Can the lifelong effects of childhood lead exposure ever be reversed?

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Guilarte and Timothy Allen, director of the Neurocircuitry & Cognition Lab, are working together to investigate the effectiveness of the flavonoid 7,8-dihydroxyflavone in improving learning after lead exposure. Credit: Florida International University

Tomás R. Guilarte has been exchanging emails with a mother whose child was exposed to lead. She's not the first parent he's heard from. And likely won't be the last. This is our legacy of lead.

It's Flint, Michigan. It's Newark, New Jersey. It's across America. More than 170 million people alive today—more than 50%—of the U.S. population, have been exposed to significant levels of lead as children. Globally, it is estimated that about 800 million children have blood lead levels that affect their brain. World-renowned for his nearly four decades of research on how lead-laden environments change the brain, Guilarte will tell you the story doesn't end there. Exposure is just the beginning. And that's why those numbers haunt him.

Dean of FIU's Robert Stempel College of Public Health & Social Work and an environmental health sciences professor, Guilarte has been among the first to document what's happening at the cellular level of the brain that triggers a cascade of lifelong consequences—from learning difficulties and lower IQ scores to the risk of psychiatric diseases and drug abuse in adulthood.

His work has underpinned major policy decisions, like the CDC lowering the blood lead reference value to help more children. And it's been a source of hope, especially for parents who email him, desperate to know: Can the damage lead has done to their children ever be undone?

A culmination of decades of research has brought Guilarte and his collaborators closer to an answer. They've identified a certain flavonoid, a class of nutrients present in fruits and vegetables, that reverses some of the negative effects of lead and could be a possible therapeutic solution.

"If it's effective, we'll have a basis for translational studies in children," he said.

Decades of toxicity

From a public health perspective, prevention is the first step. Despite ongoing efforts to eliminate lead from the environment, reducing exposure can still prove difficult.

Lead has been used for centuries. Ancient Romans used it in pipes that carried drinking water. Thousands of years later, it still lines pipes in the United States. True to the Latin word behind its periodic symbol Pb (plumbum meaning "liquid silver") lead is malleable and durable, which made it a near-perfect addition to everything from gasoline to house paint. What was near-perfect for products proved damaging, even deadly, to humans. Health concerns eventually prompted bans. Lead paint in new homes in 1978. Lead piping for new projects in 1986. Unleaded gasoline was phased out slowly, and by the 1980s, new cars weren't using it.

But its presence in our lives persists, contaminating the environment. It's in air, dust, soil and food. To put it simply, what we're facing today is chronic low-level exposure from different sources, Guilarte says.

Silence of the cells

In his office, Guilarte has a giant photo of a neuron that appears to glow electric green—the result of special dye used to examine cells.

It is one among more than 80 billion of the brain's vitally important messenger cells that form networks and pathways, called neural circuits, which act as information highways stretching across the brain's different regions. This "talking" between the neurons is what makes the computational capability of the brain, especially learning and memory, so powerful.

Lead silences these cells.

With his team at Johns Hopkins Bloomberg School of Public Health in the 90s, Guilarte found lead acts as the silencer by interfering with a unique protein receptor known as the N-methyl-D-asparate receptor (NMDAR). He calls this receptor "the tip of the iceberg," not only because NMDAR is on the surface of neurons, at points of communication or synapses, but because below, a flurry of activity supporting the cell's survival and connectivity is taking place.

NMDAR binds metals, like calcium and zinc, to operate. Lead acts as an imposter, binding at the receptor's sites reserved for zinc and preventing it from functioning properly. Messages can't be recognized. Brain connections don't happen or happen in ways they shouldn't. The entire trajectory of a child's development is impacted.

A glimpse below the "iceberg" revealed why. During brain development, activation of the NMDAR produces a peptide—brain-derived neurotrophic factor (BDNF)—that's essentially "food for the brain." Guilarte's team added BDNF to lead-impaired neurons in culture from the hippocampus, a brain region important for learning and memory, and it was able to reverse the detrimental effects of lead on the ability of neurons to communicate. But BDNF can't be put into a pill. It would break down in the stomach before ever crossing the blood-brain barrier.

After experimenting with different options, Guilarte and colleagues from New York Medical College and Columbia University finally identified a promising alternative—the flavonoid 7,8-dihydroxyflavone—an effective molecule currently available as a supplement and capable of reaching the brain. In the lab, it successfully came to the rescue in lead-exposed animals, reversing some of lead's damaging effects.

A major move forward, this discovery was further proof that the negative effects of lead exposure on the brain could be reversed and possibly holds the key to treating lead-exposed children. Improper functioning of NMDAR also happens in the brains of people with schizophrenia, and Guilarte's team has found evidence that there's a correlation between early life exposure to lead and psychiatric diseases in adulthood.

Growing neurons

The first evidence that lead's effects could be reversed came with what Guilarte calls one of the most surprising and exciting studies of his career.

When Guilarte witnessed the many lead poisoning cases in children during the 1980s in Baltimore's Kennedy Krieger Institute, when he was a faculty member at Johns Hopkins University Bloomberg School of Public Health, he observed how chelation therapy removed the toxic metal from the body. But what was gone from the blood had already left its mark on the brain. For many, learning would be a challenge. Guilarte wanted to address this looming problem with lifelong repercussions.

One idea was to stimulate brain function in order to increase the formation of new neurons and their connections that were impaired by lead. It turned out small changes made a big difference. In animal studies, a running wheel for exercise and exposure to new toys every week helped improve the cognitive functioning of lead-exposed rats that showed impairment during development. For humans, an enriched environment might look like a visit to a museum, art lessons or exercise.

An enriched environment highlights an important issue tied to lead exposure. "Children in poor, low- income neighborhoods in the U.S. and other parts of the world are more likely to be exposed to lead and those different environments will modulate how the brain develops. It's that simple, and also that complex."

So, the search for more solutions continues. And he's certainly not searching alone.

Why are children at greater risk?

Children are at greatest exposure risk for many reasons—their small size, a rapidly developing nervous system, and because they behave like, well, babies. In fact, children are at greatest risk for the highest levels of lead exposure when they are around 2—the time they are crawling around on the floor the most and there's a lot of hand-to-mouth activity.

Once in the mouth, lead moves to the stomach. The body mistakes it for other essential metals, like zinc and calcium, giving it a free pass to the bloodstream. Then, it breaks through the heavily guarded blood-brain barrier and into the brain, and in children this barrier is not yet fully developed.

Collaboration is key

The scientist working alone is not Guilarte's style. Whether he's in the lab helping one of his students with their data or reading academic papers, he thrives on connections with other people.

When he started FIU's Brain, Behavior and the Environment Program in 2016, the labs were created purposefully with no walls to separate them. The idea was to get people talking, sharing information. Eventually, Guilarte envisions the creation of an entire Brain Science Institute that unites researchers from across the university and beyond to chase solutions to big problems together.

In the meantime, the next stage of his research is rooted in collaboration with Timothy Allen, director of the Neurocircuitry & Cognition Lab in the College of Arts, Sciences & Education. It's an inspired pairing. Whereas Guilarte studies impacts at the neural level, Allen looks at how the neural circuits in the hippocampus and prefrontal cortex interact—the key to learning, memory and behavior.

So far, they've determined early lead exposure, comparable to what kids in many poor urban neighborhoods in the U.S. and in other parts of the world experience, causes entire cognitive areas in the brain to become hyperactive in adulthood.

Hyperactivity disrupts the harmony of the brain, making neurons go into overdrive. This can cause absence seizure. A child might be sitting in a classroom and suddenly stare off into space. Would this be labeled daydreaming? Not paying attention? This is another example of how lead causes "real pernicious problems for society," that aren't easy to identify, according to Allen.

Guilarte and Allen plan to test the effectiveness of the flavonoid 7,8-dihydroxyflavone in improving learning after lead exposure—the jumping off point for future studies in children.

On the horizon

Lead is a silent poison, easily pushed aside in a world bombarded by other problems. Guilarte understands this. But the problem doesn't disappear because it's no longer in the daily news cycle. Guilarte understands this, too. That's why he's dedicated his life to unraveling the mystery behind how lead and other environmental toxins alter the body's most mysterious organ.

This work has not gone unnoticed. It's garnered numerous recognitions over the years from the Society of Toxicology (SOT), one of the largest scientific societies of its kind with more than 8,000 members who are experts in toxicology. These are some of the most personally meaningful honors for Guilarte because SOT played a central role throughout his career, giving him an opportunity to develop relationships and collaborations.

"Dr. Guilarte's collective work links metal exposure to neurotoxicity and is an example of how toxicology can inform potential mitigation strategies when preventing exposures is not feasible. This has the potential to transform public health," said Koren K. Mann, professor and department chair at Lady Davis Institute for Medical Research and SOT's president of the Metals Specialty Section.

Guilarte's research to help children who never asked to grow up in a world laden with lead is far from over. For as long as it takes, he'll be working with his teams of collaborators to find a treatment.

Provided by Florida International University

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