Michigan House of Representatives
Great Lakes and Environment Committee
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Thank you, Representative Warren and members of the committee, for inviting me to speak to you today. I have been asked to provide some background information and talk about potential health effects of four chemicals—mercury, lindane, a flame retardant called deca-brominated diphenyl ether, and bisphenol A. I'll refer to decaBDE as just deca- from now on. These chemicals may be addressed in legislation coming before this committee.

Let me begin with a few framing comments.

Various environmental chemicals can increase the risk of a number of diseases including cancer, asthma, infertility, birth defects, heart disease, and childhood learning, attention, and behavioral problems, among others.

In addition to personal and family consequences, the economic impacts of these diseases or disabilities are substantial. For example, published analyses estimate the lifetime cost of current lead exposures for each year's cohort of children in the US at 43 billion dollars and 8.7 billion dollars for mercury. When we begin to add in the environmentally-attributable costs of other diseases or disabilities, the numbers become extraordinarily large.

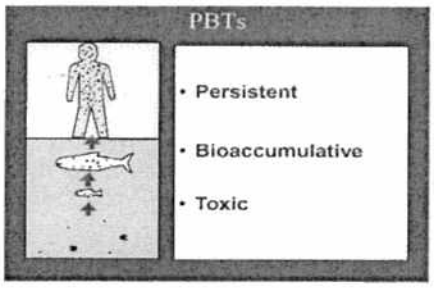
In most cases, developing children are more susceptible to toxic exposures than adults. When exposures occur during so-called "windows of vulnerability", the development of brains, other organs, and reproductive, hormonal, and immune systems can be permanently altered—even though that same exposure may have only temporary or even no discernable effect in adults. It's also worth noting that vulnerability to environmental agents can be increased by inadequate nutrition, poor socioeconomic circumstances, or exposure to mixtures of environmental contaminants.

Developing children are also disproportionately exposed to environmental contaminants that may be present in food, water, and air. Pound for pound, children eat and drink more and breathe more air than adults. In addition, their normal behavior of mouthing objects and putting their hands in their mouths, assures that infants and young children ingest more environmental contaminants from soil, house dust, and household products.

Several of the chemicals of concern today are widespread environmental contaminants and can be measured at some level in most people including infants, children, and pregnant women who pass them on to their developing fetuses.

Some are persistent when released into the environment, meaning that they do not quickly or easily degrade nor are they quickly and easily metabolized and excreted from the body. I will identify them as I go along.

Two of the four chemicals also bioaccumulate—meaning that their concentrations tend to build up as they move up the food chain and accumulate over time in individuals. This means that very small concentrations can build up and can matter a great deal. For one, the data are still unclear.

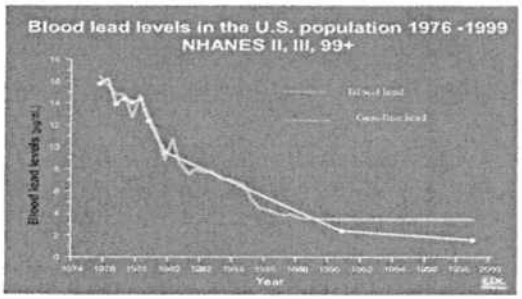


Evidence of health impacts of environmental chemicals comes from laboratory studies, including tests in laboratory animals, and from studies of exposed individuals and groups of people. Frequently, laboratory animal studies are carried out long before any human studies are even begun.

One question sometimes comes up: "Why pay attention to animal data? Why not wait for human data?" Testing the effects of chemicals in laboratory animals is well-accepted and valid for understanding health effects. Scientists in universities and government regularly use animal data to draw conclusions about the health effects of pharmaceuticals, pesticides, and chemicals encountered in the workplace and used in consumer products. Pharmaceuticals never make it to market without some evaluation in clinical trials in people, but those kinds of studies are not done with non—pharmaceutical compounds for obvious ethical reasons. As a result, animal data are used and the evidence is supplemented with information from epidemiologic studies in exposed workers or the general public when available. A challenge for policy makers is deciding when evidence is sufficient to act. Waiting until evidence of harm in humans is well-established and universally accepted means that early warnings were missed or ignored. I'll come back to this point in a few minutes.

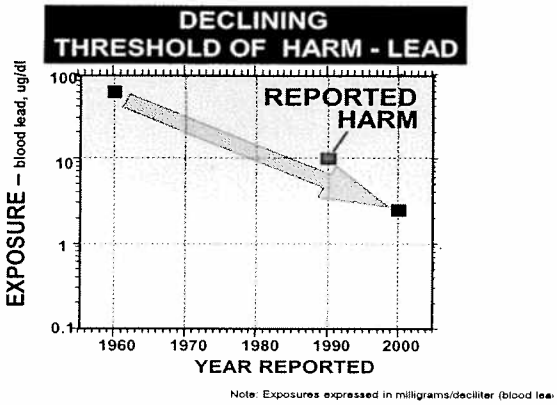
Mercury, lindane, deca-, and bisphenol A have been used in consumer products for a long time. During that time, we have learned a great deal about their potential health effects. Their stories share some common features with the story of lead. In the 1960s, no one worried much about the effects of lead if a child was not obviously sick. And many were at that time—with seizures, severe abdominal pain, and more—illnesses that couldn't be missed. But then scientists began wondering about more subtle effects of lead—effects on IQ, behavior, attention spans, and so on. Now we know that even low level early life lead exposures impair IQ, learning, and attention; increase the risk of hyperactivity, impulsiveness, aggression, failure in school, and trouble with the law. More recently we have learned that higher lifetime lead exposures increase the risk of dementia and Parkinson's diseases.

While this evidence was accumulating, the lead industry fiercely defended their products, misrepresented the science, and tried to destroy the careers of scientists reporting the impacts of lower level exposures. This is all documented in papers published in the American Journal of Public Health. Meanwhile, children continued to be damaged. Finally, when lead was removed from gasoline, beginning in the late 1970s, blood lead levels in the US population began to drop dramatically.



The problem has not been solved because there are other sources of exposure for some people. But the benefits of the intervention are undeniable.

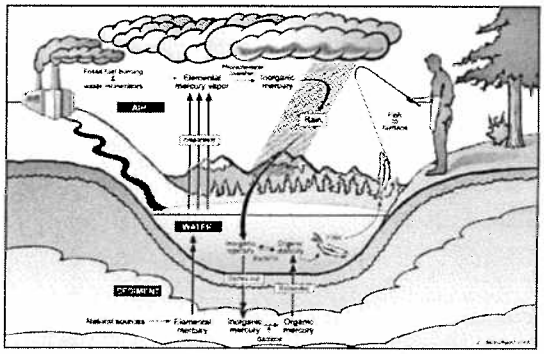
Here is a timeline of our understanding of threshold effects of lead.



Mercury:

A similar story has unfolded for mercury.

The Mercury Cycle



Mercury gets into the environment from a variety of sources. In the US coal fired power plants are the single largest source, but mercury is also released from waste incinerators and landfills.
This slide shows mercury's atmospheric transport, deposition on wetlands and water bodies, and conversion to organic mercury. Methyl mercury, the organic form, is taken up by aquatic organisms and

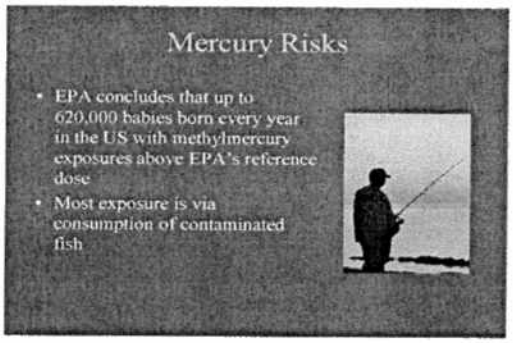
biomagnifies as it moves up the food chain.

Most people are exposed to mercury from eating contaminated fish, although there are other sources. Some kinds of freshwater fish in the Great Lakes region and all over the country, as well as various marine species, are sufficiently contaminated with mercury to pose health threats.

Mercury is toxic to the nervous system. It easily crosses the placenta and enters the brain of the fetus where it interferes with normal development by disrupting a number of critical processes.

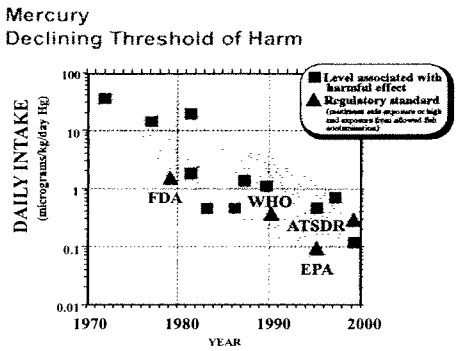
Extensive laboratory animal testing data have now been supplemented with information from epidemiologic studies in people, in which exposures to mercury were carefully measured in pregnant women or in infants at the time of birth. These studies show impacts on attention, language, memory, and visual-spatial and motor skills in children exposed to higher levels of mercury during gestation. Several studies also report that adults with higher levels of mercury exposure are at increased risk of sudden death from cardiovascular disease.

The US EPA used data from these studies of developing children to derive a so-called reference dose for mercury. That is a dose below which they do not anticipate any adverse effects in the developing brain and above which the risk begins to increase. Because the relevant exposure occurs during fetal development, they expressed the reference dose as a maternal intake of mercury from dietary sources.



Then, after matching that dose against actual levels of mercury measured by the Centers for Disease Control in a representative population of women of reproductive age, they concluded that up to 620,000 babies are born in the US each year who would have been exposed to mercury above the reference dose during gestation.

Not unlike lead, this is the timeline of our understanding of the amounts of mercury necessary to cause harmful effects:



It's my understanding that you will be considering legislation that will restrict both the sale and disposal of mercury-containing products in incinerators and landfills in Michigan. This is similar to legislation that has been adopted in other states and will be very helpful in continuing to address the problem of environmental releases of mercury.

Lindane:

Last year this committee considered a bill that would have required lindane to be applied under supervision in a clinician's office when it was prescribed. It's my understanding that the bill has been reintroduced this year. I supported that bill for several reasons.

Lindane is a persistent, bioaccumulative insecticide. Historically, it was used in agriculture, in veterinary medicine, and to treat lice and scabies in people. It is no longer allowed for use in agriculture, veterinary medicine, or military use on skin or clothing in the U.S. It continues to be approved by the Food and Drug Administration (FDA) as a second line treatment for head lice and scabies. Lindane is completely banned in over 50 countries as well as in the state of California. According to the EPA, lindane is a "bioaccumulative chemical of concern" in the Great Lakes, an "extremely hazardous substance", and a "priority pollutant" under the Clean Water Act. Lindane was identified in Detroit Wastewater sludge in 2002 and 2004. Its most likely source was from pharmaceutical use.

Lindane is particularly toxic to the nervous system of people and laboratory animals. It is absorbed through the skin. Although it continues to be approved by the FDA as a second line treatment for head lice and scabies, it is labeled with a highly unusual "black box" warning that says:

WARNINGS:
"Lindane Shampoo should only be used in patients who cannot tolerate or have failed first-line treatment with safer medications for the treatment of lice.

Seizures and deaths have been reported following Lindane Shampoo use with repeat or prolonged application, but also in rare cases following a single application according to directions. Lindane Shampoo should be used with caution in infants, children, the elderly, and individuals with other skin conditions, and those who weigh < 110 lbs (50 kg) as they may be at risk of serious neurotoxicity.

Lindane Shampoo is contraindicated in premature infants and individuals with known uncontrolled seizure disorders.

Instruct patients on proper use of Lindane Shampoo, the amount to apply, how long to leave it on, and

avoiding re-treatment."

The FDA has control over lindane as a pharmaceutical agent and has shown increasing concern about its safety since it was registered for use. Transcripts of FDA deliberations in the 1980s—available on the FDA website—show that officials wanted to advise against the use of lindane in infants and pregnant and lactating women but were resisted by the drug's sponsor. At that time, and continuing today, the FDA knew that side-effects from lindane, like other drugs, are markedly under-reported and that misuse, including overuse, of the drug was common. The agency held lengthy discussions about how best to educate people, including physicians, about the proper use of lindane. Negotiating with the drug's sponsor at that time, they developed labeling instructions warning people not to use lindane shampoo in the bath or shower, warned against using the lotion after a warm bath or shower, warned against unnecessary skin contact, and said that assistants should wear rubber gloves and other protective clothing. They knew then that lindane can cause seizures and wondered what lindane might be doing to the brain in people who did not have seizures as an obvious side effect. (http://www.fda.gov/ohrms/dockets/ac/accutane/1782t1a.pdf)

Now we know even more. Laboratory animals given doses of lindane lower than those required to produce hyperactivity, seizures, or other evidence of obvious toxicity show permanent alteration of behavior, brain chemistry, and brain architecture. Indeed, the FDA warns that the immature central nervous system may have increased susceptibility to the effects of the drug, based on animal testing at levels of exposure close to those expected in people who use lindane lotion to treat scabies.

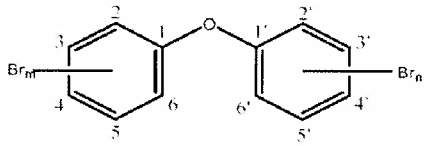
We also now know that we should consider the impacts of lindane later in life. Lindane disappears from the blood within hours but it is not gone from the body. Rather, because lindane is fat soluble, it is deposited in tissues and organs with high fat content. Because of its high fat content, the brain is one of the repositories where lindane can linger for some time. An autopsy study published in 2000 reported significantly higher levels of lindane in the brains of people with Parkinson's disease than in a control group. This study is consistent with a large body of evidence linking pesticide exposures to an increased risk of Parkinson's disease.

Acute side effects of lindane, such as dizziness and seizures, are quite obvious and can be fairly easily linked to use of the drug. But subtle impacts on brain development or impacts that may not become apparent for years are an entirely different matter. Animal tests and epidemiologic studies in people clearly demonstrate increased risks, but we will never know the extent to which lindane may have those kinds of effects in any individual person.

DecaBDE

Another chemical that you may be considering is deca-dibrominated diphenyl ether. I will refer to it as simply as deca.

Generalized Structure of PBDEs (where (m+n) = 2 to 10 bromines)

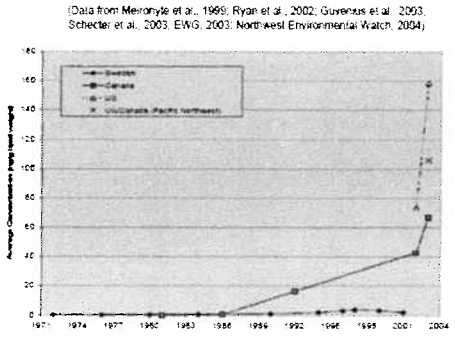


decaBDE 10 bromines
octaBDE 8 bromines
pentaBDE 5 bromines
etc.

Deca- is a flame retardant added to consumer products, including electronics, fabrics, and foam cushions. We now know that deca, like other BDEs, can migrate out of products into the general environment. Deca has been identified in food, wildlife, human blood, milk, and fat tissue. It is present in fish and sediments in the Great Lakes region.

This slide shows trends of all PBDEs in human milk (deca is among them)

Trends of PBDEs in Human Milk for Sweden, Canada, and the United States



Testing in one family in California showed that the young children had much higher levels of deca in their blood than their parents. Scientists recently concluded that contaminated dust inhalation and ingestion is likely to be an important pathway of exposure for young children. Mouthing of objects containing deca adds more.

Deca is persistent in the environment and to some extent is also debrominated to lesser-brominated BDEs in the environment. Debromination depends on environmental conditions, including duration and intensity of sunlight. One of the lesser brominated compounds that results is octaBDE, which is now banned in Michigan.

In animal testing, deca is also to some extent metabolized in the body to lesser-brominated BDEs that are themselves toxic and longer lasting than deca.

Deca is the only PBDE that has been tested for its capacity to cause cancer. Some evidence of cancer causation was found for rats following exposure to high levels of deca in their diet.

But the effects of deca on neurological development look like a much more sensitive endpoint--that is, an effect occurring at far lower levels of exposure.

In mice, deca causes persistent hyperactivity after administration of a relatively low dose when the test animals are just 3 days old or when administered for several days in a row during the newborn period. (6-20 mg/kg)

The brain growth spurt in mice and rats spans the first 3-4 weeks of post-natal life. In humans, a comparable spurt of brain growth begins during the third trimester of pregnancy and continues throughout the first 2 years of life. During this time the brain undergoes a series of critical developmental processes and their disruption can result in irreversible changes.

There are no published studies addressing the impacts of deca on brain development in humans. However, the brominated flame retardants have structural similarities to PCBs and PCBs have been widely studied in animals and people. One lesson learned: When comparing the sensitivity of neurodevelopmental effects in rodents and people, human infants are far more sensitive than the animals. That is, effects in human infants are detectable after exposures to PCBs that are thousands of times smaller than those necessary to show effects in animals. Some of these differences may be due to species differences in how the chemicals are distributed in the body or excreted, but they may also be due to increased sensitivity of the human brain.

In 2008, the Michigan DEQ released a report summarizing the science related to deca and other BDEs. They concluded that deca should be banned in MI, contingent on the availability of safe alternatives. The Dept. of Ecology in Washington, one of the states that has banned deca in products, has published a report on alternatives, which do exist.

The final chemical is

Bisphenol A:

Bisphenol A is a high production volume chemical used in many consumer products. It is polymerized into polycarbonate plastic, which is used to make food and beverage containers, including baby bottles, and a number of hard plastic products. It is also a component of the resin that lines the inside of many food cans, including infant formula. Some bisphenol A leaches out of the plastic container or resin can-lining and contaminates the food or beverage contents.

It has been known since 1936 that bisphenol A has properties similar to the human female hormone estrogen. No one initially paid much attention to that until it became evident that exposure to hormonally-active chemicals could disrupt normal development when exposures occurred during "windows of

vulnerability". But even then, since bisphenol A seemed to be a relatively "weak" estrogen, regulatory agencies had little concern about current exposure levels.

However, in recent years, concerns about low level health effects of bisphenol A have grown rapidly, based on new testing in laboratory animals and preliminary reports in humans.

Testing by the Centers for Disease Control confirms that bisphenol A exposures are virtually ubiquitous in the US. They identified the chemical in 93% of a representative population. Not all sources of bisphenol A exposure are known, but diet is generally thought to be a major pathway

Once ingested, bisphenol A is ultimately converted to an inactive form and then excreted in the urine. However, the ability to convert bisphenol A to the inactive form is not well developed in the fetus or infant. Consequently the active form of bisphenol A lasts much longer in fetuses and young children.

Scientists have used a wide range of doses when studying bisphenol A in animal tests. I will briefly comment on only those studies that have used bisphenol A at doses that are fairly close to what people are exposed to.

Health concerns about low-dose BPA: animal and human studies

Impaired brain development, behavior
Prostate, breast cancer
Onset of puberty
Diabetes
Cardiovascular disease

In animal tests, in which low doses of bisphenol A were administered during pregnancy, various impacts have been demonstrated. They include altered brain development (with changes in behavior and learning), accelerated onset of puberty, and changes in the tissue architecture of the developing mammary and prostate glands that persisted into adulthood. Those changes in the prostate and mammary gland made them more susceptible to developing cancer in adulthood.

Most of these studies have been carried out in laboratory rats and mice but a recent study in young adult monkeys showed that low levels of bisphenol A also impaired nerve connections in the primate brain.

In animals, bisphenol A also causes insulin resistance, a hallmark feature of type 2 diabetes, which is increasingly prevalent in our communities. Recently, scientists analyzed data from the Centers for Disease Control and reported that people with the highest levels of bisphenol A were more likely to have diabetes or cardiovascular disease. By themselves these findings of course do not prove a causal relationship, but they are consistent with the animal data and add to the concerns. It is entirely plausible, based on what we now know, that bisphenol A could be a newly identified risk factor for these common diseases—joining other well-established risk factors on a growing list.

In recent years, there has been considerable controversy surrounding the relevance and reproducibility of animal testing with low doses of bisphenol A. Some of the controversy, reported in the press, has taken on features of the lead debate in the 1960s and 70s. In 2008, after an initial review of data, and after they were sent back to consider data that they had ignored, a committee of the National Toxicology Program concluded that they had concerns about effects of bisphenol A on the brain, behavior, and prostate gland at current exposure levels in the US.

CERHR—Natl Toxicology Program

- **The NTP has *some concern for effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current human exposures to bisphenol A.***

NTP-CERHR 2008

Last year, the FDA reviewed several industry-sponsored animal studies and decided that polycarbonate was safe for use in food containers, including baby bottles. Then they convened their scientific advisory board to review their analysis. In a sharp repudiation, the science advisory board criticized the agency for disregarding a large body of published literature, some of which I have summarized here. The agency has now decided to continue to study the problem.

Last year, Health Canada decided to ban polycarbonate baby bottles and is developing strict leaching targets for bisphenol A in infant formula cans. They decided that current exposure levels in children are just too close for comfort to levels that cause effects in animal testing. And, they noted that alternatives for baby bottles exist today. Alternative resins for use in food cans also exist but their performance depends to a large extent on the chemical nature of contents of the can and no single material seems to be universally applicable.

In closing,

These four chemicals illustrate the problem of deciding when evidence is sufficient to act. Unlike in a criminal trial or deciding when something has been scientifically proven, where evidence must be beyond a reasonable doubt, or greater than 95% certain, public health interventions can and usually should be undertaken before that level of proof is ever established. Otherwise, opportunities to prevent unnecessary harm are missed.

For example, virtually everyone in the population is exposed to bisphenol A, including fetuses, infants, and children. The FDA says that they need to determine that current levels are not safe before acting. Health Canada has decided to act without requiring indisputable evidence of harm. They have decided that they know enough to act and there are safer alternatives.

We are unlikely ever to know if bisphenol A exposures in infancy or childhood increase the risk of breast or prostate cancer in people decades later. Just imagine the study that would be required to answer that question. And we may never know for certain if bisphenol A increases the risk of behavioral disorders or diabetes in people. But if it does increase the risk of these diseases or disorders, even a small amount, the public health consequences are huge, since even small increased risks, spread across an entire population, result in a very large disease burden. These are the realities that you will need to consider as you contemplate pending legislation for each of these chemicals.