

Tell me what you eat, and I will tell you what you are.

Jean Anthelme Brillat-Savarin  
*The Physiology of Taste* (1825)

DIET & NUTRITION

## Hyperactive Ingredients?

The question of whether food additives such as preservatives, artificial flavorings, and artificial colorings trigger hyperactivity has been debated for more than 30 years. Research generally has not supported food additives as influencing hyperactivity—whose characteristics include overactivity, inattention, and impulsive behaviors, traits that in extreme forms define attention deficit/hyperactivity disorder (ADHD)—but some studies have found small effects. Most recently, a study published 3 November 2007 in *The Lancet* suggests that the preservative sodium benzoate and commonly used artificial food colorings in fact may exacerbate hyperactive behavior in young children.

In the *Lancet* study, researchers led by Jim Stevenson, a professor of psychology at the University of Southampton, United Kingdom, built upon a previous double-blind placebo-controlled study of preschool children. In that study, published in the June 2004 *Archives of Disease in Childhood*, 3-year-old children on a diet free of artificial dyes and benzoate preservatives exhibited increased hyperactivity when challenged with a drink containing a mixture of the widely used sodium benzoate plus the dyes Sunset Yellow, carmoisine, tartrazine, and

Ponceau 4R (in their later paper, Stevenson and colleagues termed this combination “mix A”). Again using a double-blind placebo-controlled design, the Southampton team expanded the study group to include 153 3-year-olds and 144 8- and 9-year-olds representative of the general population.

Children ate diets free of the elements in mix A and a second, more concentrated mixture of additives (“mix B,” comprising sodium benzoate plus the dyes Sunset Yellow, carmoisine, Quinolone Yellow, and Allura Red AC) for six weeks. During that time, they drank a daily serving of plain juice (placebo) or juice containing one of the two mixes; the test drink changed weekly. To measure hyperactivity, the team calculated a global hyperactivity aggregate (GHA) based upon questionnaires completed by parents, teachers, and trained observers. Older children also completed a computer-based assessment of attention. Small but significant increases in GHA occurred with mix A in both age groups, with 3-year-olds showing a greater effect. Mix B was associated with a small significant effect in 8- and 9-year-olds, but not in 3-year-olds, who had a wide range of individual responses.

“The outstanding feature of the results was the similar pattern of an adverse effect across both ages for both mixes—although this did not reach statistical significance in every case,” says Stevenson. An unpublished study based on genetic samples from the

children examines these individual differences in greater detail. “Our [forthcoming] data indicate that genetics rather than anything else accounts for these individual differences in response within an age group,” Stevenson says.

Although the Southampton researchers conclude that their results strongly support a relationship between food additives and behavior, they do not claim that food additives cause clinically defined ADHD. “It is very important to clarify that the food additives and preservative studied only increased activity level modestly,” says Andrew Adesman, chief of developmental and behavioral pediatrics at Schneider Children’s Hospital in New Hyde Park, New York. “I think the reasonable lessons from this study are that there may be modest effects on activity level from additives or preservatives and that better, more precise studies are needed to determine whether it is the additives alone, the preservatives alone, or the combination that is responsible for these modest adverse effects.” The authors describe these research needs with the additional requirement of considering the time elapsed between additive consumption and subsequent behavior.

Nevertheless, after reviewing the Southampton study, the British Committee on Toxicity concluded that the results could be clinically relevant for individual children, particularly those who already show a tendency toward hyperactivity. On the basis of this study the British Food Standards Agency, which funded the research, has advised parents to consider eliminating the colorings used in the study from the diets of children who exhibit hyperactive behaviors.

“It will be interesting to see how the [U.S.] Food and Drug Administration reacts to this study,” says Adesman. “Hopefully, they will either encourage or mandate additional studies looking at food effects of additives on children and also adults.”

The FDA is aware of the Southampton study but has not received the study data, according to administration spokesman Mike Herndon. “We will examine this recent report to see if the results suggest whether any action to modify our current regulations is appropriate,” he says. “However, we have no reason at this time to change our conclusions that the ingredients that were tested in this study that currently are permitted for food use in the United States are safe for the general population.”

—Julia R. Barrett



**Dyeing for more data.** The question of whether food additives such as colorings contribute significantly to hyperactivity remains open.

Ross Niblock/istockphoto

## AGRICULTURE

## Pesticides Disrupt Nitrogen Fixation

Talk about a vicious cycle. Some organochlorine pesticides suppress bacteria from replenishing natural nitrogen fertilizer in soil, resulting in lower crop yields, stunted growth, and an ever-greater need for additives to boost production. This previously unrecognized effect stems from pesticides interfering with flavonoid signaling from leguminous plants such as alfalfa, peas, and soybeans to soil bacteria that fix nitrogen. “People assume that endocrine disruption by pesticides occurs only in humans and animals with estrogen receptors, but we find there are nontraditional targets affected by pesticides,” says Jennifer Fox, a postdoctoral researcher at the Center for Ecology and Evolutionary Biology at the University of Oregon.

Plants produce chemicals, many that are structurally similar to phytoestrogens, that attract *Rhizobium* soil bacteria to their root systems to form nodules for nitrogen fixation. Inside the nodules, the bacteria convert atmospheric nitrogen into the natural fertilizer ammonia. These symbiotic soil bacteria respond to plant-produced flavonoid molecules through nodulation D (NodD) receptors, which act similarly to estrogen receptors in vertebrates. In the May 2004 issue of *EHP*, Fox and colleagues reported a study using *Sinorhizobium meliloti*, a soil bacterium that fixes nitrogen in symbiosis with alfalfa. The researchers found that the organochlorine pesticides pentachlorophenol (PCP) and methyl parathion at levels found in farm soils inhibited NodD signaling by 90% and that DDT cut signaling by 45%.

In recent greenhouse experiments, Fox and colleagues at Tulane University treated alfalfa seeds inoculated with *S. meliloti* with PCP, methyl parathion, and DDT, which are found in soil after farmers spray crops, especially in countries where these pesticides have not been banned. Six weeks after treatment, PCP-treated alfalfa plants produced no nodules, and plant yields fell to 17% compared with control plants not treated with pesticides. Methyl parathion and DDT reduced nodule numbers and

plant yields by about half. The researchers estimate that the amount of inhibition measured in this experiment could translate in real-world conditions to a one-third loss of plant yield each growing season.

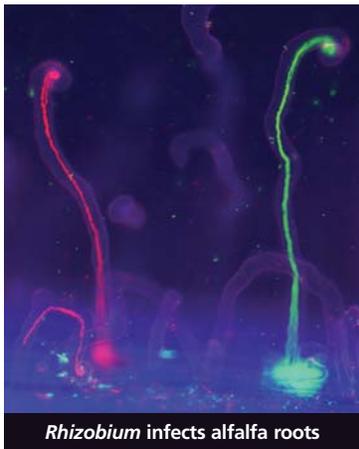
The results, published 12 June 2007 in the *Proceedings of the National Academy of Sciences*, indicate that pesticide residues in soil could not only reduce harvest yields, but also increase the need for synthetic fertilizers, thereby raising costs for farmers and contributing to environmental pollution. The observations also may explain a trend in the past 40 years toward stagnant crop yields despite record high use of pesticides and synthetic fertilizers worldwide.

In unpublished experiments, co-author John McLachlan, director of the Tulane Center for Bioenvironmental Research, showed that the same three pesticides disrupt NodD signaling in *Rhizobium* sp. strain NGR234, a bacterium that fixes nitrogen in symbiosis with more than 100 leguminous plants growing in tropical and subtropical soils. “Many of the species that NGR234 nodulates are trees and bushes, such as teak and rosewood, that promote vital soil improvement within nutrient-poor tropical soils,” he says. McLachlan says farmers in poorer countries especially cannot afford to lose natural fertilizer because synthetic fertilizers cost so much.

The connection between pesticides and nitrogen fixation shows that “pristine and natural interactions between bacteria and plants are being jeopardized by what we put into the soil,” says Ann Hirsch, a plant molecular biologist at the University of California, Los Angeles. Similarly, the effects of pesticides on human disease continue to be documented, with a report in the October 2007 issue of *EHP* linking childhood exposure to DDT with a fivefold higher risk of breast cancer in women. “Now we are affecting our agricultural assets,” Hirsch says, “something people take for granted.”

Fox plans to test the effects of pesticides on alfalfa and soybeans under real-life field conditions. “We want to screen pesticides to see which ones cause minimal damage to certain types of crops and maximize the amount of natural fertilizer made,” she says.

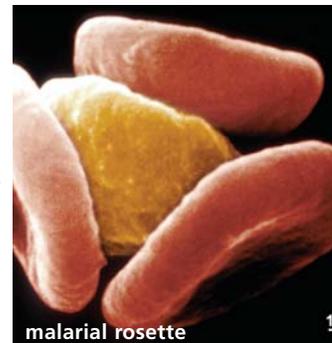
—Carol Potera



*Rhizobium* infects alfalfa roots

## O Happy Day for Malaria Treatment

A new understanding of malaria pathogenesis could guide the development of new antimalarial drugs. A study published in the 30 October 2007 issue of *Proceedings of the National Academy of Sciences* showed that people with blood type O were 66% less likely to experience severe, life-threatening cases of malaria. In type O patients, rosettes—obstructive clumps of infected red blood cells bound to uninfected cells—occurred less frequently; rosettes that did occur were not as well formed as those in patients with other blood types. The authors believe a future vaccine could promote antibodies that inhibit rosetting and thus prevent some cases of severe malaria.



malarial rosette

## Breastfeeding Trumps DDT

Given that a number of organochlorine pesticides such as DDT can be passed from mothers to infants through breast milk, breastfeeding has been questioned as the best way to feed babies of exposed mothers. Pre- and postnatal exposures to these chemicals have been linked to disruptions in neurologic development that can affect mental and psychomotor functioning. However, in a report in the October 2007 issue of the *American Journal of Epidemiology*, Spanish researchers showed that, regardless of DDT exposure prenatally and via breast milk, children who were breastfed for more than 20 weeks performed better on tests of verbal skills and memory at age 4 years than peers breastfed for shorter periods.

## Artisanal Diamond Mining Gets a Hand

Although artisanal diamond mining doesn't use toxic chemicals such as mercury in the way artisanal gold mining does, the process does contribute to deforestation and remove tillable land from cultivation, and is associated with higher rates of diseases such as malaria and schistosomiasis. The Diamond Development Initiative, founded in 2005 to improve working and economic conditions for the more than 1 million artisanal diamond miners in Africa, announced in October 2007 that the Swedish Ministry of Foreign Affairs and The Tiffany & Company Foundation will provide grants totaling more than \$750,000 in support of initiative programs. The monies will provide the initiative with core operating support for its work as well as funds for a standards and guidelines project on artisanal diamond mining.



## CHEMICAL EXPOSURES

## Cats as Sentinel Species

Pet cats may be like canaries in coal mines when it comes to evaluating the health impacts of polybrominated diphenyl ethers (PBDEs), persistent chemicals used in carpet pads, furniture, and electronics. Chronic PBDE exposure may partly explain an epidemic of hyperthyroid disease in older cats, says Janice Dye, a U.S. EPA research biologist. In turn, studying the effects of chronic PBDE exposure in cats could offer clues as to the effects in their human counterparts.

Veterinarians first noticed a dramatic surge in feline hyperthyroidism (FH) in the 1980s, coinciding with the use of PBDEs as flame retardants in consumer products. FH, the most common endocrine disorder in cats, causes rapid weight loss due to increased concentrations of thyroxine. Histologic changes in FH mirror those seen in older humans experiencing toxic nodular goiter (TNG), in which an enlarged thyroid gland overproduces thyroxine. The causes of FH and TNG remain unknown.

Dye looked at whether hyperthyroidal cats had greater body burdens of PBDEs. She and her colleagues measured numerous PBDE congeners in serum samples collected from 23 cats, 11 of which were positive for FH. They report in the 15 September 2007 *Environmental Science & Technology* that total average PBDE levels were three times higher in older cats with FH than in younger cats without FH, but the difference was not statistically significant because of high within-group variability. “All cats are high [compared with humans], and some cats are incredibly high,”



**Taking a cue from kitty.** Health effects seen in cats exposed to PBDEs may offer insights into how these chemicals affect humans.

Dye notes. She also found that cat food, particularly canned fish-flavored brands, contains high levels of PBDEs. Cats swallow PBDEs in food and by licking PBDE-laden house dust from their fur.

PBDE congeners contain bromine atoms that mimic the iodine in thyroxine. PBDEs may interact with thyroid-binding proteins to displace thyroxine, and chronic exposure may lead to sustained increases in secretion of thyroid-stimulating hormone and thyroid hyperplasia. “When that happens,” says Dye, “it’s pedal to the metal, and the cat’s thyroid makes too much thyroxine.”

The potential link between FH and PBDEs suggests that house cats may be sentinels for chronic indoor PBDE exposure in people. By understanding more completely how PBDEs alter thyroid hormone levels in cat sentinels, “we can assess whether comparable risk exists for exposed people, especially children,” Dye says. Like cats, toddlers may be inordinately exposed to PBDEs in dust by crawling on floors and placing objects in their mouths. A case study of one family, described in the October 2006 *EHP*, found that a toddler had PBDE levels up to 10 times higher than those of his parents. “We don’t know what PBDEs do to children during critical stages of development,” says Dye, but cats offer hints about “where chronic exposure may lead.” People in the United States have the highest PBDE levels reported worldwide, according to a meta-analysis published in the 15 February 2004 *Environmental Science & Technology*.

Heather Stapleton, an environmental chemist at Duke University, points out that the link between PBDEs and health problems in cats is reminiscent of the revelation 25 years ago that children ingesting lead in household dust experienced learning problems. Says Stapleton, “It’s important to understand the effects of exposure to these brominated flame retardants in humans.” —Carol Potera

## PARTICULATE MATTER

## The Clot Thickens: New Clues to PM Action

Particulate matter (PM), largely sooty particles from the exhausts of diesel vehicles and fossil fuel-burning power stations, has long been associated with increased cardiovascular events, with peaks occurring within 24 hours of spikes in ambient PM concentration. Researchers, however, have not been sure why this is so. A new report in the October 2007 issue of the *Journal of Clinical Investigation* shows that the increase in cardiovascular events seen after spikes in PM pollution may be due to macrophages in the irritated lungs producing increased amounts of interleukin-6 (IL-6), a cytokine that promotes clotting. This increases the chances of suffering a heart attack or stroke, especially in

individuals already at risk due to lung disease or atherosclerosis.

“This has been a long-standing question,” says first author Gökhan Mutlu, an assistant professor of pulmonary and critical care medicine at Northwestern University. “These particles, once inhaled, cause inflammation of the lungs, but how this is connected to cardiovascular events was unclear.”

To study the effects of PM exposure, the researchers intratracheally administered a solution of PM<sub>10</sub> (particles less than 10 μm in diameter commonly found in polluted city air) to mice. According to the article, the 10-μg dose administered is the equivalent of that to which a person would be exposed when ambient PM<sub>10</sub> concentrations hit a moderate elevation of 150 μg/m<sup>3</sup>.

During this work the team noticed that incisions made in animals exposed to PM<sub>10</sub> 24 hours earlier bled far less than did those in unexposed mice; exposure seemed to speed up clotting times. Tests showed that exposed mice had an

increased number of platelets, reduced prothrombin and activated partial thromboplastin times, a higher concentration of plasma fibrinogen, and increased levels of blood factors II, VIII, and X—conditions that are all consistent with increased and quicker clotting. In addition, plasma thrombin-antithrombin III complex levels were four times higher in the exposed mice, further suggesting that exposure promotes intravascular thrombosis.

“Since IL-6 increases the transcription of procoagulant proteins, we checked its concentration in the bronchoalveolar fluid of exposed mice and found it to be increased sixteenfold,” explains Mutlu. “[This IL-6] seemed to be produced by the increased number of macrophages in the lungs of these animals; when we depleted [these macrophages] with liposomal clodronate, the IL-6 level was not raised. Moreover, when we exposed transgenic mice that do not produce IL-6, their clotting times were not shortened. All this indicates that irritation of the lungs causes

ehpnet

## Global Alliance for Improved Nutrition

A third of the world's population lacks sufficient vitamins and minerals in their diet. Each year nutritional deficiencies contribute to the deaths of 1 million children under the age of 5 years and 50,000 women during or just after childbirth. Such conditions also commonly cause mental and physical health problems such as learning disabilities, birth defects, and blindness. In addition, \$6 billion dollars in lost adult work performance will add up annually due to malnutrition, significantly impacting the economies of developing countries. At a special 2002 UN session on child health, the Global Alliance for Improved Nutrition (GAIN) was formed to address the problems of inadequate diet in at-risk populations using food fortification, as described at <http://www.gainhealth.org/>.

To date GAIN has had three rounds of grant funding, with 18 projects in food fortification and infant/young child nutrition aiming to improve the nutrition of almost 600 million people. The Food Fortification subsection of the Our Programs page outlines the different levels of GAIN grants and initiatives in this area. Project leaders are working to establish and strengthen national food fortification programs in several developing countries with efforts to fortify such products as cooking oils, maize meal, wheat flour, and sauces. Smaller-scale targeted projects focus on four main program areas: schools, maternal and child health, populations affected with HIV/AIDS, and policy development. GAIN also supports global initiatives, one of which focuses on fortification of food that is being distributed to refugees, internally displaced persons, and other vulnerable groups.

GAIN explains the direction of its work in the Why Fortification? portion of its website, including a brief discussion of why GAIN has decided to channel its resources into fortification along with scientific data to support this move. Overviews of the five primary micronutrient deficiencies—vitamin A, iodine, folate, iron, and zinc—discuss how these nutrients are used in the body, how deficiencies in each impact health, and the primary sources of the nutrients in food. Four major strategies for eliminating nutritional deficiencies are laid out on the Possible Responses page along with the pros and cons of each. —Erin E. Dooley

an increase in the number of macrophages and IL-6 secretion, which makes blood clot more easily, raising the chances of suffering a stroke or heart attack.”

Particles smaller than PM<sub>10</sub> that are also common constituents of diesel-polluted air may have similar effects, Mutlu adds.

Although no increase in IL-6 was seen in the control mice, some experts think that the model may not exactly reflect what happens in humans. Terry Tetley, a professor of lung cell biology at the National Heart and Lung Institute, Imperial College, London, explains it is not clear how the instilled dose of PM<sub>10</sub> in the study relates to real-world doses retained in the human lung, a significant percentage of which is exhaled.

William MacNee, clinical director of the Edinburgh Lung and the Environment Group Initiative at the Colt Laboratory, United Kingdom, agrees: “The authors’ argument that the ten-microgram dose instilled is a ‘moderate’ dose that in some

way relates to human inhalation exposure is arguable. In fact [this represents] a very large dose in a mouse, delivered instantaneously at a high dose rate by instillation. Contrast the dramatic effects seen here with the very minor effects in measurable coagulant parameters [reported in other studies] following actual inhalation of concentrated ambient particles.”

Both experts agree, however, that IL-6 may certainly be involved in PM-induced deaths, although this remains to be proven. Unfortunately for the man in the street, avoiding exposure to elevated PM<sub>10</sub> may be the only way to prevent its irritating effects. Says Tetley, “At present, it is unclear whether predicting air pollution episodes and using strategies such as taking aspirin or wearing face masks if cycling through heavy traffic will be realistic or even useful as we don’t know the exact mechanisms involved or how to deal with the consequences. Possibly the best strategy is to reduce health effects by reducing air pollution.” —Adrian Burton

## Folic Acid Lowers Blood Arsenic

Arsenic-contaminated drinking water occurs in at least 70 countries, and chronic arsenic exposure, which currently affects 100 million people worldwide, is linked with adverse health effects including certain cancers and cardiovascular disease. A study conducted in Bangladesh that appears in the October 2007 *American Journal of Clinical Nutrition* finds that folic acid supplementation in populations deficient in this B vitamin reduces total blood arsenic levels by 14%. The folic acid helps the body convert a toxic metabolite of arsenic, methylarsonic acid, to a form that is more easily excreted. The authors note that folic acid supplementation may also reduce stores of arsenic in the body that remain after exposure ends.



## Child Asthma Hospitalizations Plunge in NYC

A September 2007 report from the Office of the New York City Comptroller outlines a number of health disparities among the city's income groups. Despite several negative findings, one statistic is positive: hospitalization due to asthma-related causes among children from the poorest third of the city dropped by around 50% from 1995 to 2005. Some experts attribute this decline in part to city policies that took aging diesel buses off the streets and replaced them with cleaner diesel, natural gas, and hybrid electric models. Another factor in this trend may be the city health department's Asthma Partnership, a broad-based network of more than 300 groups and individuals that sponsors workshops on topics including asthma management and indoor air quality.

## Making Over Egypt's Mudbrick Industry

Cairo, Egypt, has some of the world's worst air pollution, partly due to local factories' use of mazot, a petroleum by-product that when burned releases substantial amounts of greenhouse gases and nearly 60 other pollutants. A Canadian agency has teamed with a group of Cairo's mudbrick factories—some of the biggest mazot consumers—to convert them to natural gas. This change is not only reducing pollution but doing so at a profit, plus the gas-fired bricks are of much higher quality than their mazot-fired counterparts. Each of the 50 factories that have already been converted has seen a 37% reduction in yearly greenhouse gas emissions; the conversion of this group of factories provides the air improvement equivalent of taking 300,000 cars off of Cairo's roads annually. Another 311 factories are now in line for conversion.

