Marine and Fresh Water Toxin Disease Reporting Hotline (1-888-232-8635) operates 24 hours a day, 365 days a year, to provide diagnostic, treatment, and educational information. The hotline is a project of the Community Outreach and Education Program of the University of Miami NIEHS Marine and Freshwater Biomedical Sciences Center (MFBSOC), in cooperation with the Florida Department of Health (FDH) and the Centers for Disease Control and Prevention (CDC).

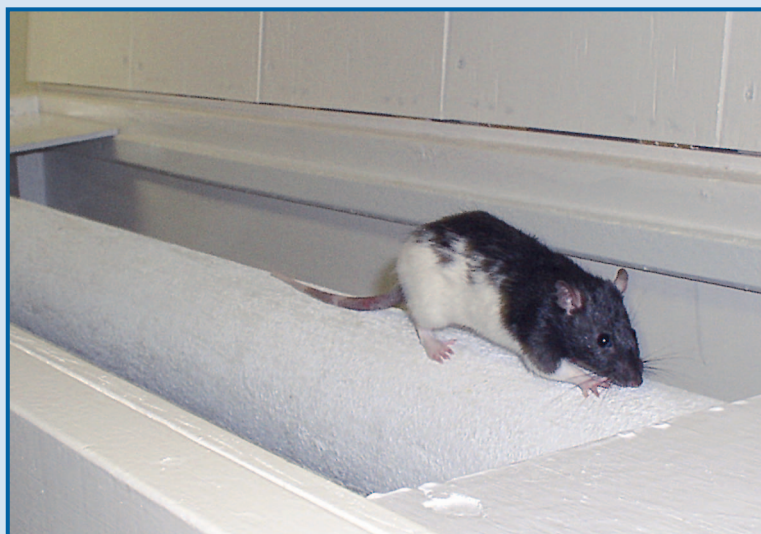
The hotline, which receives calls from all over Florida, the United States, and abroad, provides information primarily in English, Spanish, and Haitian Creole (125 other translated languages are available). Callers can get referrals for clinical treatment and laboratory testing. Those who need more information are referred to personnel at the MFBSOC, FDH, or CDC. More information is sent to callers at their request and is posted online at <http://www.rsmas.miami.edu/groups/niehs/general/readings.jsp>.

The hotline serves not only as an information resource, but also as a starting point for case surveillance of marine and freshwater toxin diseases, which are highly underreported. Better monitoring and understanding of these illnesses will help scientists and public health officials ensure that it's safe to go back in the water. —**Kimberly G. Thigpen**

Headliners

NIEHS-Supported Research

Toxic Synergism



MeHg/PCB Combination Impairs Motor Skills in Young Rats

Roegge CS, Wang VC, Powers BE, Klintsova AY, Villareal S, Greenough WT, Schantz SL. 2004. Motor impairment in rats exposed to PCBs and methylmercury during early development. *Toxicol Sci* 77:315–324.

Methylmercury (MeHg) and polychlorinated biphenyls (PCBs) both accumulate in the environment and in the tissues of fish. Both compounds have been linked to neurological and motor deficits in humans in a number of epidemiological studies. A study by researchers at the FRIENDS Children's Environmental Health Center, a five-institute research consortium based at the University of Illinois at Urbana–Champaign College of Veterinary Medicine, provides new evidence that MeHg and PCBs act together to cause nervous system impairment. Among the researchers are NIEHS grantees Susan L. Schantz and Victor C. Wang of the University of Illinois at Urbana–Champaign.

The researchers exposed female rats to low doses of MeHg, a PCB mixture, a combination of the two compounds, or control conditions starting 4 weeks prior to breeding and continuing through 16 days after birth of offspring. The offspring of the groups were run through a battery of three motor skills tasks that involve cerebellar functions. Rat pups from the combined exposure group showed significant motor skill impairment in a test that involved traversing a rotating rod. Rats exposed to the PCB mixture alone were somewhat impaired, and rats exposed to MeHg alone were unimpaired as compared to the control animals. There were no significant deficits related to PCB or MeHg exposure on the less complex tasks of vertical rope climbing or completing a parallel bar test.

This study demonstrated that combined treatment with MeHg and PCBs may produce additive neurological effects. The researchers point out that PCB exposure contributed more to motor impairment than did MeHg, possibly due to the low dosage used. Rats exposed to MeHg alone demonstrated no significant impairments. The current study could offer an explanation as to why previous epidemiological studies of humans exposed to MeHg by eating contaminated fish have produced conflicting results. The scientists will continue their studies to determine if PCBs and MeHg have the same or independent mechanisms of action. —**Jerry Phelps**