Taking It All In:
Environmental toxins and your health

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The Joseph B. Martin Conference Center
The New Research Building
Harvard Medical School
77 Avenue Louis Pasteur
Boston, MA 02115

THE Longwood SEMINARS
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Taking It All In:
Environmental toxins and your health

Moderator

David Christiani, MD, MPH, MS

- Professor of Medicine,
  Harvard Medical School
- Elkan Blout Professor, Environmental Genetics,
  Harvard T.H. Chan School of Public Health
- Director, Harvard Education and Research
  Center, Harvard T.H. Chan School of Public Health
- Physician, Division of Pulmonary and Critical
  Care Medicine,
  Massachusetts General Hospital

Speakers

Monica Colaiácovo, PhD

- Professor, Department of Genetics, Harvard
  Medical School
- Associate Editor, *Genetics*
- Guest Associate Editor, *PLOS Genetics*

Maitreyi Mazumdar, MD, MPH

- Assistant Professor of Neurology,
  Harvard Medical School
- Assistant Professor, Department of
  Environmental Health,
  Harvard T.H. Chan School of Public Health
- Pediatric Neurologist,
  Boston Children's Hospital

About the Speakers:

David Christiani, MD, MPH, MS

David Christiani is a professor of medicine at Harvard Medical School, the Elkan Blout Professor of Environmental Genetics and the director of the Harvard Education and Research Center at the Harvard T.H. Chan School of Public Health (SPH) and a physician in the Division of Pulmonary and Critical Care Medicine at Massachusetts General Hospital. With his SPH colleagues, Christiani has led a molecular and genetic analysis of lung cancer, examining genetic factors that make people susceptible to it and help predict the outcome of treatment. With collaborators at Mass General, he leads the Christiani Lab for Molecular Epidemiology of ARDS (acute respiratory distress syndrome) that conducts research on environmental conditions of the lung, including acute lung injury, lung cancer and respiratory responses to environmental toxticants, as well as biomarkers predictive of outcome and survival for acute lung injury. Christiani runs a landmark 35-year-long study of respiratory disease in cotton-textile workers in Shanghai, China. This study has determined the rate of loss in lung function among dust-exposed workers and uses molecular biology's tools to evaluate the relationship between exposure to endotoxins produced by bacteria in cotton and acute and chronic lung disease. In 2012, President Barack Obama appointed him to serve on the National Cancer Advisory Board.

Monica Colaiácovo, PhD

Monica Colaiácovo is a professor in the Department of Genetics at Harvard Medical School. She studies how environmental exposures impact the biological mechanisms that are critical to reproductive health. One of the world's leading researchers in the cell division process of meiosis, which results in the formation of eggs and sperm, her rapid screening of how everyday chemicals permanently affect DNA illustrates the costs of increasingly artificial environments and equip the global community with actionable information to enhance environmental public policies. Colaiácovo is an associate editor of the journal *Genetics* (2009 - present) and a guest associate editor for the Public Library of Science *PLOS Genetics* (2010 - present). She has received the March of Dimes Basil O'Connor Starter Scholar Research Award (2006 - 2008), the William F. Milton Fund Award in 2007, the Charles E.W. Grinnell Trust Award in 2011, the Stewart Trust Fund Award in 2011 and the Dr. Harold and Golden Lamport Research Award at Harvard Medical School in 2013.

Maitreyi Mazumdar, MD, MPH

Maitreyi Mazumdar is an assistant professor of neurology at Harvard Medical School, an assistant professor in environmental health at the Harvard T.H. Chan School of Public Health and a pediatric neurologist at Boston Children's Hospital. Mazumdar's research program focuses on the role environmental hazards play in the development of neural tube defects (spina bifida). Her studies take place in Bangladesh, where an estimated 70 million people have been chronically exposed to high concentrations of arsenic through contaminated drinking water. Mazumdar is a 2016 recipient of the Outstanding New Environmental Scientist Award from the National Institutes of Health.

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Nutritional psychiatry: Your brain on food

Posted November 16, 2015
Updated November 17, 2015

Eva Selhub, MD
Contributing Editor

Think about it. Your brain is always "on." It takes care of your thoughts and movements, your breathing and heartbeat, your senses — it works hard 24/7, even while you're asleep. This means your brain requires a constant supply of fuel. That "fuel" comes from the foods you eat — and what's in that fuel makes all the difference. Put simply, what you eat directly affects the structure and function of your brain and, ultimately, your mood.

Like an expensive car, your brain functions best when it gets only premium fuel. Eating high-quality foods that contain lots of vitamins, minerals, and antioxidants nourishes the brain and protects it from oxidative stress — the "waste" (free radicals) produced when the body uses oxygen, which can damage cells.

Unfortunately, just like an expensive car, your brain can be damaged if you ingest anything other than premium fuel. If substances from "low-premium" fuel (such as what you get from processed or refined foods) get to the brain, it has little ability to get rid of them. Diets high in refined sugars, for example, are harmful to the brain. In addition to worsening your body's regulation of insulin, they also promote inflammation and oxidative stress. Multiple studies have found a correlation between a diet high in refined sugars and impaired brain function — and even a worsening of symptoms of mood disorders, such as depression.

It makes sense. If your brain is deprived of good-quality nutrition, or if free radicals or damaging inflammatory cells are circulating within the brain's enclosed space, further contributing to brain tissue injury, consequences are to be expected. What's interesting is that for many years, the medical field did not fully acknowledge the connection between mood and food.

Today, fortunately, the burgeoning field of nutritional psychiatry is finding there are many consequences and correlations between not only what you eat, how you feel, and how you ultimately behave, but also the kinds of bacteria that live in your gut.

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How the foods you eat affect how you feel

Serotonin is a neurotransmitter that helps regulate sleep and appetite, mediate moods, and inhibit pain. Since about 95% of your serotonin is produced in your gastrointestinal tract, and your gastrointestinal tract is lined with a hundred million nerve cells, or neurons, it makes sense that the inner workings of your digestive system don't just help you digest food, but also guide your emotions. What's more, the function of these neurons — and the production of neurotransmitters like serotonin — is highly influenced by the billions of "good" bacteria that make up your intestinal microbiome. These bacteria play an essential role in your health. They protect the lining of your intestines and ensure they provide a strong barrier against toxins and "bad" bacteria; they limit inflammation; they improve how well you absorb nutrients from your food; and they activate neural pathways that travel directly between the gut and the brain.

Studies have shown that when people take probiotics (supplements containing the good bacteria), their anxiety levels, perception of stress, and mental outlook improve, compared with people who did not take probiotics. Other studies have compared "traditional" diets, like the Mediterranean diet and the traditional Japanese diet, to a typical "Western" diet and have shown that the risk of depression is 25% to 35% lower in those who eat a traditional diet. Scientists account for this difference because these traditional diets tend to be high in vegetables, fruits, unprocessed grains, and fish and other seafood, and also tend to contain only modest amounts of lean meats and dairy. They are also void of processed and refined foods and sugars, which are staples of the "Western" dietary pattern. In addition, many of these unprocessed foods are fermented, and therefore act as natural probiotics. Fermentation uses bacteria and yeast to convert sugar in food to carbon dioxide, alcohol, and lactic acid. It is used to protect food from spoiling and can add a pleasant taste and texture.

This may sound implausible to you, but the notion that good bacteria not only influence what your gut digests and absorbs, but that they also affect the degree of inflammation throughout your body, as well as your mood and energy level, is gaining traction among researchers. The results so far have been quite amazing.

What does this mean for you?

Start paying attention to how eating different foods makes you feel — not just in the moment, but the next day. Try eating a "clean" diet for two to three weeks — that means cutting out all processed foods and sugar. Add fermented foods like kimchi, miso, sauerkraut, pickles, or kombucha. You also might want to try going dairy-free — and some people even feel that they

feel better when their diets are grain-free. See how you feel. Then slowly introduce foods back into your diet, one by one, and see how you feel.

When my patients "go clean," they cannot believe how much better they feel both physically and emotionally, and how much worse they then feel when they reintroduce the foods that are known to enhance inflammation. Give it a try!

To learn more…
This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from our Harvard Health Blog, available at health.harvard.edu/blog.

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Lead poisoning: What everyone needs to know

Posted February 02, 2016

Claire McCarthy, MD
Faculty Editor, Harvard Health Publications

The lead poisoning of thousands of children in Flint, Michigan is tragic — and should never have happened. If we are going to make sure that nothing like it happens again, all of us, especially parents, need to learn about lead poisoning.

Lead is a chemical that used to be commonly found in paint, gasoline, and factory emissions. It also was used to make pipes, as well as the solder that holds them together. But once the toxicity of lead was fully understood, there were laws and regulations put in place to limit its use, and to limit the exposure of children and pregnant women to lead. The problem is, there's still a whole lot of lead out there, especially in older, poorer communities.

The reason we really don't want children and pregnant women to be exposed to lead is that it can affect the developing brain. Exposure to lead can lead to a lower IQ, as well as learning and behavior problems that can last a lifetime. Slowly and silently, it can change a child's life forever.

That's what's so hard about lead: it can be invisible, and do its damage without being noticed. If children eat something with a lot of lead — like a bunch of lead paint chips — and therefore have a high level of lead in their blood, they may have noticeable symptoms such as headache, constipation, vomiting, or confusion. But those kinds of exposures are (thankfully) uncommon.

The more common kinds of exposure are from dust in houses with lead paint, from water contaminated with lead (by passing through old pipes, which is what happened in Flint), or from toys, jewelry, tableware, or home remedies that may be contaminated with lead. These kinds of exposures don't usually cause symptoms before they cause damage.

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Here's what parents and caregivers of children need to know and do:

- If your home was built before 1978, make sure you know if it has any lead paint. If you aren't sure, get it inspected.
- If you are going to have lead removed, or do renovations in an older house that may have lead paint under layers of other paint or wallpaper, make sure that the work is done by people who are certified in lead removal. For more information about this, check out the EPA's web page.
- Ask questions about the possibility of lead in your tap water. Lead can leach into the water from old pipes in your house, as well as pipes leading to your house. In Flint, the problem was that the city's supply was changed to a river that had very corrosive water, and this water made lead leach into the water. (Sadly, even though they've changed the water supply, the damage done to the pipes is causing lead to still get into the water.) If you aren't able to get good answers, or if you just aren't sure, get your water tested. If you have well water, it should be tested when the well is first built and again if a pregnant woman or child younger than 18 moves in.
- Be mindful of possible exposure from household objects, usually ones made in other countries. The Consumer Products Safety Commission has information about recalls, as well as about products that may contain lead.
- Get your child tested for lead. Every child should be tested at least at ages 1 and 2, and again at 3 and 4 in areas with older housing stock. However, your doctor can do a simple blood test (preferably not a finger stick) to check at any time if there is a concern about a possible exposure. While no level of lead is normal or fine, a level of 5 or higher is considered dangerous.

The American Academy of Pediatrics has lots of great resources about lead and its effects, as does the Centers for Disease Control and Prevention. It's so important that all of us learn about this terrible, silent poison — and keep our children safe from it.

To learn more…
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Air pollution and heart disease

Deepak Bhatt, MD, MPH
Editor in Chief, *Harvard Heart Letter*

Q. *I live near a busy highway. Are there any heart risks from air pollution?*

A. Yes. More than two decades of research has shown that air pollution can trigger heart attacks, strokes, and irregular heart rhythms, particularly in people who have or are at risk for heart disease. The most dangerous pollutants appear to be very tiny particles less than 2.5 micrometers in diameter, which the Environmental Protection Agency reports as PM2.5. These particles come from car and truck exhaust, power plants and other industrial sources, wildfires, and wood-burning stoves.

Because they're so tiny, these particles are able to lodge deep in the lungs, where they irritate lung tissue. This inflammation then seems to spill out into the bloodstream and damages blood vessels, potentially contributing to cardiovascular problems.

Thanks to air quality regulations in the United States, particle pollution levels have dropped since the 1970s. This reduction appears to have translated to fewer deaths from both heart and lung disease, according to a long-term Harvard study of six cities.

Still, people — especially those with heart disease — should likely avoid exercising outdoors near busy roads or industrial areas. Sometimes, smog and haze will alert you to poor air quality, but often you can't see the pollution. News outlets report the local Air Quality Index, a color-coded scale of pollution levels.

To learn more…
This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from the December 2015 issue of the *Harvard Heart Letter*, available at http://hvrd.me/YNr9I.

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The mercury myth

Rob Shmerling, MD
Contributing Editor, Harvard Health Publications

When I was a kid, mercury was fun. I can recall going to the dentist and being given a thimble-sized blob of mercury in a cup, which I could pick up, push around, spill onto the floor, split into several smaller blobs and watch merge with each other. It was unusual stuff, with a consistency half-way between liquid and solid, and unlike anything else in my experience. It easily kept me occupied until it was my turn to see the dentist. Perhaps my dentist and my mother were unaware of the hazards of mercury at the time. Fortunately, it seems to have caused me no harm.

The toxic effects of mercury have become well-known over the last several decades. It would (and should) *never* be used as a toy for kids now. Mercury poisoning can cause irreversible nerve damage to a developing baby's vulnerable brain and nerve damage leading to numbness, tingling, imbalance, hearing loss, and poor vision in adults.

But we are still exposed to mercury from a number of sources, as the box below shows.

Where is mercury found?

- **Fish** – Fish have naturally-occurring amounts of mercury in their bodies. Larger fish have more mercury than smaller ones. Different fish of the same species may vary in their mercury content. For example, white or albacore tuna has more mercury than light tuna.
- **Dental fillings** – Since the 1800s, dentists have been filling cavities with mercury. Fillings may contain a combination of silver, mercury, copper, and tin; 50% of these "amalgams" are mercury. After brushing, mercury vapors are released. The popularity of these fillings has declined in recent years in favor of "resin" fillings, mostly because they blend in with the tooth color.
- **Thermometers** – Older thermometers may contain mercury, although exposure is only likely if you break one. The use of mercury in thermometers has been banned in most places — and digital thermometers are much more accurate anyway.
- **Household items** – Clock pendulums, fluorescent light bulbs, and some batteries and medical devices (including blood pressure instruments) may contain mercury. Small amounts of mercury may be found in *thimerosal, a* topical disinfectant and preservative present in many vaccines and some over-the-counter products, including contact lens solutions, mercurochrome, and a number of nasal sprays and herbal medicines. It's even in some cosmetics and toiletries, and in children's sneakers that light up.

But just how much exposure to mercury is too much and how far should you go to avoid mercury exposure? These are controversial issues that I'll sort out here.

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Separating fact from fiction

Consider the following statements:

- Dental fillings that contain mercury are a hazard to your health.
- Fish containing any amount of mercury should not be eaten.
- Over-the-counter (OTC) products that contain mercury are a proven health hazard and should be taken off the market.

Each of these may sound reasonable considering that mercury is a known toxin. But how much of a threat to your health do they really pose? Consider what the available research says.

- A U.S. Food and Drug Administration (FDA) expert panel that met in early September 2006 reviewed 34 studies on the safety of mercury dental fillings. It found that although blood and urine levels of mercury rise with increasing numbers of mercury-containing fillings, the levels are well below those considered harmful. Still, experts continue to study the issue.
- Experts have also concluded that mercury in fish could pose a threat, especially for kids or a developing fetus, if fish is eaten in excess. Shark, swordfish, tilefish, and king mackerel have the highest amounts and should be avoided by pregnant women or young children, according to the FDA. "Medium" levels of mercury may be found in lobster, tuna, halibut, haddock, bluefish, saltwater trout, crabs, grouper, and orange roughy. People should eat no more than 2 servings per week. Light tuna is a better choice than white tuna if mercury exposure is a concern. The FDA recommends no more than 1 serving of white tuna per week for pregnant women and children.

Multiple studies with negative results do not prove that fillings or other sources of mercury are harmless, but at some point it's difficult to ignore the evidence. Perhaps the effect is so small that it's difficult to detect the evidence of harm. Maybe definitive studies on these issues will never be done because of the difficulty and the expense of designing them. Even if you design a study with thousands of people and detect nerve damage or other health problems in people who eat fish compared with people who don't, it might be impossible to link the problems directly to the mercury. Other differences in diet between the two groups could be responsible.

The bottom line

For now it's unclear whether mercury exposure should be on your short list of major health concerns. It's hard to avoid mercury completely, but it's unlikely that you're being exposed to harmful levels unless you eat three or more servings of white tuna a week or you're exposed to mercury regularly at work. One thing is for sure: my kids won't be playing with mercury at the dentist's office.

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What you need to ask before getting an imaging test

Howard LeWine, MD
Chief Medical Editor, Internet Publishing, Harvard Health Publications

Know why the test is being done, and how it will guide your treatment.

If your doctor were to recommend that you have a computed tomography (CT) scan or x-ray, would you question whether you really needed it or if it's worth the risks? Most people don't ask — they just assume that the decision to have a medical imaging test is up to their doctor, according to results of a patient survey published in March 2013 in *JAMA Internal Medicine*.

Medical imaging isn't always necessary or appropriate. The authors of the survey noted that up to a third of imaging tests performed in the United States are ordered when the benefits don't outweigh risks such as radiation exposure. Some tests can have a bigger effect on your bank account than they do on your outcome. For example, research has found that most people with lower back pain start to feel better within a month, regardless of whether they undergo an x-ray, CT, or magnetic resonance imaging (MRI) scan. In fact, those who have an MRI within the first month are eight times more likely to have surgery, which multiplies their medical expenses fivefold without expediting their recovery.

Regardless, more of us are undergoing medical imaging tests than ever before. Between 1996 and 2010, the use of CT scans nearly tripled, from 52 scans to 149 scans for every 1,000 patients. Rates of MRI scans almost quadrupled during the same time period, from 17 to 65 scans per 1,000 patients.

There are good reasons for having imaging tests. By providing an extremely detailed internal view of your body, these scans can identify diseases and injuries and help your doctor plan your treatment. "For many conditions, diagnostic imaging tests can provide valuable information to a practitioner, which may account for the increase in utilization," says Dr. James Brink, radiologist-in-chief at Massachusetts General Hospital and professor of radiology at Harvard Medical School.

Usually there's little risk from having an annual dental x-ray or screening mammogram, but when tests that emit higher levels of radiation — such as CT and positron emission tomography (PET) scans — are used excessively or without good reason, they have the potential to cause needless side effects. A 2007 study in *The New England Journal of Medicine* suggested that 20 million American adults may be unnecessarily exposed to CT scan radiation each year. "I think whenever a patient is being considered for a test or a doctor is recommending a test, they both should consider the benefits and the risks associated with that test," Dr. Brink advises.

What are the risks?

The main concern with tests like CT scans and x-rays is radiation. In large doses, exposure to ionizing radiation can damage cells, potentially contributing to cancer development. What's still unclear is how medical scans specifically affect cancer risk.

"There's a fair amount of uncertainty related to this," says Dr. Brink. "Most of the evidence that we have comes from the atomic bomb exposure data from Nagasaki and Hiroshima in World War II, and it's really hard to extrapolate that risk to medical exposures." People exposed to the atomic bomb blast had a significantly increased risk for cancer, but it's hard to compare one large, immediate radiation exposure with repeated smaller exposures from medical tests.

It's also been difficult to study the long-term cancer risk of radiation exposure from medical imaging because researchers need to follow thousands of patients over many decades to reach meaningful conclusions. Some studies on radiation exposure in large groups of people are being conducted, and researchers should know more about the effects within a few years.

By the best current estimates, having one CT scan that emits a dose of 10 millisieverts of radiation will increase your risk of a life-threatening cancer by about one in 2,000. By comparison, your risk of getting a fatal cancer in general is about one in five — so the radiation exposure from a single scan has a minimal impact on your total lifetime cancer risk.

Diagnostic tests: What to expect

Test	Why it's performed	How it works	Risks
Computed tomography (CT)	To locate and diagnose bone and lung problems such as fractures and pneumonia; to detect and monitor diseases like cancer.	The CT scanner takes multiple x-ray images of your body from different angles. A computer then combines the pictures into detailed cross-sectional images.	CT exposes you to radiation in larger amounts than you'd receive with a standard x-ray.
Magnetic resonance imaging (MRI)	To diagnose conditions such as multiple sclerosis, stroke, cancer, structural problems of the heart, damage to the heart caused by a heart attack or heart disease, tumors, and joint or bone problems.	The test uses magnetic fields and a computer to create detailed, cross-sectional images of your organs and tissues.	MRI does not use radiation, but it can interfere with electronic devices in your body (such as a pacemaker or implantable defibrillator). Metal objects in your body can get pulled toward the magnet and cause injury.

Positron emission tomography (PET)	To diagnose cancer or see if it has spread, to show blood flow to the heart, to diagnose heart problems, or to see how well you are responding to treatment for cancer or another condition.	A small amount of radioactive tracer material is given through a vein. The tracer collects in your organs and tissues, creating pictures that a computer converts into three-dimensional images.	PET involves radiation exposure (somewhat more than a CT scan). Some people have allergic reactions to the tracer material.
Ultrasound	To evaluate a breast lump, to diagnose an infection or cancer, to check your thyroid gland, or to assess how well blood is flowing through blood vessels.	A transducer emits high-frequency sound waves, which produce images of the structures in your body.	This test uses sound waves rather than radiation to create images, so there is no radiation risk.
X-ray	To diagnose a range of conditions, including bone fractures, dental decay, or lung infections; to screen for and diagnose breast cancer (mammography is a type of x-ray), heart failure, or digestive system problems.	Radiation passes through your body, creating an image of bones and denser tissues. Less-dense soft tissues appear dark, while tumors and other dense objects show up white, helping your doctor spot them. Some x-ray procedures use contrast material such as iodine or barium to make organs more visible.	The test involves a small amount of radiation exposure. People who are sensitive to contrast material may have reactions such as itching, hives, or light-headedness.

Aside from radiation exposure, another potential concern is sensitivity to the contrast materials used in CT scans and other imaging tests. These can range from mild skin irritation — like itching or hives — to a life-threatening allergic reaction.

Should you have the test?

Whether to have a diagnostic test is a decision you should make in partnership with your doctor after carefully considering and weighing your options. In some cases, the answer is clearly yes. “If a patient is coming into the emergency room with concerns of appendicitis, the risk of not doing the scan and missing the appendicitis is exponentially greater than the exposure risk,” Dr. Brink says.

In other cases — for example, if you’ve already been diagnosed with a condition and the scan won’t significantly influence your treatment — it might be better to say no. “Ask questions and make sure that the benefit is going to exceed the risk,” Dr. Brink advises.

Be cautious about the risks, but don't let fear steer you away from a test you truly need. "If your health care really warrants imaging and the doctor has determined that CT is the best test, or MRI or ultrasound, don't be afraid of those tests. They're useful and helpful, as long as they're done appropriately," he adds.

Questions to ask before having an imaging test

- Why do I need this scan?
- How will the results change my treatment?
- Are there any lower-radiation or radiation-free alternatives that will provide equivalent information? For example, can you do an MRI instead of a CT scan?
- If additional scans are needed to guide my treatment, what is the plan to minimize my long-term radiation exposure?

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Silent Spring at 50: Connecting human, environmental health

Posted June 11, 2012
Patrick J. Skerrett, Former Executive Editor, *Harvard Health*

Fifty years ago this week, the first installment of *Silent Spring* appeared in the pages of *The New Yorker*. Rachel Carson's provocative warning about the danger of indiscriminate pesticide use opened gently:

"There was once a town in the heart of America where all life seemed to be in harmony with its surroundings."

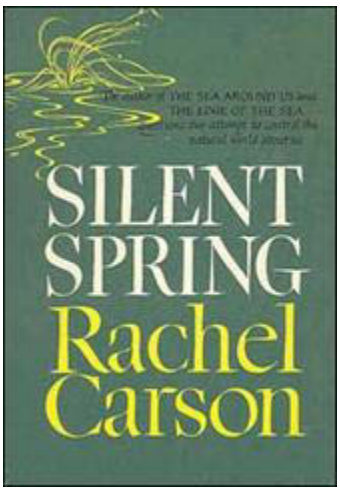
But it quickly built to a sustained, meticulously reported account of the toll that widespread aerial spraying of DDT, dieldrin, aldrin, chlordane, heptachlor, and other synthetic pesticides was taking on birds, raccoons, fish, bees, and even the supposed beneficiaries of spraying — humans.

Silent Spring is often portrayed as a book about saving birds and other wildlife. Another important theme is the essential but fragile connections between environmental health and human health.

"Rachel Carson was one of the first people, if not the first, talking about ecological change as a result of human activity and how those changes could circle back and affect human health," says Dr. Eric Chivian, the founder and director of the Center for Health and the Global Environment at Harvard Medical School.

For example, Carson reported that residues of synthetic pesticides, which linger in soil, water, and the body, "are now stored in the vast majority of human beings. They occur in mother's milk, and probably in the tissues of the unborn child." A *Time* magazine reviewer chided her for this and other "emotional and inaccurate outbursts" which would only "do harm by alarming the nontechnical public."

Carson's warning was neither emotional nor inaccurate. And it has since been borne out in studies of pesticides and other synthetic compounds. Take polychlorinated biphenyls, or PCBs, which were widely used as coolants and lubricants in transformers and electric motors. Although the Environmental Protection Agency banned the use of PCBs in the United States in 1979, we still carry them in our bodies. Precisely how pesticide residues and other persistent pollutants affect human health is still a matter of debate.



Reading *Silent Spring*

I first read *Silent Spring* a few weeks after the first Earth Day. As a naïve city kid, it got me thinking about the natural world, the balance of nature, and what we were doing to our planet. I just read the book again, prompted by several articles in the Spring 2012 issue of *Sanctuary*, the journal of the Massachusetts Audubon Society. Its messages are still timely and important.

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(Over the weekend I read in my local newspaper about plans for aerial spraying against mosquitoes in southeastern Massachusetts.)

This time, though, I was struck by Carson's careful and detailed reporting. She relied on interviews, correspondence with scientists, newspaper reports, articles in scientific and trade journals, and governmental reports — more than 500 citations listed in her "list of principal sources." It's a masterful marshaling of evidence.

Carson's response to the criticism that came her way after *Silent Spring* was published is equally impressive. She calmly and persistently stated her case, using the facts she gathered for the book, and ultimately prevailed — all while she was battling the breast cancer that would kill her within two years of *Silent Spring's* release.

"She was eviscerated by industry and powerful corporate lobbies," Dr. Chivian told me. "They attacked her in every possible way, undermined her arguments, and ridiculed her science. But she was fearless in her beliefs and in her accuracy as a researcher and a writer, and she was totally determined to tell the American public of a grave danger that they faced. Her quiet leadership still serves as a role model for others undergoing such attack."

Silent Spring was instrumental in banning the use of many dangerous pesticides. It helped spark the modern environmental movement, launch the Environmental Protection Agency, and pass the Clean Water Act and the Endangered Species Acts. It is in the Modern Library's 100 best nonfiction books, and *Discover* magazine named it one of the 25 greatest science books of all time.

If you haven't read *Silent Spring*, the 50th anniversary is as good a time as any. Rachel Carson's message that human health and environmental health are inextricably linked continues to resonate today, and still carries the same urgency that it did in 1962.

To learn more…
This information was prepared by the editors of the Harvard Health Publications division of Harvard Medical School. It is excerpted from our Harvard Health Blog, available at health.harvard.edu/blog.

How genes and environmental forces raise cancer risk

Fall 2008

By Amy Roeder, Developmental Communications Coordinator in the Office for Resource Development
(From *Harvard Public Health*)

Monica Ter-Minassian is scouring the genome for time bombs. Using gene-reading technology and analytic techniques, this Harvard School of Public Health doctoral student is on the hunt for subtle variations in human DNA that might help identify the causes of rare neuroendocrine and esophageal tumors, or provide a deeper understanding of why smoking provokes lung cancer in some people but not in others.

Like most complex diseases, cancer results not from a single flawed gene, but rather the interplay of multiple genes and any accumulated damage to DNA caused by environmental factors such as exposure to chemicals, or aspects of lifestyle, such as smoking. To gain a better picture of this recipe for human disease, HSPH recently launched the Genes and Environment Initiative, pulling together students and faculty trained in environmental health, population science, biostatistics, and basic biological science.

Few scientists are fully grounded in so many areas. But Ter-Minassian came to HSPH with a range of expertise developed as a researcher in the genetic epidemiology branch of the National Cancer Institute (NCI) from 2002 to 2004. Previously she worked as a genetic counseling intern in Boston-area hospitals, gaining an appreciation, she says, of the need to help patients understand the interplay between their DNA and external forces that influence their risks for disease. Now, based in the School's Department of Environmental Health, she analyzes populations for genetic factors that raise or lower cancer risk.

"Cancer researchers must understand how genes are expressed and interact with environmental toxins or nutrients at different points in tumor development. A strong biology and genetics background helps," says Ter-

Minassian, whose talent earned her a prestigious Taplin Fellowship for 2007 and 2008.

"It's hard to find people with Monica's mix of skills," says her advisor, Professor of Occupational Medicine and Epidemiology David Christiani, who has taught at HSPH for more than 20 years. "In the field of gene-environment interactions, she's one of the most capable people I've ever met."

MINING THE SNPS

Ter-Minassian is analyzing common variations in four genes linked to lung cancer, exploring how these subtle points of difference may be modified by age, gender, and smoking status. These variants, known as SNPs ("snips," short for single nucleotide polymorphisms), occur all along the chromosomes without affecting gene function. Because they lie nestled within functional stretches of DNA representing as-yet-unidentified genes, scientists searching for new genes related to a particular disease like to start by comparing SNPs of people with and without that disease.

After mining online catalogs of SNPs compiled by many scientists, Ter-Minassian, with the Christiani team, chose 1,536 candidate SNPs from genes already linked to lung cancer. A lab tested for their presence in DNA from study subjects at the Massachusetts General Hospital, in Boston. Now Ter-Minassian is searching for SNP patterns that go hand in hand with a confirmed lung cancer diagnosis.

In a second study, Ter-Minassian took a closer look at a subset of four SNPs. "We did see some interesting results in one particular SNP in a gene called FASLG," Ter-Minassian says. "We looked at different subgroups of patients, and the strongest evidence showed this FASLG SNP poses the greatest risk for younger people." The biological reason, she says, is that expression of this SNP's gene decreases in people over 60.

Ter-Minassian is also exploring possible genetic roots of susceptibility to esophageal adenocarcinoma, for which smoking is a known risk, and neuroendocrine cancers, which have no known environmental factors. She hopes to identify SNPs that not only point to cancer susceptibility, but also hint at patients' survival times. This is particularly important for esophageal cancer patients, at least one-third of whom die within a year.

POTENTIAL FOR NEW TREATMENTS

Ter-Minassian is still relatively new to these sorts of population-based studies, but her interest goes back to her undergraduate years at the Massachusetts Institute of Technology. "My senior thesis was on bacterial genetics, but I was fascinated with a course in human genetics, where we had an almost 'grand rounds' experience of case studies, meeting patients with inherited diseases like Duchenne's muscular dystrophy and Huntington's disease," she says.

It was while studying genetic diseases in families at NCI that Ter-Minassian first began wondering about the role of environmental factors, such as sunlight exposure in familial melanomas in Italy, or alcohol and spicy food consumption in esophageal cancers in north-central China. Since then, she has seen a "dramatic shift" in the way people think about disease susceptibility. "Instead of focusing on inherited gene mutations," she says, "researchers now consider a mix of genetic and environmental effects." Inspired, Ter-Minassian sees real potential for research on cancer susceptibility and survival to lead to better patient treatments.

"There is still a lot we don't know about complex diseases like cancer, where the mode of inheritance is not clear," says this multi-faceted scientist, who plans to graduate next year. "There's definitely a lot to be done."

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Green chemistry: reducing production of hazardous substances through innovative design

2011

By Jessica W. Chen
(From *Science In The News*)

In today's society, contributions from the field of chemistry are evident all around us. Advancements in chemistry have led to the production of medicines to alleviate our pain, polyester to keep us warm, fertilizers to provide our crops with nutrients, cooking oil to add flavor to our food, and many other things. These same advancements have also generated numerous toxic chemicals, from the insecticides sprayed on our crops to the compounds found in water-based paints. Not only are these toxins harmful to our health, they are also damaging to the environment. For example, the release of chlorofluorocarbons (CFCs) and related compounds generated during chemical processes contributes to the depletion of the ozone layer, which in turn increases the amount of harmful solar radiation that makes it to the Earth's surface. In the year 2000, 7 billion pounds of toxic materials were released by the U.S. alone.

Green chemistry is an approach that aims to eliminate the usage and generation of hazardous substances by designing better manufacturing processes for chemical products. Specifically, the goal of making the finished product and by-products less toxic directs the decisions made during chemical production. Aspects of the manufacturing process considered include the initial selection of chemicals, the mechanism of chemical synthesis, the end products of the process, and the management of toxic products generated during production. By limiting the hazard intrinsic to the chemical products, the risk introduced by the product is consequently reduced. In addition to protecting the environment, green chemistry has the potential to benefit the large and diverse group of people whose job or residence places them at risk for exposure to toxic chemicals produced by manufacturing.

Governmental promotion of green chemistry

In an attempt to eliminate the risks presented by chemical processes, the U.S. Environmental Protection Agency (EPA) was formed in 1970. By the 1980s, the EPA had passed more than 100 environmental laws. With the passage of the Pollution Prevention Act of 1990, the green chemistry movement was initiated. The 1990 Act was unique because it prioritized reducing the amount of pollution generated. In contrast, a "command and control" approach was taken pre-1990 to regulate pollution, where the priority was to limit risks by reducing exposure to environmental toxins through regulation of the use, handling, treatment, and disposal of chemicals. Consequently, in the pre-1990 years, the laws regulating pollution restricted the amount of pollution that could be released into the atmosphere and presented timetables for reducing pollution that often overlooked practical considerations like feasibility and cost.

Shortly after the formation of the EPA, the first research initiative for green chemistry, the "Alternative Synthetic Pathways for Pollution Prevention" (eventually renamed the "U.S. Green Chemistry Program"), was launched. This initiative provided generous financial support for research conducted with the intention of preventing pollution through the innovative design and synthesis of chemicals. Because there was not yet enough technology for measuring the toxicity of chemicals or understanding their negative effects, green chemistry led to collaborative research efforts across many disciplines in the industrial, academic, and government sectors.

Current trajectory of green chemistry

One component of the U.S. Green Chemistry Program was the adoption of the Presidential Green Chemistry Challenge, which recognizes the innovative ideas and accomplishments made to advance green chemistry. The awardees must create either less toxic methods for making chemicals, or make less toxic chemicals to replace existing harmful chemicals [5]. The aims of the Challenge are in-line with the guiding principles of green chemistry. The 12 principles provide a framework for designing new materials, products, processes, and systems that may lead to a greener chemical manufacturing process.

1. *Prevention*. It is easier to prevent waste formation than to treat waste after it is generated.

2. *Atom economy*. Design of synthetic methods that aim to maximally incorporate as much as possible of the materials used to generate the final product(s).

3. *Less hazardous chemical syntheses*. Where feasible, the substances used and created in the manufacturing process should pose little or no toxicity to human health and the environment.

4. *Designing safer chemicals*. Chemical products are designed to have the lowest levels of toxicity.

5. *Safer solvents.* Solvents, which are used to dissolve other substances into a solution during the production of chemicals, should be of minimal toxicity. As many solvents are toxic, flammable, or cause pollution, current research is focused on making chemicals without using solvents or using non-toxic solvents to reduce the damage to the environment caused by current solvents. One candidate replacement is carbon dioxide, as it is inexpensive, renewable, non-toxic, and has many desirable chemical properties.

6. *Design for energy efficiency*. The impact of the energy requirements in chemical production on the environment and economy should be recognized and lessened when feasible.

7. *Reduce derivatives*. Unnecessary steps that produce by-products should be avoided where practical, for they increase the total waste generated.

8. *Use of renewable raw material*. The raw materials used should be renewable and not depleting whenever technically and economically feasible. Currently, many of the chemicals that are manufactured industrially are created by chemically modifying petroleum. These modifications often require the use of toxic chemicals such as heavy metals. An attractive alternative is the development of chemicals derived from living matter such as plants. These bio-based materials are renewable and could reduce or eliminate the need to use toxic compounds. However, there is currently only one bio-based material source available in the large quantities required for industrial-scale manufacturing.

9. *Catalysts*. Selective catalytic agents, which can make a chemical reaction proceed faster, are preferred because they reduce the amount of chemicals required in a chemical reaction.

10. *Design for degradation*. The products used should be biodegradable to reduce their effect on the environment.

11. *Real-time analysis for pollution prevention*. Real-time monitoring methods need to be created to control the formation of toxic chemicals.

12. *Inherently safer chemistry for accident prevention*. The substances used in chemical processes should be chosen based on minimizing the potential to cause chemical accidents, such as explosions, fires, and releases into the environment.

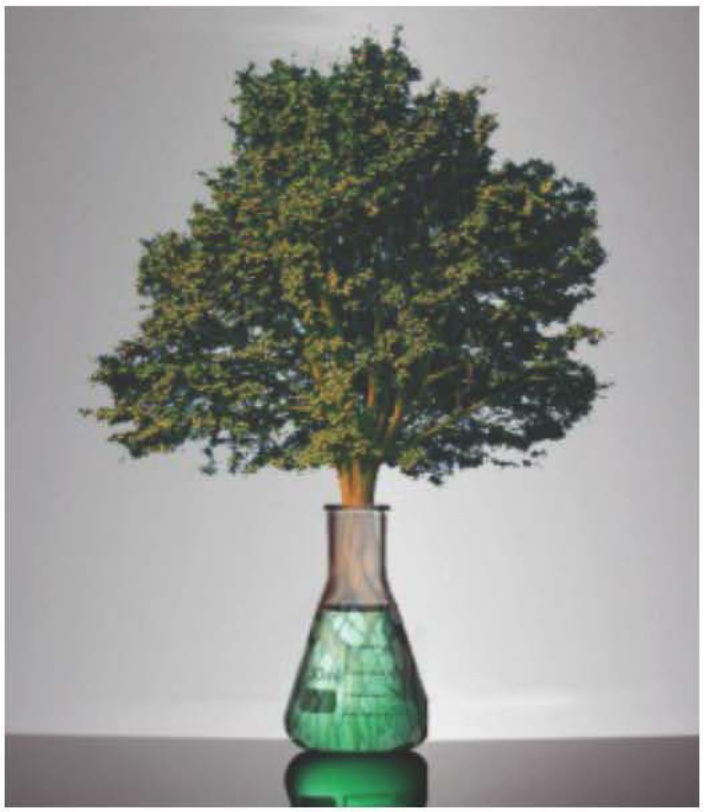
Green chemistry has influenced many areas of chemical production, including the choice of materials used, the methods used for making chemicals, and the design of safer chemicals. Nevertheless, as discussed above, much remains to be done before the green chemical approach can be deemed a success.

Future direction

Green chemistry is an innovative approach introduced in the early 1990s to reduce the release of toxic chemicals into our environment. While advances have been made in the fields of research and engineering, many barriers to the implementation of green chemistry still exist. For example, the cost of cleaner technology is extremely high and tax incentives are not offered by the government to alleviate this cost. Furthermore, innovative technology is often patented, which rewards the inventors but may prevent the widespread

adoption of cleaner technology at low-cost. Lastly, the research advancements made in the different sectors of academia, industry, and government are often not shared among each other because of a lack of communication. Regardless of these limitations, green chemistry is advancing and is transforming the status quo in chemical production to one that is less toxic and more environmentally conscious. The changes instituted by green chemistry will thereby lead to safer work environments and safer products for consumers.

Jessica W. Chen is a PhD student in Biological and Biomedical Sciences at Harvard Medical School.



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Keeping workers safe from health hazards on the job

September 16, 2013

By Karen Feldscher
(From Harvard T.H. Chan School of Public Health)

Harvard School of Public Health's Education and Research Center (ERC) for Occupational Safety and Health has been awarded a five-year, $1.8 million per year grant from the Centers for Disease Control and Prevention's National Institute for Occupational Safety and Health (NIOSH). The renewal of this sustaining grant represents the center's continued success in competing for funding since its inception in 1977, and will enable the continuation of important work both in training occupational safety and health professionals and in conducting research on a wide variety of occupational health problems.

"The NIOSH grant's degree-granting training aspect, which accounts for more than 60% of the ERC budget, is extremely important in helping us train professionals who can work both on the research side and also do real-world hazard assessment and intervention," said Center director [David Christiani], Elkan Blout Professor of Environmental Genetics. Such training is critical, he added, because, "given the size of the American workforce—roughly 155 million—the number of professionals trained to deal with workforce health comes up pretty short."

The center is heavily focused on training practitioners and researchers in workplace disease and injury prevention, Christiani said. He added that the Center also conducts research on new workplace hazards and new technologies that could impact health, such as nanotechnology, and issues related to worker health and disease susceptibility, such as sleep disorders, obesity, and genetic factors.

ERC researchers have both a regional and a national focus, Christiani said. Among New England workers, they have investigated workplace health in the construction, health care, manufacturing, and fishing industries. Nationwide they have studied occupational hazards facing firefighters, welders,

construction workers, truckers, bicycle messengers, and workers in office buildings, hospitals, labs, and greenhouses, to name a few.

Christiani noted a few of the health hazards workers face. Welders are exposed to dangerous fumes and textile workers to airborne bacteria. Nurses suffer back pain. Professionals like radiologists have repetitive motion disorders from computer use. Another challenge is addressing the workplace health needs of a large foreign-born segment of the workforce, who often face the most hazardous conditions at work, in addition to lacking access to adequate health-promoting activities outside of the workplace, Christiani said.

"We look not just at what the workplace does in terms of exposures and how to mitigate that, but also how to reduce the consequences of what people bring to the workplace in terms of their own genetics and their lifestyles," Christiani said. For instance, ERC investigators have examined how sleep disorders and obesity can affect truck drivers and first responders.

One of Christiani's own long-term occupational research pursuits has focused on how cotton dust affects the health of textile workers. Although he has studied garment workers in Shanghai, his findings have ramifications for many different types of U.S. workers as well. "Workers can be exposed to harmful dust if they work in zoos, in plywood production, in wastewater treatment plants, or if they live or work in water-damaged areas, buildings, or homes, for example," said Christiani.

Given the current budget climate, Christiani said, "It's a big deal to get our grant renewed." It's tax dollars well spent, he thinks. "Our center is aimed at prevention—at saving hearts and limbs and eyes and lungs—and this saves money in the long run," he said. "It helps us preserve the health of the U.S. workforce."

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Green eggs and HIM

July 9, 2014

By Stephanie Dutchen
(From Harvard Medical School News)

Uncovering the reproductive effects of chemical exposure

Monica Colaiácovo has made a career of studying meiosis, the type of cell division that produces eggs and sperm.

Meiosis is essential for healthy reproduction. Chromosomal abnormalities resulting from errors in meiosis cause Down syndrome, more than 35 percent of miscarriages and 4 percent of stillbirths, and other conditions.

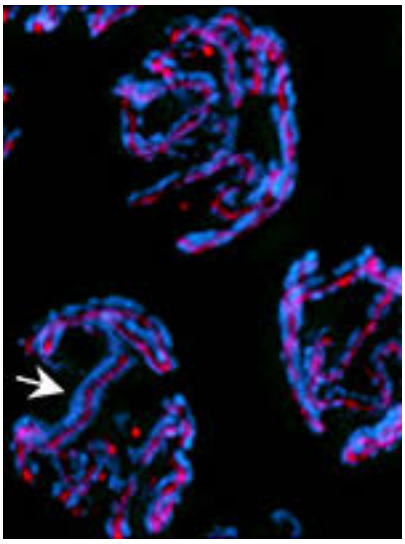
In her search to "understand everything that matters to make sure you end up with the right number of chromosomes in the eggs and sperm," Colaiácovo, associate professor of genetics at Harvard Medical School, has discovered that meiosis can be disrupted not only by genetic mutations but also by exposure to toxic chemicals present in the environment.

Worse, she's finding evidence that those disruptions may be passed down not only to an exposed organism's children, but also to its grandchildren and great-grandchildren.

"The basic questions we're asking are: What are the genetics that regulate meiosis? Which chemicals in the environment cause problems in reproductive capacity? How do they cause those problems, and at what dose? Can some exposures lead to transgenerational effects?" said Colaiácovo.

In addition to answering fundamental questions about the details of meiosis, her research could influence policy decisions and industrial chemical design with the hope of safeguarding the genetic health of future generations.

Meiosis unzipped



Synaptonemal complexes (red) zip chromosome pairs together (blue) in cells undergoing the first phase of meiosis. Image: Colaiácovo lab

Colaiácovo focuses on the first phase of meiosis, when a single parent cell duplicates its chromosomes and then divides in two. As the cell prepares to divide, its chromosome pairs line up, swap DNA segments and separate. A temporary structure called the synaptonemal complex zips the chromosome pairs together as they exchange genetic material.

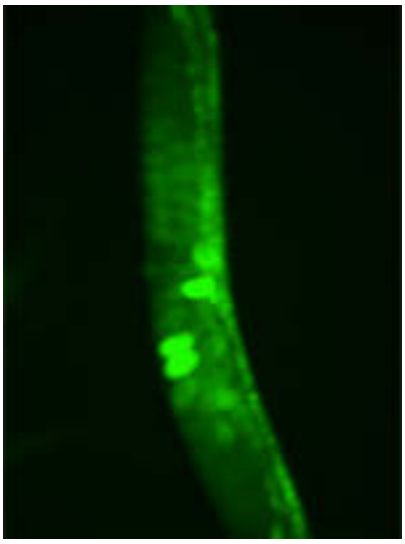
Several years ago, Colaiácovo dosed tiny *Caenorhabditis elegans*worms with the common plasticizer bisphenol A (BPA) to see if anything went awry during meiosis. Defects appeared in the synaptonemal complex zipper. As a result, the chromosome pairs didn't fully align, repair damage or separate properly.

These findings replicated what other researchers had seen in mouse models. Colaiácovo went further and identified a set of genes important for DNA repair whose activity was dampened in the BPA-exposed worms. They were among the more than 60 percent of genes that *C. elegans* shares with humans. Mouse studies soon confirmed the findings.

"This meant we had found an ideal model with the worms to understand how chemical exposures can interfere with reproductive health," she said.

Green screen

To study more than one chemical at a time, Colaiácovo scaled up.



Eggs with chromosomal abnormalities due to environmental toxin exposure glow green in a *C. elegans*worm. Image: Colaiácovo lab

She applied a screening system called “green eggs and HIM.” A fluorescent tag made the worms’ eggs glow green if they had the wrong number of chromosomes—in this case, a missing copy of the X chromosome. She put her worms in well plates, added a different chemical to each well and watched what happened.

After validating her screening model using 13 chemotherapy compounds, she examined 47 chemicals mined from an Environmental Protection Agency database. Her team classified the chemicals from the database as non-, intermediate or highly “reprotoxic” based on 30 years of mammalian reproductive data. The green-eggs screen confirmed the classifications for 69 percent of the chemicals.

Many of the chemicals that didn’t match were predicted to be non-reprotoxic but turned out to be reprotoxic. A literature search turned up overlooked corroborations in mammalian studies and suggested that not all of the mismatches could be attributed to differences between human and *C. elegans* metabolisms.

“That tells us there are chemicals being used in the United States that have been categorized as safe at certain concentrations which apparently are not safe,” said Colaiácovo.

Her lab is now testing another batch of chemicals that includes pesticides, fungicides and substances used in fracking and crude oil processing. She's also investigating the effects of different doses and exposure to multiple chemicals.

"We've selected around 50 chemicals people can be exposed to in everyday life," said Nara Shin, a postdoctoral researcher in the lab. "We want to study their mechanism because we really do not understand how many of these chemicals work, how they interfere with our reproductive system or how their effects can be transferred to the next generation."

From generation to generation

C. elegans lives less than three weeks and lays 300 eggs at a time, making it a convenient model for studying the impact of environmental chemical exposure on subsequent generations.

Colaiácovo is now adjusting her green-eggs test to track whether exposing a worm in generation zero to a toxin can cause chromatin modifications—which can alter a gene's activity—not only in generation one but also in two, three, four or more.

In collaboration with Yang Shi, HMS professor of cell biology and pediatrics at Boston Children's Hospital, she previously found that interfering with genes that regulate chromatin modifications resulted in faulty repair of DNA damage and caused sterility that grew more pronounced with each generation.

"Those findings have led us to focus on identifying the chemical exposures that can result in heritable effects, and to try to determine whether there is really an epigenetic basis—meaning factors beyond the DNA sequence, such as changes to chromatin—for those effects," said Luciann Cuenca, a graduate student in Colaiácovo's lab.

Effecting change

Colaiácovo doesn't intend for her findings to stay in the lab.

"We want to not only understand the science of how these things work, but also have that information come out in a public forum," she said. "We want the

broader society to be aware of the effects of exposure to certain chemicals and put some pressure on the system for changes in policy."

She publishes in journals run by the EPA and the National Institute of Environmental Health Sciences to make sure "the entities that matter are in the loop." She collaborates with biostatisticians at the EPA to ensure that her science is as strong as it can be.

Ultimately, she wants her findings to inform decisions about how to engineer the next generation of chemicals and what to do with meiosis-disrupting chemicals that have already seeped into the environment. Her lab is trying to determine whether there are groups of chemicals with particular structures that interfere with meiosis in similar ways.

"If our hypothesis is correct, it would alert industry that there are certain designs of chemicals that have to be rethought completely," said Colaiácovo.

She also believes her *C. elegans* model could provide a cheap and quick "first-pass" screen for chemicals under development that are meant to be introduced into the environment.

"The health impact of meiosis is so significant, yet there's a lot we don't understand about it. It's been extremely interesting to learn a little more about the reproductive effects of what we're exposed to every day," she said.

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New chapter for a ‘textbook’ disease

February 13, 2015

By Nancy Fliesler
(From Harvard Medical School News)

Study finds arsenic poisoning can resemble cystic fibrosis

Research in Bangladesh suggests that arsenic poisoning from sources such as contaminated well water can cause cystic-fibrosis-like illness. Image: justinkendra/iStock

Since the 1980s, when its causative gene was sequenced, cystic fibrosis (CF) has been the “textbook” genetic disease.

Several thousand mutations have been identified in the CFTR protein, which regulates the flow of chloride in and out of cells. When CFTR is lost or abnormal, thick mucus builds up, impairing patients’ lungs, liver, pancreas,

and digestive and reproductive systems and making their lungs prone to opportunistic infections.

But new research could add a chapter to the textbook, pinpointing an unexpected environmental cause of CF-like illness. A study reported in the Feb. 5, 2015, *New England Journal of Medicine* found that people with arsenic poisoning have high chloride levels in their sweat—the classic diagnostic sign of CF.

Christopher Hug, Harvard Medical School assistant professor of pediatrics and a pulmonologist at Boston Children's Hospital who treats children with CF, had seen clues in the research literature, particularly work from the lab of Bruce Stanton at Dartmouth College, indicating that arsenic causes the CFTR protein to break down. Hug knew his friend Maitreyi Mazumdar, HMS assistant professor of neurology at Boston Children's, was studying arsenic poisoning's neurological effects in Bangladesh.

"He asked me, 'You study arsenic, why don't you do sweat tests in this population?'" recalled Mazumdar, who also studies lead poisoning in affiliation with the Harvard T.H. Chan School of Public Health. "I replied, 'Why don't we study this together?'"

In November 2013, they visited Bangladesh with members of Mazumdar's research team. Their findings could spark research on better treatments for both conditions and could prompt immediate measures for improving global health.

A man-made epidemic

Arsenic poisoning is epidemic in Bangladesh, the unintended result of public health efforts to reduce cholera and other diseases from fecally contaminated pond water.

In the 1970s, UNICEF and other organizations campaigned to get people to switch to well water, and hundreds of millions of wells were dug. Unfortunately, many of them turned out to have high levels of arsenic.


A well outside a home in Pabna. Image: Maitreyi Mazumdar

Today, an estimated 33 to 77 million people in Bangladesh—a third of the population—are exposed to high arsenic levels.

The skin lesions that sometimes accompany arsenic poisoning are often mistaken for leprosy, making it hard for people to get married; young Bangladeshi women with the lesions have been turned out of their homes. Arsenic poisoning is associated with higher rates of lung cancer and cardiovascular disease. Many exposed people have chronic noncancerous respiratory disease, and some develop diabetes—also a common complication of CF.

Mazumdar, Hug and Bangladeshi collaborators at Dhaka Community Hospital, Bangabandhu Sheikh Mujib Medical University and the Harvard Chan School studied 100 people from Pabna, an arsenic-endemic area in western Bangladesh.

Hug was immediately intrigued. “They struck me as people with chronic lung infections,” he said.


Christopher Hug (second from left) discusses sweat test procedures with research collaborators. Image: Christopher Hug

More than half of their sample had abnormal sweat tests and elevated arsenic levels in their fingernails. These subjects also had higher concentrations of arsenic in their drinking water. Many had symptoms of chronic lung disease and pulmonary function test results consistent with a CF diagnosis.

Subjects with abnormal sweat chloride on confirmatory tests had their CFTR gene completely sequenced. No one had a genetic diagnosis of CF.

New leads for treatment

Mazumdar and Hug believe their pilot study, supported by the Harvard University Center for the Environment and the Harvard–National Institute of Environmental Health Sciences at the Harvard Chan School, could fuel multiple directions of research.

The global health implications could be significant. Recognition of a CF-like illness in people exposed to arsenic would transform their treatment options. While targeted CF drugs would be prohibitively expensive (Vertex's Kalydeco, for example, costs about $300,000 per year), many affordable interventions are available: chest physiotherapy, exercise to improve lung function,

antibiotics for lung infections, monitoring for diabetes and nutritional treatments, such as pancreatic enzymes and vitamins.

"There are 30,000 CF patients in the United States," said Hug. "In Bangladesh, there may be 1,000 times more people with symptoms like CF because of arsenic exposure."

Nor is arsenic poisoning limited to Bangladesh. Arsenic is found in U.S. groundwater and is known to be associated with respiratory disease, diabetes and other health problems, with an estimated 13 million Americans at risk. The *NEJM* study suggests that patients exposed to arsenic should be monitored for CF-like symptoms that might not otherwise be considered.

Finally, a better understanding of the interaction between arsenic and the CFTR protein could fuel the development of more affordable drugs.

"Interestingly, not everyone exposed to arsenic has lung disease," said Mazumdar. "There may be individual differences that could be exploited and that could lead to protective therapies for CF."

Mazumdar and Hug hope to return to Bangladesh and do a larger study looking not only at lung disease but other complications typical of CF, such as diabetes, gastric motility dysfunction and reduced fertility. They would also conduct detailed biochemical evaluations.

Another patient population ripe for study is already at hand: Arsenic is currently part of the treatment of certain cancers, particularly adult leukemias.

"We could look at these patients to see if sweat chloride concentration changes after the administration of arsenic and whether they develop symptoms of cystic fibrosis," said Mazumdar.

Adapted from a post Vector*, Boston Children's clinical and research innovation blog.*

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Chemical Flavorings found in e-cigarettes linked to lung disease

December 8, 2015

By Amy Roeder, Harvard Chan School Communications
(From *Harvard Gazette*)

Diacetyl, a flavoring chemical linked to cases of severe respiratory disease, was found in more than 75 percent of flavored electronic cigarettes and refill liquids tested by researchers at Harvard T.H. Chan School of Public Health.

Two other related, potentially harmful compounds were also found in many of the tested flavors, which included varieties with potential appeal to young people such as cotton candy, "Fruit Squirts," and cupcake.

The study was published online today in Environmental Health Perspectives.

The Occupational Safety and Health Administration and the flavoring industry have warned workers about diacetyl because of the association between inhaling the chemical and the debilitating respiratory disease bronchiolitis obliterans, colloquially known as "popcorn lung" because it first appeared in workers who inhaled artificial butter flavor in microwave popcorn processing facilities.

"Recognition of the hazards associated with inhaling flavoring chemicals started with 'popcorn lung' over a decade ago. However, diacetyl and other related flavoring chemicals are used in many other flavors beyond butter-flavored popcorn, including fruit flavors, alcohol flavors, and, we learned in our study, candy-flavored e-cigarettes," said lead author Joseph Allen, assistant professor of exposure assessment sciences.

There are currently more than 7,000 varieties of flavored e-cigarettes and e-juice (nicotine-containing liquid that is used in refillable devices) on the market. Although the popularity and use of e-cigarettes continues to increase,

there is a lack of data on their potential health effects. E-cigarettes are not currently regulated, although the U.S. Food and Drug Administration (FDA) has issued a proposed rule to include e-cigarettes under its authority to regulate certain tobacco and nicotine-containing products.

Allen and colleagues tested 51 types of flavored e-cigarettes and liquids sold by leading brands for the presence of diacetyl, acetoin, and 2,3-pentanedione, two related flavoring compounds that the Flavor and Extract Manufacturers Association lists as "high priority," i.e., they may pose a respiratory hazard in the workplace. Each e-cigarette was inserted into a sealed chamber attached to a lab-built device that drew air through the e-cigarette for eight seconds at a time with a resting period of 15 or 30 second between each draw. The air stream was then analyzed.

At least one of the three chemicals was detected in 47 of the 51 flavors tested. Diacetyl was detected above the laboratory limit of detection in 39 of the flavors tested. Acetoin and 2,3-pentanedione were detected in 46 and 23 and of the flavors, respectively.

"Since most of the health concerns about e-cigarettes have focused on nicotine, there is still much we do not know about e-cigarettes. In addition to containing varying levels of the addictive substance nicotine, they also contain other cancer-causing chemicals, such as formaldehyde, and as our study shows, flavoring chemicals that can cause lung damage," said study co-author David Christiani, Elkan Blout Professor of Environmental Genetics.

Other Harvard Chan School authors included Skye Flanigan, Mallory LeBlanc, Jose Vallarino, Piers MacNaughton, and James Stewart.

This study was supported by an NIH/NIEHS Center grant.

For More Information

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Our national lead problem is bigger than Flint
Tom Ashbrook
February 18, 2016
WBUR, Boston's NPR News Station
http://onpoint.wbur.org/2016/02/18/flint-water-crisis-lead-poisoning-nationwide

Testing for chemicals harmful to human reproduction (video)
July 14, 2014
Harvard Medical School
https://www.youtube.com/watch?v=7Jts30g2dhs

Flavored e-cigarettes may contain chemicals linked to respiratory diseases
James McIntosh
December 8, 2015
Medical News Today
http://www.medicalnewstoday.com/articles/303664.php

Science matters with Monica Colaiácovo: Unraveling answers (video)
November 26, 2013
Harvard Medical School
https://www.youtube.com/watch?v=jklzhRbvu9Q

The air we breathe: An assessment of urban air pollution (video)
Science In The News
http://sitn.hms.harvard.edu/seminars/2015/urbanpollution/

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Megan Avakian
September 2013
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