

Legacy of Lead

Babies at Risk Decades after Mothers Exposed

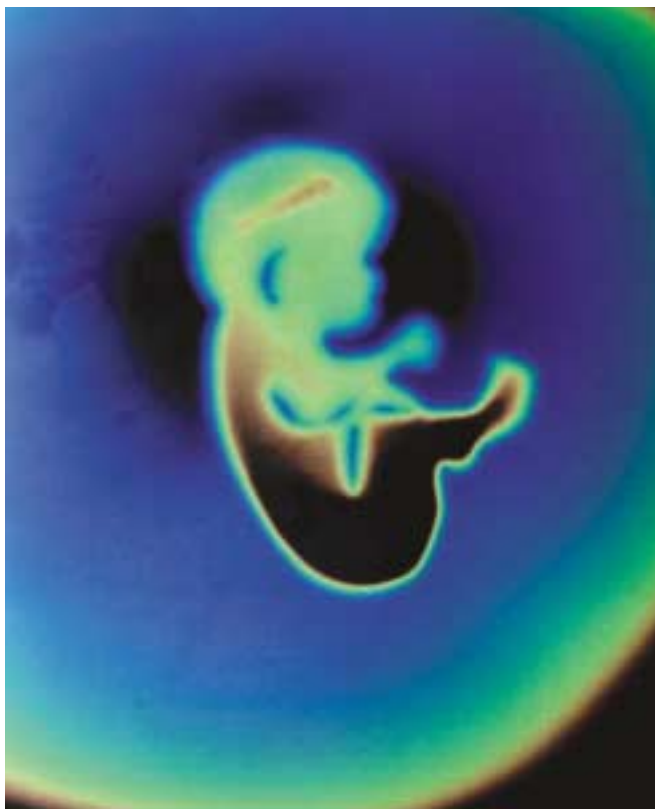
Fetal lead exposure is associated with delayed embryonic development of several organ systems and cognitive deficiencies in early childhood. Infants and children are more susceptible to the metal's effects than adults, and women exposed to high levels of lead decades ago may still pass the toxic metal to their unborn children. In a bid to better estimate fetal lead exposure from the mother, Hung-Yi Chuang of the Harvard School of Public Health and colleagues studied lead transfer *in utero* in Mexico City, where residents are exposed to large amounts of the metal through sources such as lead-based gasoline and lead glaze commonly used in cooking vessels [*EHP* 109:527–532]. They found that estimating maternal plasma lead concentrations using structural equation modeling yielded a more accurate estimate of fetal lead exposure than the traditional method of measuring maternal whole blood lead concentrations.

Lead in the circulatory system is held mostly in the red blood cells; less than 1% is in the plasma. But only plasma lead can cross the placenta to the fetus. Measuring plasma lead concentrations is costly and difficult, so researchers had previously estimated concentrations based on the lead concentrations in whole blood. The two may not be in equilibrium, though, particularly during pregnancy, when stored lead is released into plasma from bone.

Structural equation modeling, a technique most often used in the social sciences, allowed the researchers to account for interrelationship among variables, unlike the more traditional multivariate regression technique. This was important because plasma lead concentrations are affected by several variables, including use of lead-glazed ceramics, years spent in a lead-polluted area, and bone lead concentrations.

The researchers studied 615 pregnant women receiving prenatal care at one of three hospitals in Mexico City in 1994 and 1995. They gathered maternal and umbilical cord blood samples within 12 hours of each infant's delivery, then measured maternal bone lead within one month of delivery. The researchers also asked their subjects several lifestyle questions to assess their recent and lifetime exposure to lead and obtained data on regional air lead concentrations during the two months before each delivery. By examining all these factors, the researchers developed what they believe is a highly accurate estimate of fetal lead exposure.

The researchers found that maternal bone lead is a significant source of fetal exposure. Bone serves as the main depository of lead in adults. Because it has a half-life of 7–20 years in bone, stored lead could stem from exposure many years earlier. Pregnancy and lactation cause large amounts of minerals to release from bone in order to help build the fetus's skeletal system. Because lead is a “calcium imposter,” substituting for calcium in the bone-mineral matrix, it's released along with calcium even though it isn't needed by the fetus—and along with calcium, it's incorporated into the fetus's developing bones and tissue.



Toxic transfer. Researchers found that a mother's plasma lead is a more accurate indicator of fetal lead exposure, which can result when maternal bone lead is incorporated into the body of the developing fetus.

Infants also require calcium in breast milk to support their growth, so lead is released from the mother's bone to breast milk along with calcium and other minerals.

Although the researchers limited their study to Mexico City, they believe babies in the United States and other industrialized countries face the same risk from mothers raised in an era when lead in the atmosphere was not as well controlled as it is now. Their study suggests that blood testing combined with X-ray exams and a lifestyle questionnaire could help predict the risk of fetal lead exposure before a woman becomes pregnant. (Nonessential X rays are considered too risky to administer during pregnancy.) Women at high risk then could be treated to minimize lead transfer to their fetuses. Animal studies have shown that calcium supplements minimize mineral loss from bone during pregnancy. Researchers involved in this study are now testing how calcium supplements affect the transfer of lead from pregnant Mexico City women to their fetuses. —Cynthia Washam

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Pfiesteria 'Fesses Up

A New Clue to Its Toxicity

Like Houdini, the mysterious dinoflagellate *Pfiesteria piscicida* hasn't been inclined to surrender the secrets of how it works. But with enough creative poking and prodding, something was likely to give, and it has. Researchers from the National Oceanic and Atmospheric Administration's National Ocean Service and from North Carolina State University in Raleigh sought to identify the receptor targeted by the still unknown *P. piscicida* toxin or toxins [*EHP* 109:457–462]. In doing so, they have found a vital clue that may reveal how the microbe's toxin attacks people and wildlife.

Pfiesteria has come under increasing scrutiny in the past decade after a series of outbreaks in at least two U.S. states killed more than a billion fish and caused a variety of serious human health problems. Research in the past few years has begun to breach the wall of mystery surrounding the dinoflagellate, which morphs through several life stages—only some of which are toxic to humans or fish—during its complex life cycle. No major *Pfiesteria*-related fish kills were confirmed in the United States in 1998, 1999, or 2000, although there were several cases where *Pfiesteria* was the prime suspect in outbreaks of fish lesions and some human health problems. Excess nutrients such as nitrogen and phosphorus remain the chief suspects in boosting toxic *Pfiesteria* outbreaks.

Building on techniques and information developed by themselves and others, the team has discovered that the toxin behaves as an agonist

of the P2X7 receptor, a receptor commonly found in the immune system of people and some wildlife. The toxin may trigger a chronic cascade of inflammatory responses, an overreaction that can quickly kill some fish and likely causes the acute and chronic human health problems associated with *Pfiesteria* exposure, which include memory loss, learning impairment, breathing difficulty, nausea, lethargy, and skin lesions.

The team used a process of elimination to pin down which receptor was being affected by the *Pfiesteria* toxin. Using GH₄C₁ rat pituitary cells, the team evaluated a number of substances for their ability to increase or inhibit levels of engineered bioluminescence in the cells. They found that adenosine-5'-triphosphate (ATP), a ubiquitous energy source for enzyme reactions and a messenger for certain cellular functions, bonded to an unknown receptor and increased bioluminescence. But after researchers boosted ATP to a certain concentration, it inhibited bioluminescence and began to kill cells. The same test with a purified solution of *P. piscicida* toxin showed a similar pattern, suggesting that the toxin could act like ATP. (Additional testing eliminated the possibility that the suspected toxin actually is ATP because the toxin did not mimic the energy-related functions of ATP, only its messenger functions.)

Additional bioluminescence tests with other ATP mimics, antagonists, and the toxin helped researchers narrow the candidates to several P2X receptors, then to the P2X7 receptor. That receptor is present in several components of the human immune system, including macrophages, mast cells, microglia in the central nervous system, and pituitary cells. The series of tests did not eliminate the possibility that the toxin may affect other receptors, too.

Given that the compound is not ATP and other clues unveiled during this study—that the compound works in a way different from all other known compounds and that it appears to have a unique chemical structure—the researchers suspect that the *Pfiesteria* toxin likely is in a little known or even undiscovered class of compounds. According to John S. Ramsdell, a team member and chief of the National Ocean Service's Coastal Research Branch, they also suspect that the toxin works in concert with another unknown substance, perhaps the *Pfiesteria* cell itself, that first breaches the defenses of a fish or person. The *Pfiesteria* toxin then takes advantage of the breach in some way and does its damage. —Bob Weinhold

The Price of Gold

Indians at Risk in French Guiana

The Wayana Amerindians of French Guiana live along the Maroni River and depend upon its fish as a significant source of food. However, that food source may be threatened by gold mining operations upstream, which release mercury pollution into the river. French researchers investigating the effects of mercury pollution upon the Wayana have found that all the natives over 1 year of age who were tested were ingesting more mercury than recommended by the World Health Organization (WHO) in their traditional fish-based diet [EHP 109:449–456]. Nadine Fréry, a researcher

at the National Institute of Public Health Surveillance in Saint-Maurice, France, and colleagues from the University of Bordeaux also report that the mercury load appears to cause what are characterized as subtle neurologic effects on the population, especially on children.

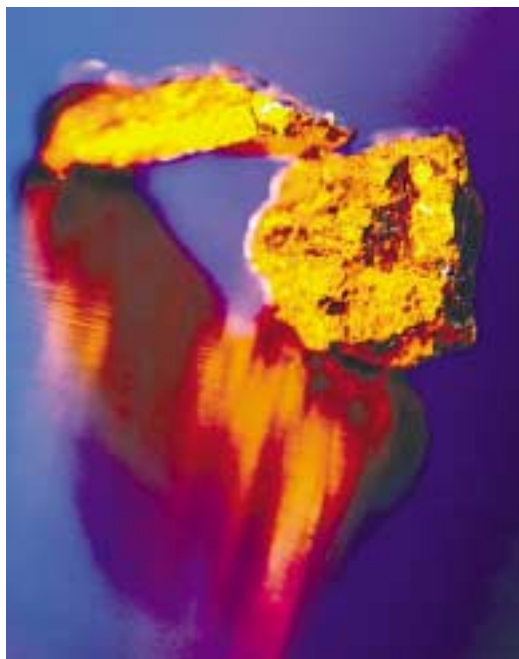
According to Fréry, gold mining activities have been responsible for important discharges of mercury into the environment. In the mercury amalgamation method, gold obtained from river sediments, soils, and groundwater rocks is separated from elemental mercury by open-circuit heating, an activity that discharges this volatile form of mercury into water and air. Mercury can then find its way into carnivorous fish in its highly toxic methylmercury form. Along the aquatic food chain, there is a bioamplification of metal concentrations, leading to very high concentrations in the top predators—including people, such as the Wayana.

Fréry and colleagues conducted the studies over seven days in each of two seasons, March and November 1997. Those periods are marked by changes in diet, particularly as fish and game sources fluctuate seasonally. The investigators gathered data on 165 subjects, including fish consumption over a 1–14 day period. Each day, they made records of the fish consumed—species, size, weight, and weight after evisceration and deboning. They also recorded the weight, sex, and age of the persons participating in each meal. The total weight of consumed fish allowed the scientists to calculate the daily amount of mercury ingested by the families. Hair sampling analysis was performed by Canada's Center of Toxicology of Quebec to measure the transfer of mercury from endogenous fish species to the human subjects.

Hair sampling revealed that 57% of the 165 people studied had mercury concentrations 2–3 times higher than the WHO safety limit of 10 micrograms per gram/liter. Furthermore, from their food alone all of the Wayana subjects over 1 year old received 6–9 times the International Programme on Chemical Safety's estimated daily human intake of total mercury of 6.7 micrograms per day. (This figure allows for both direct exposures sources, such as polluted drinking water, and indirect sources, such as fish in which mercury has collected.) Similar results occurred among riverside populations eating a fish-based diet in portions of the Amazon River basin in Brazil following a gold rush that began in the late 1980s.

Along with the dietary study, Fréry and colleagues gave each child a neurologic examination and neurobehavioral development tests. The results of the tests showed a correlation between mercury concentrations and neurologic or behavioral deficits. "Children are very vulnerable to the effects of mercury," Fréry says. "We have observed that some of the children have difficulty in coordination and appear to have other subtle neurologic problems."

Fréry and coauthor Alain Boudou are returning to French Guiana this year to determine the severity and importance of the neurologic effects noted, and to see if programs can be established to decrease mercury ingestion by the Wayanas, even in the face of continued gold mining operations. Jointly to these studies on Wayana communities, a multidisciplinary program is being conducted in French Guiana to investigate the chemical fate of mercury in air, soil, and fresh water and to analyze the transfer process along the food web. —Ed Susman



Of metal and mercury. Amerindians in French Guiana are at risk for mercury poisoning from pollution released by gold mining operations upstream.