Researcher explores link between flame retardants and thyroid cancer

January 7 2014

Rates of thyroid cancer have risen sharply in the past 20 years, particularly in women. A Yale School of Public Health researcher is studying whether the compounds used in flame retardants, commonly added to household product, plays a role in the increase.

Flame retardants are everywhere around us. Governments require manufacturers to put these chemicals into our rugs, cars, furniture, curtains, mattresses and pillows, and even many items of apparel, especially for infants. It's hard to name an item that doesn't contain them. They're in cell phones and computers, stereos and televisions, coffee makers and microwaves. They are supposed to keep us safe by

preventing products from bursting into flame and causing dangerous fires.

But evidence is mounting that this prevention carries unforeseen costs for human health. For the last several decades the chemicals used in most flame retardants have come from a class of compounds called polybrominated diphenyl ethers (PBDEs). Data from animal studies and several human studies have linked PBDEs to a host of biological and neurophysical ailments, including disruptions in the endocrine glands (including the thyroid), decreased fertility in women, lower birth weights and developmental problems in children.

Because PBDEs interfere with the production of essential thyroid hormones, researchers have started to explore whether these chemicals are implicated in the rising incidence of thyroid cancer. That question will be partly answered in two studies now under way by Yale epidemiologist Dr. Yawei Zhang, associate professor in the Department of Environmental Health Sciences.

The rise of thyroid cancer

The first investigation, a population-based case-control study, will look for links between PBDEs and the risk of thyroid cancer using all cases of thyroid cancer diagnosed in Connecticut in 2010 and 2011 and age- and gender-matched general populations in Connecticut. The second and more extensive project is a longitudinal study in collaboration with the Centers for Disease Control and Prevention and the Department of Defense (DOD). Using serum from the DOD Serum Depository, Zhang and her colleagues hope to trace the role of PBDEs in the development of thyroid cancer in 800 cases and 800 controls between 2000 and 2012.

"Thyroid cancer was once very rare," says Zhang, "with only five cases per 100,000 person-years. But in the last 20 years it has increased to

almost 15 cases per 100,000. No other cancer shows such a rapidly increasing trend." This is especially bad news for women, she adds, since thyroid cancer hits them three times as often as men. It has become the fifth most common cancer among women. The causes remain unknown, another factor that motivates Zhang's research.

The surge in thyroid cancer seems to overlap with the introduction and proliferation of PBDEs. These compounds now show up in the blood of about 97 percent of the U.S. population, including newborns, and at levels 10 times higher than in Europe. The highest levels in the United States—twice the national average—are found in Californians. The reasons lie in the history of PBDEs.

In the mid-1970s California decided to protect its citizens from accidental fire by requiring that all furniture and household products sold in the state be capable of resisting an open flame for 12 seconds. Manufacturers began suffusing products bound for California with flame retardants, mainly PBDEs. Other states followed California's lead, passing similar though less-stringent mandates. European countries added their own versions. Faced with this variety of regulations, manufacturers simply saturated all household products with enough flame retardant chemicals to satisfy the strict standard in the major market of California.

The production of PBDEs skyrocketed to meet consumer demand for new fireproof couches, office furniture, mattresses and cribs. Over the next three decades PBDEs became pervasive in households and offices throughout the country. And not in mere trace amounts—a couch with foam cushions might be saturated with up to two pounds of flame retardant.

PBDEs began showing up in blood tests and even in the milk of new mothers. In the 1980s, that led researchers to begin investigating the

chemicals, mostly through animal models. They wanted to know how PBDEs got into humans, why they were so prevalent and what their health effects might be.

Between the 1970s and the early 2000s, three kinds of PBDEs were being used, named after the number of bromides in them: pentaBDE, octaBDE and decaBDE. PentaBDE, prevalent in polyurethane foams for furniture, mattresses and carpet padding, was the most widespread. Research suggested that it was also the most toxic. In animal studies pentaBDE caused reproductive and neurodevelopmental disorders, as well as toxicity in the thyroid and liver. OctaBDE, used mostly in plastics, textiles and nylon, had similar effects. Other studies showed that the compounds accumulated in human breast milk and were passed on to infants.

These alarming findings eventually led to government action. In 2004 the European Union banned penta- and octaBDE. California banned pentaBDE that same year. Ultimately eight states outlawed penta- and octaBDE. In 2009, the two compounds were put on the Stockholm Convention's list of persistent organic pollutants (POPs), joining other notorious POPs (and known carcinogens) such as polychlorinated biphenyls (PCBs) and dichlorodiphenyltrichloroethane (DDT). Production of penta- and octaBDE ceased.

But that did not mean the end of them or their consequences for human health. "Like other POPs," says Zhang, "these chemicals are very persistent in the environment and they also bioaccumulate." That is, they collect in the body and linger there. In humans, the half-lives of PBDEs range from two to 12 years.

The role of PBDEs

PBDEs get into humans in two ways—ingestion and inhalation. The

compounds now appear in every corner of the world and are almost impossible to avoid—in 2004 it was reported that they were found in Arctic polar bears. So it's not surprising that they have infiltrated our food supply. Fatty fish such as tuna and salmon bioaccumulate PBDEs, and when we eat them, they pass on part of their chemical load. Livestock also bioaccumulate PBDEs, which we absorb through fatty meats and high-fat dairy products. But the main source—a recent estimate is 80 percent—seems to be our household and office furnishings. PBDEs leach out of them and stick to ambient dust, which we inhale. Crawling infants get this contaminated mixture on their hands and transfer it to their mouths, which probably accounts for the high levels often found in small children.

The biological consequences of PBDEs were demonstrated in animal studies beginning in the 1980s. More recently these effects have been found in humans, particularly children. Researchers in Spain (2011), the Netherlands (2009), New York (2010) and California (2013) have reported similar results: young children exposed in uteroto PBDEs later show neurobehavioral impairments in their attention, cognition and motor skills—similar to the effects reported for prenatal exposure to PCBs, which are chemically similar to PBDEs.

This is where the thyroid comes in. In pregnant women, the hormone produced by the thyroid is crucial to the normal development of the unborn infant's brain. If something disrupts or interferes with this hormone, and hence with the proper growth of the brain, the result is neurodevelopmental problems. In animal and human studies, PBDEs have been shown to disrupt thyroid function and cause thyroid toxicity. Further, studies demonstrate that PBDEs can cross the blood-placenta barrier and the blood-brain barrier. Since the period of "rapid brain growth" in infants lasts from the third trimester of pregnancy to at least age two, their developing brains may get years of continuous exposure to PBDEs through the placenta, breast milk and contaminated floor dust.

These findings caught Zhang's attention, especially the connection between PBDEs and hormone interference, an area of special interest for her. Zhang came to Yale in 1999 from China, where she worked as a preventive medical doctor. After getting her advanced degrees here, she spent a year as a postdoc at the National Cancer Institute, working on hormone issues and chemicals related to cancer. She joined the Yale faculty in 2005.

"PBDEs seem to mimic the thyroid hormone and disrupt thyroid homeostasis," she says. "That can cause tumors. That's why we proposed this hypothesis linking PBDEs and thyroid cancer. I would like to find the risk factors responsible for the increasing trends for this disease."

The known risk factors are radiation, family history and excessive consumption of iodine, but these account for only a small percentage of thyroid cancer cases. The majority remain unexplained, thwarting prevention. That's why Zhang and other epidemiologists want to investigate PBDEs.

"It just makes a lot of sense to look into this," says Jennifer A. Rusiecki, associate professor of epidemiology at Uniformed Services University of the Health Sciences in Bethesda, MD. (The school is run by the U.S. government and is devoted to military and public health medicine.) Rusiecki and Zhang know each other from YSPH. Both have researched links between environmental factors and cancer. They jumped at the idea of collaborating on PBDEs and thyroid cancer.

"The production of PBDEs almost doubled between 1992 and 2001," notes Rusiecki, "and that parallels the recent dramatic change in thyroid cancer incidence. When you account for the latency period of five to 20 years necessary to develop the cancer, it's a very sensible hypothesis that there may be a link." She and Zhang co-designed the study, which will be based on samples from the DOD Serum Depository, which Rusiecki

can access. The National Institutes of Health is funding the project.

Since the 1980s, everyone in the military, including reservists, has been tested for HIV every two years. The leftover serum goes to the Serum Depository, which contains an estimated 50 million samples. For researchers interested in long-term changes in individuals, the depository is a trove of invaluable data. Zhang and Rusiecki will cross-check the serum data with data from the military's tumor registry. To investigate the effects of PBDEs over time, they will identify 800 people who went from a clean diagnosis to thyroid cancer. These 800 samples will be sent to a lab at the Centers for Disease Control and Prevention, which will analyze them for PBDEs.

"It's a great opportunity to see if a high level of exposure to these chemicals is associated with the development of the cancer," says Rusiecki. Another 800 people who did not develop thyroid cancer will function as controls.

No definitive correlation has yet been found between PBDEs and thyroid cancer. That doesn't surprise Mary H. Ward, a senior investigator in the Division of Cancer Epidemiology & Genetics at the National Cancer Institute. She has studied environmental risk factors for various cancers, including thyroid cancer, and she notes that there is usually a lag between chemical exposure and carcinogenesis. She believes the time is ripe to look for links between PBDEs and thyroid cancer, and she will be part of the team assisting Zhang and Rusiecki. "We're right at the point where we can start to evaluate this," she says. "Ten years ago was probably too early, because the chemicals weren't at the levels we needed."

If Zhang and her colleagues find correlations between thyroid cancer and a person's level of PBDEs, the next step will be to discover the mechanism that leads to carcinogenesis. A few possibilities have been

proposed but not definitively demonstrated, except in animal models. Researchers know that the chemical structure of PBDEs resembles that of thyroid hormones, allowing PBDEs to mimic thyroid hormone function. "These chemicals may be competing with the thyroid hormones," say Zhang, "binding to the thyroid transporter proteins and getting delivered to all the different organs where there are thyroid hormone receptors." But since PBDEs are imposters, they disrupt the proper functioning of the system.

Another possibility, says Zhang, is that PBDEs may cause the thyroid to go haywire. For instance, they may interfere with the hypothalamic-pituitary-thyroid axis, which regulates metabolism. If PBDEs upset thyroid hormone homeostasis, cells in the thyroid may proliferate wildly, setting the stage for cancer.

As part of the DOD Serum Depository study, Zhang and Rusiecki intend to do DNA analysis to see whether specific genes are linked to PBDEs and the risk of thyroid cancer. They want to know whether certain genotypes metabolize the compounds differently and are more susceptible to the disease. Because of the project's scale and complexity, Zhang doesn't expect to have all the results until 2015.

New compounds

The one PBDE still in use, decaBDE, is scheduled to be voluntarily phased out of production in the United States by the end of this year. Its effects on human health, however, will persist while the compound migrates out of the products that contain it.

Manufacturers will replace decaBDE, as they replaced penta- and octaBDE, with new compounds whose consequences for human health vary from damaging to unknown. For instance, when penta- and octaBDE were banned, some manufacturers quietly returned to an older

compound called chlorinated tris (or TDCPP) to flameproof products containing polyurethane foam. When researchers and officials eventually realized this, they were shocked, since or TDCPP had been voluntarily withdrawn as a fire retardant three decades earlier after it was linked to cancer and labeled a cancer risk by the National Cancer Institute and the World Health Organization. The chemical also has been linked to damage of the liver, kidneys and brain. But since or TDCPP was never outlawed, companies didn't have to inform the government or consumers that car seats, nursing pillows and crib mattresses were being doused with the chemical. In the continuing absence of federal action, several states recently acted to ban or strictly regulate products containing or TDCPP.

The other replacement for pentaBDE was a brominated compound called Firemaster 550. In 2003 the manufacturer and the U.S. Environmental Protection Agency (EPA) assured the public that, unlike pentaBDE, Firemaster 550 did not leach from products and would not bioaccumulate in humans.

Within a few years Firemaster 550 began showing up all over the globe, in oceans, animals, household dust and even sewage, from the Arctic to the South China Sea, from San Francisco Bay to the coast of Maine. Since Firemaster 550 seems to be bioaccumulating in porpoises, mollusks and harbor seals, among other animals, researchers began to suspect that it's also sticking around in humans. In early 2012 the EPA announced it was reviewing Firemaster 550 as a potential health hazard. In late 2012, the first study of Firemaster 550's health effects, by researchers at Duke and North Carolina State, found that in animals the compound is an endocrine disruptor and seems to be passed on to infants through the placenta or breast milk or both.

Why are these harmful chemicals allowed into products? The answer goes back to the nation's antiquated Toxic Substances Control Act, now

nearly 40 years old, which doesn't give the federal government much power to control chemicals in consumer products. Manufacturers don't have to prove that a new compound is safe and don't need the EPA's permission to put it into nonfood products. The government can't even require manufacturers to reveal the ingredients in these compounds; the law allows manufacturers to shield such information as proprietary. "Because many of them are commercially secret," notes Zhang, "scientists have no way of testing them."

Even if a chemical is shown to damage human health, the federal government can do little. The 1976 law requires the EPA to prove that the chemical represents an "unreasonable risk"—a legal standard so difficult to meet that the EPA failed to ban asbestos, a clear health hazard and carcinogen. If big-market states such as California outlaw a compound such as pentaBDE, manufacturers simply switch to a new one. Researchers and epidemiologists are always playing catch-up.

"There are thousands of new chemicals being generated all the time," says Zhang. "But if they're not for human food, they're just put into production. Even if they're later banned in some places, they're often so environmentally persistent and bioaccumulative that the general population will continue to be exposed to them for quite a long time. Before they are put into consumer products," she adds, "we really should have some toxicology study results that demonstrate that they are safe for human health."

Provided by Yale University