Growing Up Toxic

Chemical Exposures and Increases in Developmental Disease

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EXECUTIVE SUMMARY

A growing body of scientific evidence shows that the widespread use of chemicals in our society harms our health and the health of our children. The incidence of many serious health problems – including premature birth, learning disabilities, behavioral disorders, asthma and allergies, early puberty, obesity, diabetes, reduced fertility, and some types of cancer – shows links with exposure to chemicals that can interfere with the process of growth and development.

In this report, we tell the story of the insidious impact of toxic chemicals, from the plastic ingredient bisphenol A to pesticides, drawing on evidence from more than 200 peer-reviewed scientific papers. Over and over, manufacturers have introduced new compounds into commerce – and only later do scientists discover these substances accumulating in our bodies or contributing to major health problems. Moreover, once the impact of a toxic chemical on our health becomes clear, barriers built into our chemical regulatory systems often prevent meaningful action. Manufacturers become tied to the profits chemical sales can generate, and exposure to offending substances continues.

It is unacceptable to use human lives – even unintentionally – as a giant uncontrolled experiment. Until our society reforms the way we regulate chemicals, this story will be rewritten time and again. The United States should remove the most dangerous substances from commerce and require manufacturers to ensure that the chemicals used in everyday products are safe for our families and our communities.

We are constantly exposed to toxic chemicals.

- When scientists look, they can find more than 100 potentially dangerous industrial chemicals and pollutants in the body of the average U.S. resident.
- These chemicals include substances banned in the United States since the 1970s, such as DDT and PCBs. Other widespread contaminants include plastic additives such as bisphenol A and phthalates, flame retardant chemicals, pesticides, non-stick chemicals used in cookware, carpet or clothing, and toxic metals such as lead.

Exposure to toxic chemicals comes from many sources.

- **The food we eat** exposes us to chemicals – such as DDT, PCBs, PBDEs, dioxin, and certain pesticides – that accumulate in fatty tissues and concentrate as they climb up the food chain.
- **Food containers** from soup cans to baby bottles contain Bisphenol A which leaches into the food

stored within. Some food wrappings contain phthalates.

- Our homes, from the materials used to build them to the furniture and appliances, contain toxic chemicals such as phthalates (in the vinyl flooring), stain-resistant perfluorinated chemicals (in the carpet), lead (old paint), and brominated flame retardants (in pillows, seat cushions and certain electronic devices).
- Objects in the home – or products used indoors – can release toxic chemicals which then accumulate in household dust, which people breathe, ingest, or absorb through their skin.
- Personal care products such as shampoos, lotions, deodorant and nail polish can contain phthalates that may be absorbed through our skin.

Chemical exposures can interfere with key stages of development, at levels commonplace in people today. Overwhelming evidence from studies with experimental animals and with people show links with many serious conditions throughout a human life.

- According to the U.S. National Academy of Sciences, just under half of all pregnancies in the country end in miscarriage or produce a child born with a birth defect or chronic health problem. Chemical exposures could be a factor. For example, laboratory mice exposed to bisphenol A develop chromosome sorting errors in their eggs that could lead to miscarriage or conditions like Down syndrome. The effect persists even into grandchildren that were not directly exposed.
- Premature birth has increased more than 30 percent in the United States since 1981. A variety of chemical exposures could be linked to this trend. Studies show that women exposed to higher levels of phthalates and some pesticides are more likely to give birth early or to give birth to smaller babies.
- From 2003 to 2007, the number of parent-reported diagnoses of attention-deficit hyperactivity disorder (ADHD) in their children increased more than 20 percent, with as many as one in ten children now affected. A variety of chemical exposures could be linked to this trend. Experiments show that children exposed to high levels of lead, PCBs , DDT, certain pesticides or phthalates in the womb or early in life are more likely to display inattention and poor impulse control at school, show developmental delays on tests of coordination, learning and memory or develop with lower IQ scores. Mice and rats exposed to small doses of flame retardants or bisphenol A in the womb or early in life develop hyperactive behavior and impaired memory.
- The prevalence of children with asthma has more than doubled since 1980. Children and adults in high-phthalate homes and workplaces are more likely to develop asthma symptoms. Some phthalates can cause hyperactive

immune responses when rubbed on mouse skin.

- Since 1980, the average age of first menstruation has advanced by 3 to 5 months, and the average age of breast development has advanced by 1 to 2 years. Rats and mice exposed to bisphenol A give birth to female children that reach menstruation earlier. The younger girls are when they enter puberty, the greater their risk of breast cancer later in life.
- In the last four decades, the prevalence of obesity among U.S. adolescents has quadrupled. Exposure to chemicals called "obesogens" at key points in development could lead to metabolic abnormalities that increase the odds of obesity later in life. For example, bisphenol A makes rodents grow larger and develop insulin resistance after they are exposed in the womb – factors that can lead to type 2 diabetes. The pesticides hexachlorobenzene, atrazine and tributyl-tin have similar effects.
- Sperm concentrations have declined 40 percent in the U.S. since World War II, and more than 7 million women today report symptoms of infertility. Sperm defects and infertility could be related to exposure to pesticides, dioxins, PCBs, flame retardants, phthalates, bisphenol A, and non-stick chemicals.

The timing of exposure is critically important. Often, exposures during key windows of development in the womb or early in life are most damaging.

- Windows of vulnerability when a key developmental process is vulnerable to disruption sometimes last only a matter of days – and damage can take the form of increased susceptibility to disease which might not become apparent until later in life. For example, experiments with rats reveal that exposure to a hormonally active chemical on gestational day 17 can cause birth defects in the reproductive system – but not if the exposure happens on gestational day 16.

Exposure to mixtures of chemicals can cause greater damage than exposure to individual substances alone.

- Traditionally, toxicologists have studied chemicals one at a time to determine how hazardous they are. This approach is likely to underestimate the potential danger because we are never exposed to just one chemical at a time in the real world. Scientists are discovering that mixtures of active chemicals – especially when they act on the same underlying mechanism of life – can have a greater impact together than any individual chemical alone.

Reducing our exposure to toxic chemicals can improve our health.

- Since lead was banned in gasoline in 1976, the number of children

with high blood lead levels has declined from 88 percent to just 1.4 percent, reducing developmental brain damage. Scientists estimate that the health benefits of this action produced more than $300 billion in value for the United States economy through 1999.

- After the U.S. EPA banned household uses of two pesticides (chlorpyrifos and diazinon) in 2001, women in New York City gave birth to larger, healthier babies.
- After the 1970s-era bans on DDT and PCBs, and efforts to reduce dioxin contamination, levels of these chemicals in our bodies are declining. Some scientists connect this trend with the slowing incidence of diseases like non-Hodgkin's lymphoma.

The United States should remove the most dangerous chemicals from commerce and require chemical manufacturers to demonstrate that their products are safe before widespread use. Chemical regulatory reform should:

- Empower regulatory agencies to restrict or ban the manufacture and use of chemicals that pose potential dangers;
- Require chemical manufacturers to prove that each chemical they market is safe; and
- Ensure public access to information on chemicals and their potential hazards through mandatory reporting requirements, including product ingredient disclosure.

INTRODUCTION

In April 2010, the President's Cancer Panel – a group of three distinguished experts appointed by President Bush to evaluate the nation's cancer program – raised the alarm about our ubiquitous exposure to toxic chemicals. "The American people – even before they are born – are bombarded continually," the panel wrote.[i] Chemical intruders invade our homes and our bodies without our knowledge or consent, making our lives a giant, uncontrolled experiment on the relationship between toxic chemicals and our health.

American children are growing up surrounded by synthetic chemicals. Before birth, they are exposed to synthetic chemicals in their mothers' bodies. Their toys, baby bottles and sippy cups are made with plastics that contain a cocktail of chemicals. The trees they climb and the fields they play on are treated with pesticides. They bathe with shampoos and soaps made with hundreds of manufactured additives. They sleep in beds and make forts from sofa cushions treated with flame retardant chemicals -- also found in the computers and electronic devices that they play video games on. And the toxic legacy of chemicals banned in the 1970s – such as PCBs and DDT – remains with children born today.

Toxic chemicals often do not remain securely contained within factory waste ponds or bound to consumer goods. Many chemicals escape from consumer products and end up in the dust and the air in our homes.[ii] These chemicals have become such a close part of our lives that scientists can find more than 100 industrial chemicals and pollutants in the bodies of every mother and child.[iii]

There are now more than 83,000 industrial chemicals on the market in the United States.[iv] While many of these chemicals have had many undeniable benefits for society, from improved medical care to increases in economic productivity made possible by electronics, these benefits have come with unintended consequences – harming our health often without our knowledge or consent.

Very little is known about most chemicals in commerce. The health effects of almost half of the major industrial chemicals have not been studied at all.[v] Hundreds of these substances likely have the ability to persist in the environment or accumulate in the food chain.[vi] Of those that have been studied, approximately 1,400 chemicals with known or probable links to cancer, birth defects, reproductive impacts and other health problems are still in use today.[vii]

As this report explores, scientists are continually uncovering more evidence linking chemical exposures – alone or in complex mixtures, and at levels experienced by average people today – to the development of a variety of debilitating health effects. Exposure to

these chemicals is a possible – and in some cases, likely – factor behind the rising rates of many health conditions from asthma and allergies, to learning disabilities and attention deficit disorder, to birth defects and cancer.

The President's Cancer Panel noted that the true burden of disease induced by chemicals to which people are regularly exposed in their daily lives has been "grossly underestimated." Diseases linked to chemical exposures "needlessly increase health care costs, cripple our Nation's productivity, and devastate American lives."[viii]

This is unacceptable. The panel concluded that the United States should act on what scientists know about chemical threats – even before we are certain beyond a shadow of a doubt that a particular substance is causing harm. The evidence connecting chemical exposures to developmental abnormalities is strong enough to justify a larger effort to prevent harm to children's health.

The United States must reform policies protecting public health from chemical exposures. Information must be available to make responsible choices as a society about which chemicals we choose to include in our lives – and our bodies. Consumers deserve the assurance that everyday products are safe to bring home from the store and to use in feeding, clothing, and caring for their families.

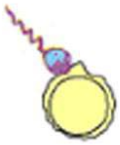
How Chemical Exposures May Be Harming Human Development

A human being begins as a single cell formed by the union of an egg and a sperm. Within this one cell is contained all of the ingredients required to produce a full-grown person. The process of growth and development unlocks this potential, leading from the first few cell divisions in the womb, to the birth of an infant, to learning and physical growth in childhood, to sexual development in adolescence, to full reproductive maturity in adulthood.

Unfortunately, the process of growth and development does not always occur flawlessly. Errors in the human blueprint in the egg or sperm may cause improper physical or neurological development. Problems can also occur when signals that guide the process do not happen as they should.

Public health researchers and agencies track the occurrence of some of these disorders. Although disease tracking capabilities are not nearly comprehensive enough, several alarming trends are arising from the data we do have. Taken together, they suggest that something is causing changes in fundamental processes of development. From conception to adulthood, many types of developmental disorders are rising, as summarized in Figures 1 and 2.

Figure 1: Timeline of Human Development



Conception

- Genetic damage in eggs or sperm can cause birth defects.

In the Womb

- Fetuses are most vulnerable to damage during specific windows of development in utero.
- According to the U.S. National Academies of Science, just under approximately half of all pregnancies in the country end in miscarriage, or produce a child born with a birth defect or chronic health problem.[9]

Birth and Infancy

- Premature birth has risen more than 30 percent in the United States since 1981.[10]
- Birth defects: Although rates of birth defects related to nutritional deficiencies have fallen, other types of birth defects have increased.
- The CDC reported an increase in deaths from birth defects caused by chromosome sorting errors in sperm or egg cells from 1980 to 1995.[11] The same chromosome sorting errors are the cause of Down Syndrome.
- The frequency of baby boys born with undescended testicles (cryptorchidism) or a malformed urethra (hypospadias) apparently doubled from 1970 to 1993, although incidence rates have appeared to stabilize since then.[12]

Childhood

- Learning disabilities in the United States rose 191 percent between 1977 and 1994.[13] Although learning disability incidence rates have declined

since the late 1990s, in part due to changes in diagnosis criteria, more than 5 percent of all schoolchildren are affected.[14]

- Parent-reported incidence of a diagnosis of attention-deficit hyperactivity disorder (ADHD) in their children increased more than 20 percent from 2003 to 2007, with as many as one in ten children now affected.[15]
- According to the most recent data available from the Centers for Disease Control and Prevention, in 2006, on average, one child in every 110 (one in seventy boys and one in 315 girls) was classified as having an autism spectrum disorder. The average prevalence of ASDs identified among 8 year olds increased 57% from 2002 to 2006.[16]
- The prevalence of children with asthma has more than doubled since 1980.[17] More than 10 million children (14 percent) in the United States have been diagnosed with asthma at some point in their lives.[18] Roughly 11 percent of U.S. children suffer from respiratory allergies, and 12 percent from skin allergies.[19]
- According to the U.S. National Cancer Institute, the overall incidence of invasive cancer in young people increased by 20 percent between 1975 and 2007.[20]

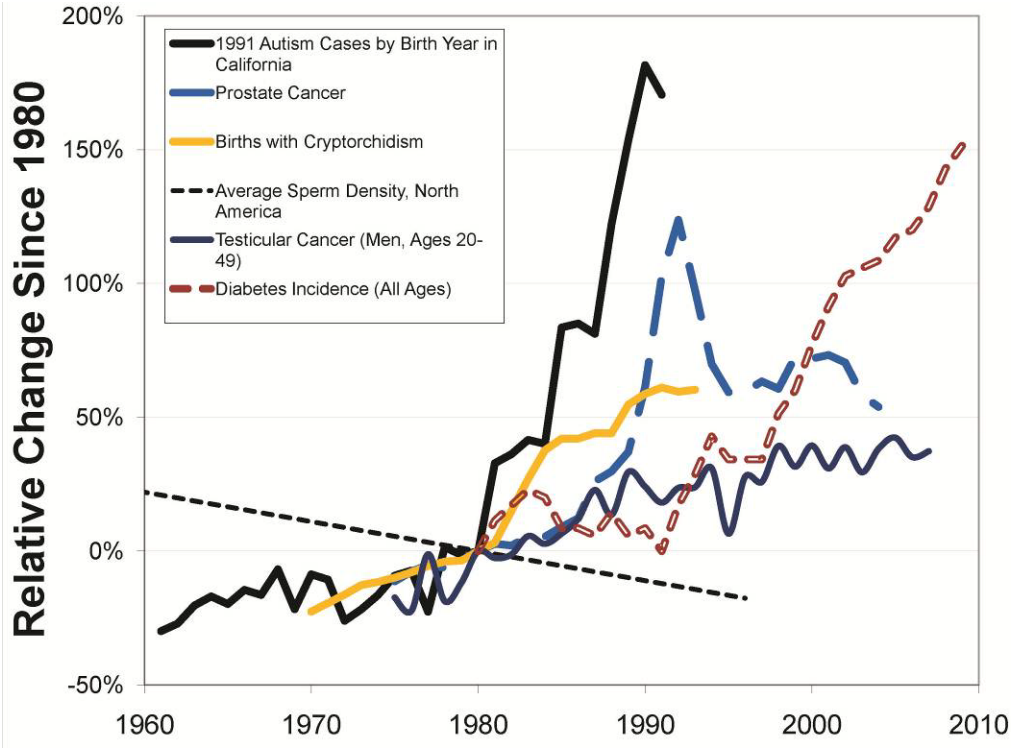
Adolescence

- Scientists are noticing changes in the timing of puberty that could signal an underlying developmental problem. Early puberty puts girls at greater risk of developing breast cancer later in life.[21] Since 1980, the average age of first menstruation has advanced by 3 to 5 months, and the average age of breast development has advanced by 1 to 2 years.[22]
- In the last four decades, the prevalence of obesity among adolescents in the United States has quadrupled.[23]

Adulthood

- Adults may face more obstacles when attempting to bear children. Scientists have found that sperm density has declined 40 percent in the U.S. since World War II.
- From 1975 to 2007, prostate cancer incidence climbed more than 75 percent.[24]

Figure 2: Relative Change in Selected Disease Incidence Rates over the Last 40 Years[25]



We have no completely satisfactory explanations for these rising trends in disease. Many different factors likely interact to produce these patterns, from heredity to changes in culture and lifestyle.

However, some scientists are testing the idea that exposures to toxic chemicals form a significant piece of the puzzle. Scientific evidence is building that toxic chemicals can interfere with the process of development in animals and people in ways that could lead to adverse health effects. First, they are discovering that chemicals can interfere with the timely and accurate exchange of information between cells in the body. Second, they are demonstrating toxic effects in animals given small doses of chemicals during specific – and sometimes very narrow – windows of time, particularly in the womb or during early infancy. Third, they are finding a variety of toxic chemicals in the blood and tissues of pregnant women and women of childbearing age at levels that could be contributing to health problems in any children they bear.[26] And most recently, they are discovering that toxic exposures may affect the exposed individual, her children – or even her grandchildren.[27]

WHAT ARE WE EXPOSED TO AND HOW?

From plastics to pesticides, the modern world contains potentially hazardous substances in far greater amounts than at any time in human history. Since World War II, annual chemical production in the United States has grown more than 20-fold.[28] Today, U.S. companies are the world's largest chemical producers, generating more than 1.2 billion tons of chemicals each year.[29] The chemical industry has introduced tens of thousands of new products – substances that did not exist anywhere on Earth before the industrial revolution.

SOME INDUSTRIAL CHEMICALS CAN INTERFERE WITH THE INNER WORKINGS OF LIVING CELLS

Scientists studying the effects of toxic chemicals on living organisms have discovered hundreds of different substances that could be harming human health by interfering with the process of development. These chemicals are capable of interfering with the transmission of signals within and between cells, the building blocks of life; or damaging important parts of cells, from genetic material to key proteins. Among these chemicals are:

- Legacy pollutants, including chemicals that have been banned in the United States for more than 30 years but can still be found in our bodies today, such as DDT, the notorious pesticide, and polychlorinated biphenyls, or PCBs, a class of chemicals that was often used as coolants or insulating fluids.
- Bisphenol A, a chemical originally invented as a synthetic estrogen hormone, but later used to make ubiquitous polycarbonate plastics, found in objects from food containers to compact discs to paper receipts.
- Phthalates, a class of chemicals often added to personal care products and to plastics like polyvinyl chloride (PVC) to make them flexible.
- Polybrominated diphenyl ethers (PBDEs), a class of chemicals used for their flame-retardant properties.
- Non-stick chemicals, including perfluoro-octanoic acid and related compounds, used in products like Teflon pans, stain-resistant carpeting, or GoreTex fabric.
- Dioxin, a byproduct of burning chemicals containing chlorine, such as polyvinyl chloride (PVC) plastic.
- Pesticides, a broad class of chemicals designed to impair or kill insects, fungus or weeds.
- Metals, including lead, cadmium, certain tin compounds, and silver nanoparticles now added to impart bacterial resistance to consumer fabrics.

Exposure to Toxic Chemicals Comes from Many Sources

Humans can be exposed through toxic chemicals from many different routes – from the food we eat, to the water we drink, to the lotions and other products we put on our skin, to the air we breathe inside our homes. For example:

- Food. Some chemicals – such as DDT, PCBs, PBDEs, dioxins, and certain pesticides – accumulate in fatty tissues and concentrate as they climb up the food chain. (Scientists call these chemicals "bioaccumulative.") One study showed that frogs can accumulate PBDEs from their food, concentrate the chemicals in their bodies, and then deposit higher levels of the chemicals in their eggs.[30] Vegetarians tend to have lower levels of PBDEs and phthalates, suggesting that these chemicals are present in meat and dairy products.[31] Pesticides can also become part of our diet after they are directly applied to crops.
- Food containers. Bisphenol A is used in the lining of most cans containing food, including infant formula containers, and it can contaminate food it comes into contact with.[32] People who drink from water bottles made from polycarbonate plastics, such as those used in office water coolers or in older Nalgene bottles, have elevated levels of bisphenol A in their urine.[33] Stain-resistant polycarbonate food containers can also contaminate food with bisphenol A. Non-stick cookware can expose users to stain-resistant chemicals. Phthalates can be found in some kinds of food wrapping.
- Building materials, appliances, and furniture. Vinyl flooring contains phthalates. Carpets can contain stain-resistant chemicals. Old paint can contain lead. Pillows, seat cushions in cars, and certain electronic devices expose people to toxic flame retardants.[34] Pressed-wood products, such as particleboard, plywood, and fiberboard; glues and adhesives; and certain insulation materials contain formaldehyde.[35]
- Household dust and indoor air. Everyday products and objects in the home can release toxic chemicals that then accumulate in household dust.[36] These chemicals – from pesticides to phthalates to flame retardants – make their way into our bodies through breathing or through our skin.[37] The levels of PBDE flame retardants in household dust, for example, are mirrored in the levels in residents' blood and in mothers' breast milk.[38] Young children in particular may be prone to ingesting contaminated dust – surveys show children have 10 times as much PBDEs on their fingers as adults.[39] One survey of homes in Arizona found more than 500 different chemicals in indoor air – including high levels of phthalates as well as 27

different pesticides.[40] Some pesticides are so resistant to breakdown (i.e. "persistent") that they still show up in household air and dust decades after they were banned.[41]

- Clothing and toys. Testing products on store shelves, California's Department of Toxic Substances Control found a child's necklace containing enough lead to be classified as hazardous waste, while a lunchbox contained both lead and cadmium in toxic amounts.[42] Some clothing manufacturers now treat products with silver nanoparticles to fight bacteria – but the silver can come out in the wash or in human sweat.[43]
- Personal care products. Use of products such as shampoos, perfumes, lotions and nail polish can lead to skin absorption of phthalates.[44] One study found that the more lotions, powders and shampoos parents used on their babies, the higher the level of phthalates that showed up in the babies' urine.[45]
- Medical products and other items. Some dental sealants expose patients to bisphenol A. Handling certain carbonless copy receipts after shopping can also lead to bisphenol A exposure. Medical plastics can expose patients to phthalates or bisphenol A. In one study, infants in neonatal intensive care units showed elevated levels of these two chemicals in their urine.[46] Even the protective coatings of some pills contain phthalates. Eating a single tablet of an over-the-counter medication in one experiment increased the amount of phthalates in a patient's urine by more than 100-fold.[47]

Chemicals absorbed into a woman's body can be passed on through her blood to a fetus in her womb, or to a nursing infant through her breast milk.[48] For example:

- Active bisphenol A travels across a pregnant woman's placenta and into the blood of the child in her womb.[49]
- Mothers and their breastfeeding babies have similar levels of phthalates in their bodies.[50]
- Stain resistant chemicals in a mother's blood can travel to her child through her breast milk.[51]
- Most women have PBDE flame retardants in their breast milk.[52]
- PBDE flame retardants can travel through a pregnant woman's blood into a child developing in her womb, where it accumulates in the child's liver.[53]

Our Bodies Are Vulnerable to Toxic Chemical Intruders

Given how ubiquitous synthetic chemicals are in our society, it should come as no surprise that scientists can readily measure the contamination in our bodies. When scientists look, they can find more than 100 potentially dangerous industrial chemicals and pollutants in the body of the average U.S. resident.[54] For example:

- A 2010 study found that the bodies of virtually all U.S. pregnant women – and possibly their unborn children – carry multiple chemicals, including some banned since the 1970s and others used in common products such as non-stick cookware, processed foods and personal care products. Researchers analyzed the data for 163 chemicals and detected about three-quarters of them at varying levels in some or all of the women. They found almost all – 99 to 100 percent – of the pregnant women carried polychlorinated biphenyls (PCBs), organochlorine pesticides, perfluorinated compounds (PFCs), phenols, polybrominated diphenyl ethers (PBDEs), phthalates, polycyclic aromatic hydrocarbons (PAHs) and perchlorate.[55]
- Scientists regularly find dozens of **pesticides** and their breakdown products in people. Scientists at the U.S. Centers for Disease Control and Prevention found at least three different pesticides in every single person they tested for pesticides in blood and urine. Out of 23 different pesticides under consideration, the average person had 13 in their body.[56] This includes legacy chemicals, some banned for more than 30 years, such as DDT.[57]
- **PBDE flame retardants** build up in fatty tissue and do not readily leave the body. As a result, these chemicals have been building up rapidly in our bodies – despite the fact that many states have taken action to ban certain types of the flame retardant chemicals. Over the last 30 years, PBDEs have built up in our tissues at exponential rates, growing by 100-fold.[58] People in the United States have PBDEs in their bodies at levels 10 times higher than people in Europe where there are more restrictions on these chemicals.[59] Two studies published in 2010 documented PBDE contamination in California children at 10 to 1,000 times higher levels than in Europe, and 5 times higher than in other locations in the United States – possibly due to the state's comparatively stringent fire safety standards.[60] Levels from individual to individual vary widely, suggesting that people's exposure to the chemicals also varies. Given how persistent these chemicals are – and the long useful lifespan for items containing PBDEs such as furniture and cars – these chemicals are likely to be with us for a long time.
- Certain types of **non-stick chemicals** are also extremely persistent and bioaccumulative. Scientists studying nearly 300 newborns in Baltimore found two of these chemicals (PFOA and PFOS) in just about every baby they tested – indicating

that children are exposed to these chemicals while in the womb.[61] Levels in U.S. adults tend to be higher than levels in residents of other countries, with more industrialized nations likely to show more contamination.[62]

- Bisphenol A does not accumulate in the body, but people are continuously exposed to it. The chemical is so ubiquitous in society that scientists almost always find it in the blood, tissues, and urine of adults and children across the United States. Scientists at the U.S. Centers for Disease Control and Prevention found bisphenol A in more than 90 percent of people sampled, at levels in urine samples ranging up to 16 parts per billion, with exposure remaining relatively steady over the past decade.[63] Because of differences in body size and ability to detoxify chemicals, scientists predict that babies are likely to have ten times more active bisphenol A circulating in their blood compared to adults.[64] Exposure to bisphenol A begins as early as the development of an egg cell within a woman's body, and continues through fetal development.[65]
- Just about every American has a variety of phthalates in his or her body. In 2009, the U.S. Centers for Disease Control and Prevention found measurable levels of 12 different phthalate compounds in urine samples from thousands of Americans.[66]

Phthalates

Phthalates are a family of chemicals, including diethyl phthalate (DEP), diethylhexyl phthalate (DEHP), dibutyl phthalate (DBP), and many other distinct types. The polyvinyl chloride (PVC) plastic industry uses large amounts of phthalates as additives to improve the flexibility of their products, including home siding, flooring, furniture, food packaging, toys, clothing, car interiors, and medical equipment including IV bags. In addition, other manufacturers use phthalates in personal care products such as soaps, shampoos, hand lotion, nail polish, cosmetics and perfumes, as well as industrial products like solvents, lubricants, glues, paints, sealants, insecticides, detergents, and inks.[67] The Worldwatch Institute estimated global phthalate production at roughly 5.5 million tons per year in 2000.[68]

Plastics labeled with the recycling code 3 are made from polyvinyl chloride (PVC), and likely contain phthalates.Scientists are finding phthalates everywhere they look. This class of chemicals is one of the most widespread contaminants in the environment today. In fact, according to EPA scientist Robert Menzer as cited by the Worldwatch Institute, phthalates are so common that, “it has become very difficult to analyze any soil or water sample without detecting phthalate esters.”[69]

KEY CONCLUSIONS TO DRAW FROM THE SCIENCE

Over the past several decades, scientists have been building up an increasingly robust – and frightening – body of evidence that toxic chemical exposures may be contributing to many of the major public health crises our society is experiencing. Scientists are demonstrating that:

- Chemical exposures can interfere with key steps in human development in ways that likely contribute to a range of diseases, from birth defects to learning disabilities to cancer.
- The effects of chemical exposures can appear at extremely low doses – within the range of exposures that people today experience in their daily lives. Experiments involving large doses cannot predict the impact of a small dose.
- Mixtures of chemicals that act via the same pathway can have a greater impact than any individual chemical alone.
- The timing of a chemical exposure is critically important – since key steps (or vulnerabilities) in the developmental process happen over a matter of days. Exposures during fetal development can lead to life-long consequences. Experiments must be carefully designed to detect these effects.
- The source of research is critically important when interpreting its results. Industries with a commercial interest in the regulatory process are much more likely to find no reason to be concerned about a particular chemical compared with scientists that have no conflicts of interest.

CHEMICAL EXPOSURES CAN INTERFERE WITH KEY STEPS IN HUMAN DEVELOPMENT

The human body depends on accurate and timely exchange of information in order to function correctly. Chemicals produced by the body carry information from one cell to another. For example, chemicals called hormones direct growth and development, regulate mood and behavior, adjust the flow of energy and nutrients, and time the menstrual cycle, among many other important functions.

The levels of hormones are finely controlled in the body. During development, changes in the levels of signaling molecules trigger important steps, from the folding of cells into tissue that will become the brain to the organization of cells into what will become the reproductive system. Hormones transmit signals at very low concentrations – equivalent to grains of salt in an Olympic-size swimming pool.

Rising hormone levels function like a finger flipping a switch. For example, during the development of a male, the presence of testosterone tells the brain

and body to develop male characteristics.

Scientists are demonstrating that some synthetic chemicals can act as signals within the body, in much the same way as hormones. In some cases, the chemical can "flip the switch" in the same way the hormone does. In other cases, chemicals modulate hormone levels by interfering with how the hormone is made or by blocking the signal at a different point. In other cases, chemicals can affect control over the translation of the genetic code, or "programming," that directs how cells work. These types of chemicals are known as endocrine disruptors.

An endocrine disrupting chemical can interfere with key steps in human development in ways that likely contribute to a range of diseases, from birth defects, to abnormal behavior, to cancer. The next major section of the report, on page 23, reviews many examples.

Effects Can Be Apparent at Extremely Low Doses

Although the amounts of chemicals found in a typical person are relatively small, these levels matter. Signals begin with tiny changes in the concentrations of hormones. Accordingly, exposure to low levels of contaminants can have significant effects.

For example, Dr. Frederick vom Saal at the University of Missouri has shown that the hormone estradiol can make cancer cells grow in a petri dish at very tiny part-per-trillion levels – roughly parallel to the area of a living room relative to the area of the entire United States.[70] Hormone signals are sent at these concentrations during the normal life of a cell.

In contrast, large doses can have completely different effects. Signals can be transmitted until the point where all available hormone receptors are bound. Toxic effects often do not occur until exposures reach far higher levels. For example, in Dr. vom Saal's experiment with estradiol, cells do not die until exposed to hormone levels more than a million times higher than necessary to make the cells grow.[71]

Endocrine disrupting chemicals often function the same way – causing one response at very low doses, and a completely different response at higher levels. Experiments must be designed to explicitly look for low-dose effects in order to find them.

People Are Regularly Exposed to Toxic Chemicals at Levels High Enough to Cause Harm

The levels of many toxic chemicals found in our bodies today are within the ranges shown to have profoundly damaging impacts on laboratory animals. For example:

- In 2007, 38 of the world's leading experts on endocrine disruption announced that average human exposure to bisphenol A – even in utero – is happening at levels shown to harm animals in laboratory experiments. Moreover, the scientists concluded that our exposure to

the chemical is higher than what the U.S. Environmental Protection Agency has deemed "safe."[72]

- According to a 2000 study, approximately one in three pregnant women in the Los Angeles area had known endocrine-disrupting chemicals in the amniotic fluid that surrounds a child in utero at levels approaching those that interfere with healthy development in mice.[73]

In some cases, scientists have even been able to document links between certain chemicals and human diseases. The next major section of the report (on page 23) will go through examples of some of these links in detail.

The Timing of Exposure Is Critically Important

Key steps in the process of the development of a human being can happen in very narrow windows of time, sometimes a matter of mere days. As a result, the timing of chemical exposure is critically important. If exposure happens during a critical window of vulnerability, damage can result. Moreover, sometimes that damage might take the form of increased susceptibility to disease, and it might not become apparent until much later on in life.[74]

In 2007, many of the world's leading experts on developmental biology and toxicology gathered to discuss the state of scientific knowledge on the topic. They concluded that:[75]

- Chemicals in the mother's body will be shared with a developing fetus or with her nursing baby – and the child's dose may in some cases be larger than the mother's relative to body weight.
- The process of development creates windows of vulnerability to a wide range of adverse effects.
- "Developmental exposures to environmental chemicals can lead to life-long functional deficits and disease."

Similarly, if exposure to a toxic chemical happens outside of a window of vulnerability, it may produce no effects. For example, experiments with rats reveal that exposure to a hormonally active chemical on gestational day 17 can cause birth defects in the reproductive system – that do not occur if the exposure happens on gestational day 16.[76]

Mixtures Can Have Greater Effects than Individual Chemicals

Traditionally, toxicologists have studied chemicals in isolation to determine how hazardous they are. However, this approach is likely to underestimate the potential danger. In the real world, we are never exposed to just one chemical at a time.

Scientists are discovering that mixtures of active chemicals – especially when they act on the same underlying mechanism of life – can have a greater impact together than any individual chemical alone. For example:

- The effects of bisphenol A can be amplified by a naturally-occurring chemical in soybeans.[77]
- Methyl mercury, polychlorinated biphenyls (PCBs), and PBDE flame retardants have an additive effect on a key signal in brain cells.[78]
- Scientists at the Technical University of Denmark and the University of London showed that a phthalate, two pesticides, and a steroid had a much greater effect on reproductive development in rats when mixed together – even when the level of each contaminant in the mixture was too small to cause an effect by itself.[79]
- Scientists at the National Oceanic and Atmospheric Administration showed that a mixture of pesticides is much more toxic to young Pacific Salmon than would be predicted based on simply adding up the potency of each chemical alone.[80]
- Dr. Tyrone Hayes and his colleagues at the University of California, Berkeley showed that a mixture of pesticides at levels actually found in the environment weakens the immune systems of tadpoles, leading to fatal infections. Exposing tadpoles to the pesticides one at a time did not produce this effect.[81]
- Dr. Kevin Crofton and his colleagues at the U.S. Environmental Protection Agency showed that a mixture of chemicals including dioxin and PCBs, each at levels that produce no effect, can together affect the function of the thyroid hormone system in rats.[82] Similarly, Dr. V.C. Moser at the U.S. EPA showed that a mixture of pesticides – each at levels which cause no effects – can together impair brain function and behavior in rats.[83]
- Researchers at the National Institutes of Health have shown that dioxin and other chemicals that promote cancer via the same mechanism – such as some PCBs and furans – have additive effects.[84]

Experiments that Show No Effects Are Not Necessarily Proof that a Chemical Is Safe

Experiments must be carefully designed to detect impacts – and experiments that show no effect are not necessarily proof that a chemical is safe.

The effects of endocrine disrupting chemicals are difficult to detect because the machinery of life is complex. Exposure to an endocrine disruptor can cause profound changes during specific windows of time, but have different or no effects at other times. Chronic exposures to low levels can have different effects than short exposures to high levels. As a result, scientists face enormous challenges trying to untangle all of the factors that can harm the normal course of development.

Traditional toxicology experiments have been designed to test the impacts of high-dose exposures and not low-dose effects. Many tests do not test a wide

enough range of doses, and many do not control adequately for the possibility that contaminants are present in all samples. As a result, many tests are more likely to detect toxic effects but not signaling effects, and therefore are predisposed to overestimate exposure levels that are safe.

Bisphenol A

Scientists first learned that bisphenol A could act as a synthetic substitute for the female hormone estrogen in the 1930s, close to 30 years after its invention.[85] However, in 1953 chemists discovered that bisphenol A could be made into polycarbonate plastic. Despite the fact that bisphenol A was known to be active in the human body, it went on to become commonplace in the manufacture of a variety of materials not meant to be drugs.

Bisphenol A is one of the top 50 products produced by the chemical industry, generating revenues exceeding $6 million per day in the U.S., Europe, and Japan.[86] Market forecasters predict that industry will manufacture 14 billion pounds of the chemical per year by 2015.[87]

Plastic items made from polycarbonate can sometimes be identified by the recycling code "7," unless the label also indicates the item is "BPA-free."

Several states and cities have taken action to restrict the use of bisphenol-A in children's formula containers, sippy cups, or other food containers, including Connecticut, Minnesota, Washington, Wisconsin and the city of Chicago.[88]

The Source of Research Can Affect Its Conclusions

The source of research is critically important. Industries with a commercial interest in the regulatory process are much more likely to find no reason to be concerned about a particular chemical in comparison with scientists that have no conflicts of interest.

The most well-known example of this phenomenon occurred when Philip Morris and the tobacco industry worked to undermine the scientific evidence that smoking and second-hand smoke was harmful to human health.[89] More recently:

- Dr. Frederick vom Saal at the University of Missouri found that, through December 2004, 94 of 104 government-funded studies of bisphenol A, many conducted in academic laboratories, found evidence of adverse effects at relevant low-level exposures. However, none of the 11 studies funded by industry found such effects.[90]
- Industry contributions to the Environmental Protection Agency's evaluation of the hazards of vinyl chloride weakened the outcome. The industry downplayed risks of cancer at sites other than the liver, and managed to reduce cancer potency estimates by 10-fold – resulting in weaker regulations.[91]
- Dr. Tyrone Hayes at the University of California, Berkeley found that studies evaluating the hazards of the pesticide atrazine which were funded by atrazine's manufacturer, Syngenta, have been poorly designed, poorly executed and published with misleading representation of the results, claiming no impacts – while experiments from his own laboratory show reason for concern.[92]
- Research funded by companies with a financial interest in vindicating their products tends to be less reliable than research without such conflicts.[93]

Flame Retardants

Household products made from flammable materials, such as polyurethane foam in furniture and plastics in computers and electronics, contain chemicals designed to reduce the spread of fire in the event of an accident. One of the most common such additives over the past three decades are polybrominated diphenyl ethers, or PBDEs.

First introduced 30 years ago, these types of flame-retardant additives are now widely found in the environment. The levels of PBDEs found in some mothers and fetuses are at the levels shown to impair learning and behavior in laboratory experiments.[94]

State legislatures have passed bans of certain toxic flame retardant chemicals in California, Hawaii, Illinois, Maine, Maryland, Michigan, Minnesota, New York, Oregon, Rhode Island, and Washington.[95] American manufacturers of the "penta-" and "octa-" variants of PBDEs have voluntarily stopped manufacturing them. After Washington and Maine banned the "deca" variant of PBDEs, historically used in the largest quantities, the only two American manufacturers of this chemical agreed to end production, importation and sales of this chemical by the end of 2013.[96] Major electronics manufacturers, such as Apple, have already ceased to use deca.

There is no guarantee that alternative, substitute chemicals will actually be safer, due to weaknesses in state and federal chemical regulatory policies. For example, manufacturers initially introduced toxic PBDE flame retardants to replace chlorinated compounds that showed signs of toxicity, persistence in the environment, and the ability to accumulate in the food chain. Only later did scientists discover that PBDEs posed similar risks.

Now, some of the chemicals being used to replace PBDEs are showing up in wildlife, indoor air, household dust and in our bodies.[97] Ten articles in peer-reviewed journals suggest that there are detectavle amounts of the deca substitute decabromodiphenyl ethane (DBDPE) in the environment.[98] Very little hazard testing has been done on the PBDE alternate chemicals now in use.

LINKS BETWEEN CHEMICAL EXPOSURES AND IMPAIRED DEVELOPMENT

Scientists studying the impact of toxic chemicals on growth and development are discovering many possible connections between chemical exposures and a range of diseases that span the entire course of life, from conception to old age.

Increases in learning disabilities could be linked to chemicals that interfere with brain development, including toxic flame retardants, pesticides and bisphenol A. Increasing genital birth defects in males could be linked to chemicals that interfere with reproductive development, including pesticides and phthalates. Increasing rates of premature birth and earlier puberty in girls could be linked to chemicals that interfere with the reproductive system, including bisphenol A and phthalates. Chemical exposures could even be playing a role in trends toward increased obesity and diabetes and in the development of a variety of cancers.

In the following sections we walk through the course of human development, outlining the evidence supporting the role toxic chemical exposures may play in current public health trends.

PRENATAL DEVELOPMENT

The single cell that results from the union of a sperm and an egg contains all the information required to produce a human being. As the embryo grows within the uterus, cells develop specialized characteristics and functions, becoming limbs, hearts, eyes, brains, and all of the critical organ systems that make life possible. From the time parents realize they are going to bring a new life into the world, they wait with anticipation for the first outlines of shape and the first signs of movement.

After approximately 38 to 40 weeks of dramatic growth and development, babies are born and enter into direct contact with the world. However, for some parents, pregnancy might bring unexpected and possibly heartbreaking complications, from miscarriages to birth defects.

Inexplicably, a growing number of children are entering the world earlier than normal or with some types of birth defects. Premature births are becoming more frequent in the United States. Premature babies, defined as babies born more than three weeks early, face a higher risk of disrupted cognitive development or behavioral problems later in life. Male infants have a higher frequency of reproductive birth defects than they did 40 years ago. Infant boys with birth defects such as undescended testicles (cryptorchidism) and malformed urinary tracts (hypospadias), face an increased risk of testicular cancer and reproductive dysfunction. While a variety of factors could be responsible for this trend, scientists are discovering that chemical exposures – involving the parents' sperm or egg cells, or the developing fetus – may play a major role.

MISCARRIAGE

Even before conception, genetic damage to an egg or sperm can cause developmental problems for the resulting embryo. Severe genetic defects can lead to miscarriage before a woman even knows she is pregnant. For example, when chromosomes sort incorrectly in a father's sperm or mother's egg, diseases – or, more often, miscarriages – result. Incorrect sorting of chromosomes leads to conditions like Turner's syndrome, in which a female has only one X-chromosome and never develops ovaries; Klinefelter's syndrome, in which a male has one or more extra X-chromosomes and is sterile; Down syndrome, in which a child has an extra copy of chromosome 21 and suffers multiple mental and physical impairments; and miscarriages, when genetic problems disrupt development too drastically to make life viable.

Roughly 10 percent to 25 percent of human embryos have an incorrect number of chromosomes. Almost all of these end in miscarriage early in pregnancy[99].

And according to the U.S. National Academies of Science, just under half of all pregnancies in the country end with miscarriage, or produce a child born with

a birth defect or chronic health problem.[100]

Evidence Tying Chemical Exposures to Miscarriage

Scientists have discovered links between miscarriage and exposure to both bisphenol A and to pesticides – in laboratory animals and in humans.

Bisphenol A

Scientists have shown that exposure to bisphenol A can lead to inaccurate sorting of chromosomes during egg and sperm development – which is the largest known cause of miscarriage.

In 2005, Dr. Sugiura-Ogasawara and his colleagues at the Nagoya City University Medical School in Japan and his colleagues found that women with a history of recurrent first trimester miscarriages had bisphenol A in their bodies at levels more than three times higher than a group of women with normal pregnancy histories. Moreover, miscarried (or spontaneously aborted) fetuses showing improper chromosome sorting as a cause of the miscarriage came from mothers with even higher bisphenol A levels.[101]

Pesticides

Scientists have discovered links between exposure to a variety of pesticides and spontaneous miscarriage.

One study found an association between pesticide use in California and an increased risk of miscarriage caused by birth defects. Dr. Erin Bell of the University of North Carolina and her colleagues showed that mothers who live within a 9-square mile area in which commercial pesticide spraying takes place during pregnancy are 40 percent to 120 percent more likely to suffer miscarriages due to congenital defects.[102] The risk was greater for pesticide exposure during gestation weeks 3-8, the critical period when many organ systems first begin to take shape. Associations were apparent for five major classes of pesticides: organophosphates, carbamates, pyrethroids, and endocrine disrupting pesticides, but strongest with halogenated hydrocarbons (examples of halogenated hydrocarbons include endosulfan, lindane, and pentachlorophenol).

Dr. Warren Porter at the University of Wisconsin discovered that rodents exposed to low doses (commonly found in the environment) of a commercial herbicide mixture including 2,4-D have reduced litter sizes.[103] This experiment is striking in that very low doses – as low as one seventh of the drinking water standard set by the EPA – produced the greatest effect.

Finally, scientists have also uncovered links between the banned pesticide DDT and miscarriage. For example:

- Dr. Matthew Longnecker at the National Institutes of Health and his colleagues found that women with higher levels of DDT in their blood were more likely to have a history of miscarriage, testing blood samples taken in the early 1960s.[104]
- Researchers in China tracked hormone levels of newly married women, finding that higher DDT

levels in blood were associated with miscarriage before the women knew they were pregnant.[105]

Premature Birth and Low Birth Weight

Rates of pre-term birth (defined as giving birth at 37 or fewer weeks gestation) rose in the latter part of the 20th century in the United States. From 1975 to 1995, preterm delivery increased 22 percent among Caucasian women, from 6.9 percent to 8.4 percent of births.[106] The increase among African American women was smaller, 3.6 percent, but the percentage of pre-term births among African Americans is very high already, accounting for 16 percent of all births in 1995. The increase appears to be continuing. Researchers at the CDC observed the same general trend from 1981 to 2008, with premature births rising more than 30 percent.[107]

Evidence Tying Chemicals to Premature Birth and Low Birth Weight

A variety of factors, including an increase in the age of childbearing women, could explain part of this trend. However, exposure to chemicals in the environment such as phthalates and pesticide residues could also be contributing to the trend toward shorter pregnancies.

If chemical exposures are causing earlier deliveries, it could have serious consequences for the health of children later on in life. Children born prematurely and undersized face more challenges than the average child growing up, including a greater risk for hospitalization due to infections throughout childhood, reduced intelligence, and behavioral problems, including attention deficit hyperactivity disorder (ADHD).[108]

PCBs and DDT

In 2001, a research team led by Dr. Matthew Longnecker at the National Institutes of Health reported that women with the highest levels of DDT in their blood were more than three times more likely to give birth to a premature child.[109] And in 2008, a group of Danish scientists at the Statens Serum Institute in Copenhagen showed that women who ate more fish during pregnancy had higher levels of PCBs – the insulating chemical banned in the United States in 1972 – in their blood and gave birth to smaller babies.[110]

Phthalates

Chemicals still in widespread use today – such as phthalates – may also affect delivery timing. For example, in 2003, a group of Italian scientists found phthalates and their breakdown products in the blood of newborn infants, with higher levels leading to a higher incidence of premature delivery.[111] They report that on average, babies exposed to common phthalates enter the world a week earlier than babies with less exposure. In 2009, Dr. John Meeker and his colleagues at the University of Michigan found that women in Mexico with higher levels of phthalates in their blood during the third trimester of pregnancy were two to four times as likely to have their babies early than pregnant women with lower phthalate levels.[112]

One theory for how this effect might come about holds that phthalates cause inflammation in the womb, which could cause premature labor.[113]

Pesticides

Scientists have associated several different pesticides with reduced birth weight. For example:

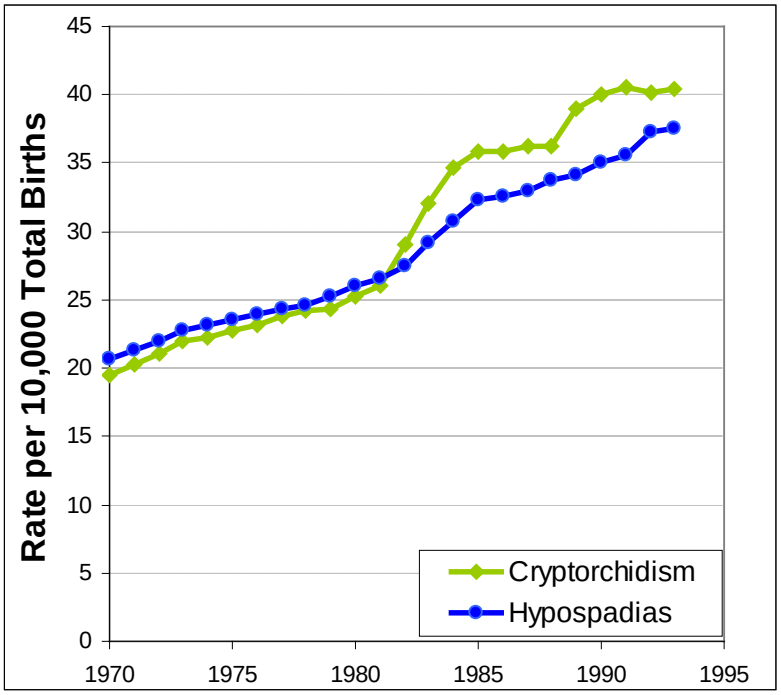
- Dr. Mark Robson's laboratory at Rutgers University in New Jersey found that women with higher levels of the herbicide metolachlor in their bodies gave birth to smaller babies.[114] Metolachlor is used in agriculture and along roadsides, and contaminates water supplies through runoff.
- Dr. Mary Wolff at the Mt. Sinai School of Medicine in New York City found that pregnant women with higher levels of DDT and organophosphate pesticides in their bodies were more likely to give birth to lower weight babies with smaller heads. This was especially true for mothers without the genetic ability to rapidly break down organophosphate pesticides.[115]
- Moreover, medication commonly used to halt pre-term labor and stave off birth could be making children more vulnerable to damage from pesticides. Dr. Theodore Slotkin and colleagues at Duke University Medical Center found that rat fetuses exposed to the pre-term labor drug terbutaline were more vulnerable to damage from the pesticide chlorpyrifos.[116] The damage affected regions of the brain associated with learning and memory, offering an explanation for previous studies that showed children whose mothers are administered terbutaline suffer cognitive defects.[117] According to the research team, more than one million women per year in the U.S. receive terbutaline or related drugs.

Non-Stick Chemicals

Several types of non-stick chemicals, which accumulate in the food chain and do not readily leave the body, could be contributing to the prevalence of premature birth and low birth weight. For example:

- Dr. Cheryl Stein at the Mt. Sinai School of Medicine in New York and her colleagues studied women living near a factory that manufactures anti-stick chemicals (specifically perfluorooctane sulfonate or PFOS). She found that women with blood levels of the chemical above the median were 50 percent more likely to have had a child with low birth weight, and 10 percent more likely to have given birth prematurely than women with lower exposure.[118]
- Dr. Benjamin Apelberg at the Johns Hopkins Bloomberg School of Public Health and his colleagues found that infants born in Baltimore who had higher levels of non-stick chemicals in their umbilical cord blood were more likely to be smaller than less

Figure 3: Trends in Defects in the Male Reproductive System in the U.S., 1970-1993.



exposed babies. Nearly every baby tested had detectable levels of the toxins in their blood.[119]

ALTERED REPRODUCTIVE SYSTEM DEVELOPMENT

Genital defects in males appear to be increasing. Although no researchers have precisely determined the cause, toxicants that affect the development of the reproductive system are a plausible factor. The number of baby boys born with hypospadias (a birth defect causing the opening of the urinary tract to develop on the underside of the penis) and with cryptorchidism (a birth defect disrupting the descent of the testicles into the scrotum) doubled in the last four decades.[120] In the early 1990s, these problems affected about four children in 1,000 births, up from two in 1,000 in 1970 (see Figure 3), although rates have apparently stabilized since then.[121] Around the world, cryptorchidism has increased from around 2 percent of births affected in the 1950s, to as much as 8 percent of births in the 1980s to 1990s, with apparently different rates in different countries.[122] Researchers however note that the apparent trends are not certain, due to deficiencies in international health monitoring systems and in comparing different studies.[123]

Exposure to chemicals in the environment could explain at least part of this apparent trend.[124] Scientists at Copenhagen University Hospital who study male defects note that in "perhaps

the majority of newborns with malformations of genitalia, no chromosomal or other genetic defect can be demonstrated with our current knowledge."[125] The causes of the disease appear complex, and could involve a range of environmental and genetic factors.[126]

PCBs and DDT

- Dr. Irva Hertz-Picciotto at the University of California, Davis and her colleagues found that women with the highest levels of PCBs in their blood were 33 percent more likely to give birth to a girl than women with the lowest levels. The researchers studied blood samples taken from pregnant women in the San Francisco Bay area in the 1960s, when PCB levels were generally higher than they are today. They hypothesized that PCBs could affect the ability of male sperm or embryos to survive.[127]
- In 2008, Dr. Françoise Brucker-Davis at the l'Archet Hospital in Nice, France, found that mothers with the highest levels of PCBs and DDT in their breast milk were three times as likely to give birth to a baby boy with cryptorchidism compared to mothers with low to medium exposure.[128] These chemicals may not cause the condition themselves, but rather could be an indicator of exposure to a mixture of some other chemicals to which people are exposed. For example, other experiments looking at DDT or PCBs alone did not detect an effect.[129]
- When Dr. Veeramachaneni and his colleagues at Colorado State University exposed pregnant rabbits to DDT or a pesticide called vinclozolin, resulting male babies showed higher rates of undescended testicles, atypical sperm, and sexual dysfunction.[130]

Disruption of reproductive system development due to chemical exposures is not limited to males. For example:

- Dr. David Sassoon and his colleague Dr. Risheng Ma at the Mt. Sinai School of Medicine in New York found that PCBs at levels people are exposed to can initiate changes in the development of the uterus in mice. They also found that some mice are genetically more vulnerable to this effect. They concluded that the female reproductive tract can be "permanently reprogrammed after exposure even to weak estrogenic compounds" such as PCBs.[131]

Phthalates

Scientists have demonstrated that a variety of different phthalate chemicals, or their breakdown products, can cause reproductive system defects in male rodents.

- In 2000, Dr. L. Earl Gray and his colleagues at the U.S. EPA reported that three types of commonly used phthalates (DEHP, BBP and DINP) disrupt sexual development in the male rat.[132] When female rats were fed

these phthalates during pregnancy, they gave birth to male pups that weighed less and showed symptoms of hypospadias, cleft phallus, reduced testes weight, and other reproductive malformations, including undescended testicles. Apparently, DEHP reduces testosterone production in the developing testes, interfering with the signals that direct normal male reproductive development.[133] A maternal dose of 750 mg/kg/day of DEHP after the second week of pregnancy reduces testosterone levels in the male testes of offspring to the same level as in female rodents.

- In 2004, Dr. Gray and others at the EPA followed up on this finding, showing that the phthalates DEHP, BBP, and DINP also reduce the levels of an insulin-like hormone.. Reduced activity of this hormone is another known cause of undescended testicles in mice.[134]
- Other research groups have implicated other common phthalates (dibutyl phthalate or DBP and diisobutyl phthalate or DiBP) as a direct cause of hypospadias and cryptorchidism in rodents. When female rats are fed DBP or DIBP at 500 mg/kg bodyweight during the third week of pregnancy, their male offspring suffer cryptorchidism, hypospadias, infertility, and/or other testicular defects.[135] DBP exposure at levels currently experienced by the human population alters the expression of genes necessary for testosterone synthesis in rats.[136]
- In 2007, Dr. Gray and his colleagues showed that a mixture of two different phthalates have an additive effect. Together, they can produce more damage to male reproductive development in the rat than either chemical alone.[137]

The evidence that exposure to phthalates in the womb can disrupt the development of the reproductive system in rats and mice is strong. And the defects seen in rodents are very similar to birth defects seen in humans.[138] Scientists are now uncovering evidence that phthalate exposure is a likely factor in the prevalence of reproductive system birth defects in humans. For example:

- In 2005, Dr. Shanna Swan at the University of Rochester in New York and her colleagues showed that exposure to a mixture of phthalates in the womb effects the development of the reproductive system in baby boys. The researchers measured phthalate levels in blood and urine samples from pregnant women representative of the general population. They later examined the reproductive development of baby boys by measuring anogenital distance – or the length of the perineum between the anus and the genitals, which is typically twice as long in males as females. They found that babies with the highest exposure to a mixture of active phthalates were 90 times

more likely to have a shortened anogenital distance. Moreover, boys with shortened anogenital distance were more likely to have reproductive system defects, including incomplete testicular descent, smaller penises, or small and indistinct scrotums.[139]

- In 2008, Dr. Gillian Ormond at University College in Cork, Ireland and her colleagues found that women exposed to hairspray or phthalates at work were more likely to give birth to boys with hypospadias.[140]
- Also in 2008, Dr. Romain Lambrot and his scientific colleagues in France discovered that exposure to the phthalate MEHP harms the development of cells that make sperm in human fetuses. The research team cultured cells from fetal testes, adding different doses of the phthalate, which caused the cells to die prematurely, without altering testosterone levels.[141] While the dose of the phthalate was higher than typical current exposure, they only tested one type of phthalate. A mixture of different chemicals might produce effects at lower concentrations.

Pesticides

Pesticide exposures could also be contributing to the observed upward trend in male reproductive birth defects.

- In a major study published in 2011, a team of British scientists at the University of London found that 30 out of 37 commonly used agricultural pesticides – used on crops such as strawberries and lettuce – had the ability to interfere with the male hormone signaling system that is critical for proper male reproductive development. Strikingly, 16 of those compounds had never before been identified as hormonally active.[142] The authors recommended that all pesticides be screened to determine if they could be toxic to male reproductive development. The study indicates that there are many potentially dangerous chemicals that scientists still know little or nothing about.
- At exposure levels far beneath those found in lakes, rivers, streams, and even drinking water, the pesticide atrazine causes male frogs to develop ovaries, abnormal testicles, or a mixture of ovaries and testicles. These effects occur at exposure levels more than 10,000 times lower than those previously identified as non-toxic to frogs, as low as 0.1 ppb.[143] In the mid 1990s, the U.S. Geological Survey looked for pesticide contamination around Los Angeles and through California's Central Valley as a part of the National Water Quality Assessment. They found atrazine at levels up to 730 times higher than the levels shown to cause reproductive development problems in frogs.[144] In some areas, atrazine was detected in more than half of all surface water samples.[145] Atrazine appears to affect the testosterone signaling pathway by promoting the

conversion of testosterone to estrogen. Adult male frogs exposed to 25 ppb atrazine show a ten-fold decrease in testosterone levels compared to controls – effectively lowering testosterone to female levels.[146]

- In one study, Danish women occupationally exposed to pesticides while working in greenhouses were three times more likely to have sons with undescended testicles than the general population in Copenhagen.[147] In another study, Danish women who gave birth to boys with undescended testicles had higher levels of a mixture of eight persistent and bioaccumulative organochlorine pesticides in their breast milk.[148]
- The pesticide methoxychlor can block an estrogen signal required for normal development of the uterus. Mice exposed to this pesticide while in the womb show altered expression of a gene necessary for healthy uterus development and function – and the effect lasts into adulthood.[149]

Bisphenol A, PBDE Flame Retardants and Non-Stick Chemicals

Other chemicals could be contributing toward the prevalence of reproductive system defects. For example:

- Female rats exposed to PBDE flame retardants while in the womb develop structural defects in their ovaries and develop fewer eggs.[150] Male rats show lower levels of testosterone, a shorter anogenital distance, altered timing of puberty, and feminized behavior.[151]
- Pregnant rats exposed to bisphenol A gave birth to female offspring with vaginal deformations, apparently caused by a disruption of the estrogen signal required for normal development.[152] The amount of bisphenol A required to show an effect is well within the range of levels found in many people today.[153]
- Male rats fed a type of non-stick chemical showed changes in the shape and size of the testes, altered hormone levels, cell abnormalities, and altered gene expression patterns.[154]

Other Birth Defects

The incidence rates of many types of birth defects in the U.S. have been declining with better nutrition and medical care. For example, adding folic acid to cereal in the 1990s has appeared to reduce the number of spina bifida defects. However, birth defects remain the leading cause of infant death, and the specific causes of most birth defects remain a mystery.[155] According to the CDC, infant deaths due to birth defects have not declined as quickly as other types of infant mortality over the last three decades.[156]

However, scientists face challenges in untangling the influences of increasing maternal age, increasing prenatal diagnosis of birth defects and elective termination, and other trends affecting infant death rates. While overall infant death rates are declining, important

questions still remain to be answered about the origin of many birth defects.

Chemical exposures are likely to be an important part of the story. For example:

Pesticides

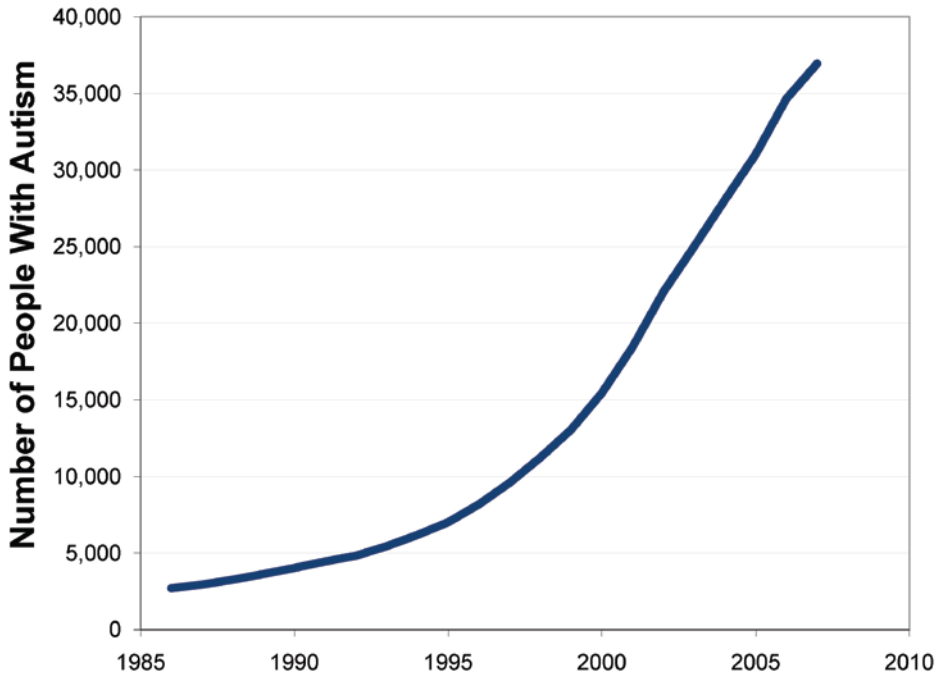
Dr. Dina Schreinemachers at the U.S. EPA found that human babies born in wheat-growing areas of the western U.S. (where chlorophenoxy herbicides like 2,4-D are used in large amounts) are more likely to have birth defects than babies in non-wheat growing areas of the West.[157] She found that:

Children born in high-wheat areas were 60 percent to 90 percent more likely to have birth defects in the respiratory system, circulatory system, and in the muscles and skeleton (fused digits, clubfoot, extra digits, etc.).

- The frequency of birth defects was highest for babies conceived in the spring, when herbicide spraying is most intense. Boys conceived in high-wheat counties in April and May were almost five times more likely to have a birth defect than boys conceived in low-wheat counties at other times of the year.
- Infant death due to congenital abnormalities was more frequent for boys in wheat-growing counties compared to low-wheat counties.

In addition to agriculture, herbicides like 2,4-D are used in home lawn care and grounds maintenance. Common lawn care products including Scotts and Weed-B-Gon weed killers and Miracle-Gro Weed and Feed contain2,4-D.[158]

Figure 4: Rising Numbers of People with Autism in California



Autism and ADHD Appear to Arise During Fetal Development

Scientists and doctors do not really know what causes autism, ADHD, or other learning disabilities. However, there are strong indications that the cause is an event during fetal development, and that genetic makeup may affect people's vulnerability.

Signs of autism exist in the womb, even though behavioral symptoms normally do not become fully apparent until well after birth. Children with autism show delayed brain growth *in utero* and accelerated brain growth in the months after birth.[159]

Early signs of ADHD exist as well, independent of any medication, indicating that increasing ADHD rates cannot be fully explained by cultural changes in society. Children with learning and attention disorders can show common characteristics at birth, including low birth weight and reduced head circumference.[160]

Dr. Francisco X. Castellanos at the New York University Child Study Center found that the brains of children diagnosed with ADHD, whether receiving drugs for treatment or not, lagged behind their classmates in growth over ten years.[161] Children with ADHD had brains on average 3.4 percent smaller than normal children, and the differences remained fixed. Dr. Castellanos believes that the fact that differences remain unchanged over time suggests that ADHD begins in the prenatal period or early in life.[162]

Evidence exists that changes in thyroid hormone levels may be part of the cause of ADHD. Dr. Peter Hauser at the National Institutes of Health found that families with a genetic problem that reduces the function of the thyroid hormone system were more likely to have symptoms of ADHD. In the study, 70 percent of children from families with genetic thyroid problems had ADHD, while the disorder affected 20 percent of children in families without thyroid problems.[163] In another experiment, Dr. Michael McDonald at the National Institute of Mental Health showed that mice with the same genetic defect in their thyroid hormone systems developed symptoms of ADHD, including hyperactivity and impaired learning ability.[164]

CHILDHOOD

As infants grow into children, they reach a number of traditionally celebrated milestones: taking their first steps, speaking their first words, and attending their first day of school. Parents often look forward to these moments and remember them with fondness. Parenting books describe the typical timelines of cognitive and physical development so that parents know when to look for the signs of proper growth in their children. For some parents, delayed or disrupted development will require minor adjustments in lifestyle and support from the community and schools. For other parents, more serious developmental disorders will mean years of testing, diagnosis, medication, and special education.

During their first few years, healthy children learn rapidly in a supportive, nurturing environment. However, if something has gone wrong with brain development, the effects begin to manifest themselves during this period.

LEARNING DISABILITIES AND BEHAVIORAL DISORDERS

Disorders of brain development can range in severity from severe mental retardation to more subtle problems such as attention deficit disorder. Small deficits in brain development could even result in simply the loss of a few IQ points – which could be hardly noticeable on an individual level, but have large consequences across society as a whole.

The causes of these disorders are mostly unknown, but scientists are accumulating evidence that chemical exposures can interfere with the process of brain development in ways that produce functional deficits. Scientists have identified more than 200 chemicals as possible factors in neurological disorders in humans, and more than 1,000 such chemicals in laboratory animals.[165]

Although no one agency tracks the prevalence of autism, learning disabilities, and related disorders in the United States, there are some indications that these problems are becoming more frequent. For example:

- Cognitive development experts report that learning disabilities in the United States rose 191 percent between 1977 and 1994.[166] Although learning disability incidence rates have declined since the late 1990s, in part due to changes in diagnosis criteria, more than 5 percent of all schoolchildren are affected as of 2009.[167]
- In 1985, there were 650,000 to 750,000 people diagnosed with attention deficit hyperactivity disorder (ADHD). By 2000, that number had risen to 4-5 million, mostly school-aged children.[168] Parent-reported incidence of a diagnosis of attention-deficit hyperactivity disorder (ADHD) in their children increased more than 20 percent from 2003 to

2007, with as many as one in ten children now affected.[169]

Autism and Learning Disabilities Are On the Rise

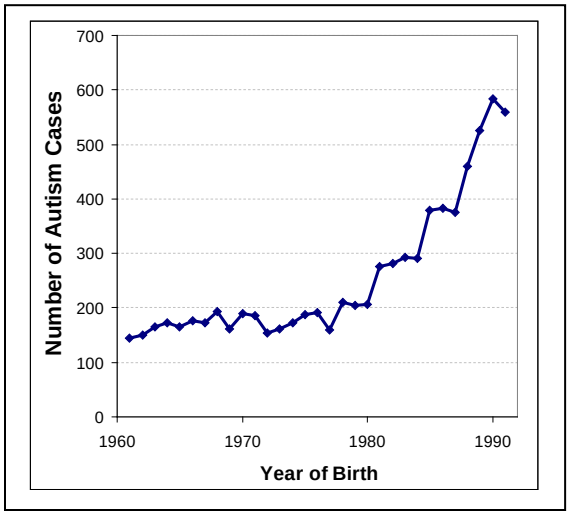
Autism spectrum disorders (ASDs) are a group of developmental disabilities characterized by atypical development in socialization, communication, and behavior. The symptoms of ASDs typically are present before age 3 years and often are accompanied by abnormalities in cognitive functioning, learning, attention, and sensory processing. The term "spectrum disorders" indicates that ASDs encompass a range of behaviorally defined conditions, including autism, Asperger disorder, and pervasive developmental disorder.

Children born with autism face a lifelong inability to form social relationships and an obsession with repetitive behaviors. According to the most recent data available from the Centers for Disease Control and Prevention, in 2006, on average, one child in every 110 (one in seventy boys and one in 315 girls) was classified as having an autism spectrum disorder. The average prevalence of ASDs identified among 8 year olds increased 57% from 2002 to 2006.[170]

The state of California has among the best available information tracking the incidence of neurological problems. The data there show a marked rise in autistic spectrum disorders, increasing on the order of ten-fold from 1986 to 2006.[171] (See Figure 4.) Children with autism were much more likely to have been born after 1980. (See Figure 5.)

When these trends were first publicized, some doctors questioned whether they were real or caused by confounding influences. In October 2002, researchers at the University of California at Davis laid these doubts to rest. They ruled out population increases, trends in diagnosis, and other potentially misleading factors for the observed increase in autism cases, reporting that "some, if not all, of the observed increase represents a true increase in cases of autism in California."[172]

Figure 5: Year of Birth Distribution of the 1991 Autistic Population (7,915)



PCBs and DDT

Scientists have known for decades that PCBs can interfere with brain development in humans. The use of the Children born to mothers exposed to PCBs by accidental poisoning in 1978 showed signs of irreparable damage associated with developmental toxicants: immune suppression, altered sexual development, delayed brain development and increased social dysfunction like hyperactivity and behavioral problems at school.[173] Over the next two decades, these results were confirmed at far lower levels of exposure by studies in North Carolina, Michigan, upstate New York, and the Netherlands: as the level of PCB exposure before birth rose, the mental and physical abilities of infants after birth declined. Even at very low levels, prenatal PCB exposure contributed to hyperactivity and attention problems discovered later in childhood.[174] The chemical has parallel effects on other mammals, such as monkeys.[175]

As recently as 2010, scientists found that the levels of PCBs in the general population were still high enough to affect thyroid hormone balance in mothers and their nursing infants, causing functional deficits.[176]

Evidence that DDT causes damage to the developing brain in humans has emerged as well. For example:

- Dr. Sharon Sagiv and her colleagues at Harvard found that children whose mothers had the highest levels of PCBs and DDT in their blood at birth were 26 to 79 percent more likely to display ADHD-like behaviors at school, including inattention and poor impulse control, as judged by their teachers.[177] A similar study at the State University of New York showed that women with higher levels of PCBs in their placentas at birth had children who developed with lower IQ scores.[178]
- Studies in areas where DDT has been used for malaria control or for agriculture show that women exposed to the pesticide – especially during the first trimester of pregnancy – are more likely to have children with impaired ability to perform on verbal, memory, quantitative, and perceptual tests associated with neurodevelopmental delay.[179]
- Both DDT and PCBs can affect thyroid hormone levels in pregnant women, which could explain how they interfere with brain development.[180]
- Moreover, PCB exposure before birth and while nursing reduces the ability of rats to perform basic tasks, such as escaping from a maze. Exposure to low doses of the chemicals interferes with the normal growth and development of the nerve cells associated with learning and memory.[181]

chemical in modern commerce – and the widespread contamination that resulted – provided the conditions for a giant experiment on the human population.

Bisphenol A

The use of bisphenol A, the foundation of polycarbonate plastic, could prove to be

another tragic experiment now playing out on the human population. Scientists are accumulating evidence – mostly in experimental animals at this point – that bisphenol A exposure could interfering with brain development. For example:Bisphenol A can mimic a signal that regulates how cells in the brain develop, called estradiol.[182] The chemical is biologically active and potent at extremely low levels, comparable to those found in people today. Estradiol plays an important role in the development of connections between nerve cells in the brain and long-term memory formation. It controls the process of cleaning out unnecessary cells when nerves are making connections between each other. Known as controlled cell death, this process is a crucial part of development. For example, controlled cell death transforms webbed hands and feet into functional appendages with separate digits by freeing each finger and toe. A similar process helps the brain to become functional as well. Disruptions in this process could interfere with the development of learning, memory and behavior.

- Bisphenol A can also affect the programming of gene expression during development. For example, mice exposed to bisphenol A in the womb show different patterns of gene methylation, which in one experiment appeared as different hair colors.[183] To the extent that gene methylation is involved in brain development, this effect of bisphenol A could explain its possible impact on brain function.
- In 2004, Dr. Masatoshi Morita and his colleagues at the Japanese National Institute for Environmental Studies found that a single dose of bisphenol A given to a 5-day-old rat leads to significant levels of hyperactive behavior, with greater hyperactivity resulting from higher doses of the chemical.[184] They also found that bisphenol A exposure changed how the dopamine signaling system developed in brain cells, resulting in fewer dopamine receptors and transporters. Dopamine is an important transmitter of nerve signals in the brain. Other Japanese laboratories recently showed that mice exposed to bisphenol A in development and infancy were temporarily more aggressive and had smaller brains, kidneys, and testes than unexposed mice.[185]
- In 2009, a different research group in Japan found that male monkeys – closely related to humans – behave more like female monkeys after birth when they are exposed to bisphenol A while in the womb.[186]
- In 2010, a group of researchers in Korea found that exposure to bisphenol A *in utero* and early in life causes mice to show increased anxiety and impaired memory. The researchers also detected functional changes in the dopamine signaling system in the brain – as well as another important signaling system – that could be linked to the observed changes in behavior.[187]

- Also in 2010, the first human study finding a link between behavioral impacts and BPA exposure in the womb was published. Researchers at Cincinnati Children's Hospital Medical Center used data from 249 mothers and their children, and found subtle, gender-specific alterations in behavior among two year old children whose mothers had encountered the most BPA early in pregnancy. During behavioral testing, girls whose mothers had high BPA levels during pregnancy were somewhat more aggressive than normal; boys were more anxious and withdrawn.[188]

Flame Retardants

Scientists have discovered that flame retardant chemicals can interfere with the thyroid hormone system and cause problems with brain development in experimental animals, in ways that are very similar to PCBs.

Flame retardants can interfere with the thyroid hormone system:

- Tetrabromobisphenol A and pentabromophenol (a related flame retardant and pesticide) are better able to bind to a part of the thyroid system than the natural hormone itself.[189] PBDEs have the same effect. When rodents are exposed to PBDEs at levels comparable to those found in people today, they show depressed thyroid hormone levels and physical changes in the thyroid gland.[190] These effects appear to be additive with the effects of PCBs and dioxins on thyroid hormone levels.[191]

Flame retardants also cause irreversible neurological damage to infant mice.

- Multiple peer-reviewed studies show that mice and rats exposed to low levels of PBDEs in the womb or as newborns develop learning and movement problems that worsen as the animals grow older.[192]
- The effect is also seen with deca BDE – the most widely used of the PBDE flame retardants, and the only one still being manufactured in the United States (through 2012).[193]

While scientists have yet to definitively prove that PBDEs are causing neurodevelopmental problems in humans, there are many reasons for concern.

- In 2010 researchers at the Columbia Center for Children's Environmental Health published a study which found that children who had higher cord blood concentrations of PBDEs at birth scored lower on mental and motor development tests at ages 1– 4 and 6 years. Developmental problems were found to be particularly evident for children at age 4, when verbal and IQ scores were lowered 5.5 to 8.0 points for children with the highest in utero PBDE exposures.[194]
- In the case of PCBs, humans were actually more sensitive than

rodents used in experiments by at least 1,000 times.[195]

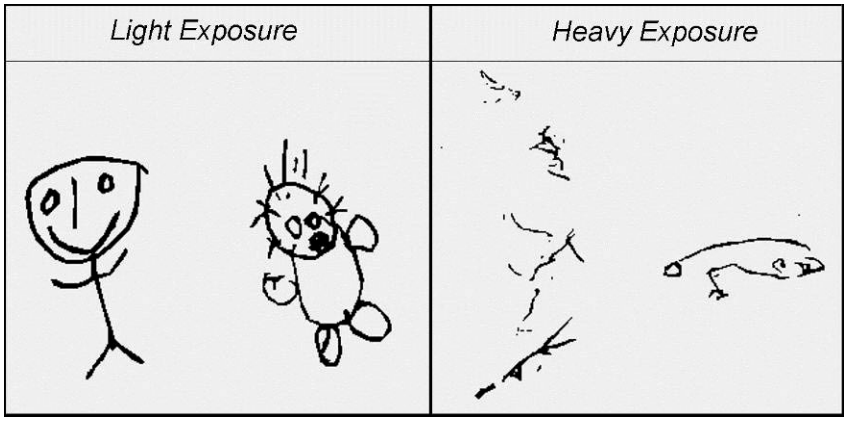
- A ground-breaking 2008 study found that babies whose mothers had higher levels of PCBs or PBDEs in their bodies were born with lower thyroid hormone levels, which could impact brain development.[196] This study was unique in that it detected the effect by controlling for whether the child was born naturally or by c-section. The authors hypothesized that the stress of a c-section could alter hormone levels in ways that would mask the impact of chemical exposures, making an association scientifically harder to detect.

Phthalates

Scientists are also discovering possible connections between problems with neurological development and exposure to phthalates. For example:

- Dr. Stephanie Engel at the Mt. Sinai School of Medicine in New York and her colleagues found that children whose mothers had higher levels of phthalates in their urine during pregnancy were more likely to show symptoms of ADHD and behavior problems during childhood.[197] Her research group also found that newborn girls of mothers with high phthalate levels were more likely to show decreased levels of attention and alertness.[198]
- Dr. Yun-Chul Hong's laboratory in Korea found that 8 to 11 year-old children with higher levels of phthalates in their urine were more likely to score poorly on tests of attention and impulsive behavior.[199]
- Dr. Shanna Swan at the University of Rochester and her colleagues found that women with higher levels of phthalate exposure during pregnancy were more likely to have male children with less male-typical patterns of play behavior at pre-school age, although the study had a small sample size.[200] Low doses of the phthalate DEHP interfere with the activity of an enzyme that is important in the development of the male rat brain.[201]

Figure 6: Drawings of People by 4-Year Old Children Exposed to Pesticides in Mexico's Yaqui Valley



Pesticides

Scientists have accumulated decades of evidence that a variety of pesticide chemicals can harm brain development in experimental animals, leading to irreversible defects in learning and behavior.[202]

However, even more dramatic evidence of chemical mixtures in use today affecting human cognitive development come from an agricultural area in Mexico, where two groups of children grew up separated by a small difference in geography, and by their exposure to pesticides.

Dr. Elizabeth Guillette at the University of Arizona and her colleagues in Sonora, Mexico looked at the effect of pesticides on preschool-age children in the Yaqui Valley, Mexico. Farmers in the community had used pesticides in the valley since the 1940s, while farmers in the foothills avoided pesticide use. Dr. Guillette compared children from both areas, and discovered dramatic functional differences.

While the children did not differ in physical growth patterns, children exposed to high levels of pesticides were less mentally able to perform basic tasks and showed behavioral problems. For example, Dr. Guillette asked 4-year olds to draw a picture of a person. Less-exposed children were able to produce recognizable drawings, while children with high levels of pesticides were not. (See figure 6.) Heavily exposed children were also deficient in stamina, balance, hand-eye coordination, and in short-term memory compared to their less-exposed counterparts. Subsequent research supports the evidence accumulated in the Mexico study that pesticide exposures at current levels are harming human brain development:

- A research group in Ecuador found that pregnant women exposed to insecticides while working in the flower industry gave birth to children that showed significant delays in intellectual development. By the age of 6 to 8 years, the children tended to be about two years behind normal on tests of coordination, learning and memory. The authors of the study concluded that "pesticide exposure therefore may contribute to a 'silent pandemic'" of damage to the human brain in today's society.[203]
- Studies of organophosphate and organochlorine pesticide exposure in Spain and New York City show associations with developmental delays and symptoms of ADHD, including hyperactivity, by 3 to 4 years of age.[204]

Non-Stick Chemicals

Non-stick chemicals could also be interfering in brain development and function in ways that could cause life-long problems. For example:

- In experiments with mice, exposure to the non-stick chemicals PFOA and PFOS in the womb can affect the function of proteins that are critical for the normal development and function of nerve cells in the brain.[205] Exposure leads to the development of what researchers call "deranged spontaneous behavior" in the mice that worsens with age.[206]
- Non-stick chemicals and other persistent pollutants in Canadian Inuit people are associated with abnormal levels of thyroid hormones, which are critical for normal brain development.[207] These chemicals reach every corner of the globe because they accumulate in the food chain and are part of the Inuit diet.
- In a study of 500 U.S. children between the ages of 12 and 15, researchers at Harvard and Boston University found that higher levels of non-stick chemicals in blood samples was associated with a doctor's diagnosis of ADHD.[208]

Toxic Metals

Scientists have long recognized that certain metals, such as lead, are toxic to human brain development and function. Despite the removal of lead from gasoline in the 1970s, the U.S. Centers for Disease Control and Prevention (CDC) estimates that 250,000 U.S. children aged 1-5 years have blood lead levels greater than "…the level at which CDC recommends public health actions be initiated." In 2004, CDC reported that at least a half million children in the United States suffer from irreversible neurological damage from lead poisoning.[209] And, according to the U.S. Environmental Protection Agency, one in six U.S. women has enough mercury in her body to risk brain damage in her children.[210]

Scientists are still discovering more ways in which toxic metals are causing

damage to the developing human brain. For example:

- Autistic children with higher toxic metal burdens – including lead and cadmium – tend to have more severe autism.[211]
- At levels of exposure below what the CDC recognizes as "safe," lead reduces children's intelligence, as measured by IQ. In a study of children in Rochester, New York, researchers found that blood lead levels between 5 and 10 micrograms per deciliter cut off 5 IQ points. The study authors note that, while this effect appears small individually, if U.S. society as a whole lost 5 IQ points, the number of children categorized as "gifted" (IQ greater than 130) would decline by 40 percent.[212] The impacts of childhood lead exposure are still visible in brain scans at adulthood.[213]
- Silver nanoparticles, used as an antibacterial agent in products such as clothing, could be an emerging new threat. In 2009, researchers at Duke University in North Carolina showed that silver nanoparticles could impair the growth and development of nerve cells with greater potency than the pesticide chlorpyrifos, a known cause of developmental problems in people. Moreover, the silver nanoparticles showed effects at levels close to those observed in human fetuses.[214]
- In one study, people who ate enough contaminated fish to raise methylmercury levels in their bodies to levels still considered "safe" had subtle changes to their heart rhythm that may affect their long-term health. While the fish also contained high levels of fish oils – including omega 3 fatty acids – that are generally considered to be protective for the heart, in this study, eating more fish oil in tandem with the methylmercury did not prevent the heart anomalies.[215]

Immune System Disorders

Some diseases affecting children – such as asthma and allergies – are closely tied to the function of the immune system. If the immune system is overly sensitized, it can react more severely to potential threats, causing asthma attacks or allergic reactions.

Asthma is much more common in children today than it was 40 years ago. The prevalence of the disease has nearly tripled in children since 1980.[216] More than 10 million children in the United States, or 14 percent of the population, have been diagnosed with asthma at some point in their lives.[217] It is the most common disease among American children.

Allergies and skin diseases like eczema are also common. According to the American Academy of Dermatology, the incidence of eczema has increased at least 30 percent since 1970. Ten percent of all children are born with the disease, and 60 percent of those will continue to suffer from it in some form later in their lives.[218] Additionally, roughly 11 percent of U.S. children suffer from respiratory allergies.[219]

The rising rates of asthma and allergies cannot fully be attributed to dirtier air or exposure to more cockroaches or dust mites. Exposure to chemicals may be playing a role in the incidence of the disease.

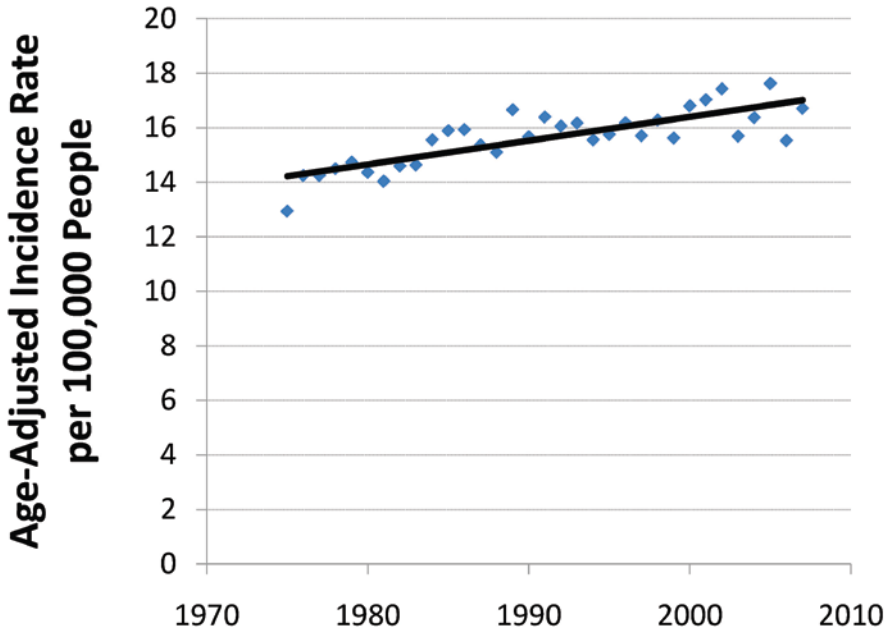
DDT and PCBs

- A set of chemicals with the ability to interfere with the estrogen hormone signaling system, including DDT and PCBs, can increase the speed and intensity of the immune response in immune system cells from rats and people. The effects of the chemicals are additive at levels that mimic a biologically-relevant signal, and enhanced by the addition of a dust mite allergen.[220]
- In another study, infants with higher-than-normal exposure to PCBs and DDT through their mothers were more likely to get respiratory infections in the first three months after birth. These infections are risk factors for asthma later in life[221]

Phthalates

- Scientists have found that rubbing the phthalate DBP onto mouse skin makes mice more prone to contact hypersensitivity allergies, like those caused by poison oak. The chemical modifies the mouse immune system, making the immune response stronger when the mouse encounters the chemical for a second time.[222]

Figure 7: Cancer Incidence in Young People (Age <20) Is Increasing



- Mice exposed to the phthalate DEHP through their mother's milk showed more severe skin allergy symptoms when exposed to an allergen than mice without phthalate exposure.[223] This is an effect that takes place at low exposures-- consistent with the theory that the phthalate is interfering with a signaling system important for the proper function of the immune system.[224]
- One group of researchers showed that Bulgarian children living in homes with the highest levels of DEHP were two to four times more likely to report symptoms of allergies and asthma than children in homes with lower levels.[225] A similar study in Sweden showed the same connection between DEHP and asthma, while also associating exposure to another phthalate with rhinitis and eczema.[226] Research also links DEHP exposure in adults work environments containing vinyl chloride plastics (which can contain roughly one-third DEHP) to adult onset asthma.[227]

Dioxin, Non-Stick Chemicals and Toxic Metals

Other chemicals can affect the development and function of the immune system, including dioxin, non-stick chemicals and lead. Mice exposed to dioxin while in the womb or early in life developed persistent changes in their immune systems that impaired their ability to fight off a flu infection later in life. The chemical changed the number of two types of white blood cells, suggesting a less effective immune response with a greater tendency toward inflammation. The effect was limited to the children rather than the mother, suggesting that dioxin impairs a key step in immune system development.[228]

- Mice exposed to non-stick chemicals through their skin – albeit at levels higher than the general public is exposed to – develop hyper-sensitive immune responses.[229]
- Lead can alter the development and function of immune system cells, promoting hyper-active immune responses that could tip the scales toward abnormal allergy and asthma symptoms.[230]

CHILDHOOD CANCERS

Every year in the United States, approximately 10,000 children develop cancer, most commonly leukemia or brain tumors.[231] Although advances in medical treatment have greatly reduced the number of children who die from cancer, it remains the leading disease-related cause of death for young people.[232]

Testifying before the President's Cancer Panel in 2008, Dr. Philip Landrigan – Director of the Children's Environmental Health Center at the Mount Sinai School of Medicine in New York – noted that the incidence of pediatric cancers is increasing.[233] Specifically, according to statistics kept by the U.S. National Cancer Institute, between 1975 and 2007:[234]

- The overall incidence of invasive cancer in young people increased by 20 percent;
- The incidence of leukemia increased 25 percent; and
- Cancers of the brain and nervous system increased 28 percent.

Dr. Landrigan noted that some of the increased incidence could be due to advances in diagnosis techniques, but felt that "this alone does not account for the continued inexorable rise. Serious consideration must be given to the possibility that environmental factors are involved."[235]

The U.S. National Toxicology Program has identified 246 chemicals in use today with known or probable links to cancer, noting that these "may constitute only a fraction of actual human carcinogens."[236]

Scientists have linked a variety of these chemicals to mechanisms that could be contributing to the incidence of cancer in children. For example, mothers administered the drug diethylstilbestrol (DES, in use from the 1940s through the 1960s) gave birth to daughters more likely to develop vaginal cancer early in adult life.[237] And parents who work in trades that increase their exposure to industrial solvents, or are exposed to solvents such as those in household paint, before or during pregnancy are more likely to have children that develop leukemia.[238]

Pesticides

Recent research has begun to establish similar links between exposure to various pesticide chemicals and childhood cancers. For example:

- After reviewing 31 separate studies published in 2009 or earlier, Dr. Donald Wigle and his colleagues at the University of Ottawa estimated that mothers exposed to pesticides at work more than double their children's risk of developing leukemia.[239]
- Dr. Youn Shim at the U.S. Agency for Toxic Substances and Disease Registry and his colleagues found that children whose parents were exposed to pesticides or herbicides at home or at work were about twice as likely to develop brain cancer.[240] Taking protective measures or washing after use reduced the apparent risk.[241]
- Researchers at a medical institute in France found that mothers who used pesticides at home during pregnancy were twice as likely to have a child who developed leukemia, and four times as likely to have a child who developed a type of cancer called Hodgkin's lymphoma.[242]
- Dr. Kori Flower at the University of North Carolina School of Public Health and her colleagues found that children of farmers licensed to apply pesticides face higher risks of developing cancer, particularly lymphomas. Additionally, fathers who did not wear protective gloves when using pesticides were twice as likely to have a child develop cancer.[243]

ADOLESCENCE

During adolescence, children become young adults. They grow taller, enter junior high school and high school, often awkwardly filling out the boundaries of their future selves. Children at this age develop the secondary sexual characteristics that will eventually bring them to sexual maturity, including pubic hair, active menstrual cycles, and other signs of reproductive development. Eventually, they develop the ability to have children of their own. Developmental textbooks generally describe this as the period between 10 and 15 years of age.

Unfortunately, several unexplained trends suggest that children face growing challenges in their health and development at this stage of life. First, girls appear to be reaching puberty at an earlier age than in the past. In some cases, girls develop breast tissue as early as three years of age. Second, increasing numbers of youth are becoming obese. Obesity is now one of the most serious public health problems facing the nation.

Although changes in nutrition, lifestyles, and genetics certainly play a role in the development of these trends, scientists are uncovering evidence that toxic chemicals may also be important contributing factors.

THE TIMING OF PUBERTY

Girls in the U.S. appear to be undergoing puberty at an earlier age than in the past. Since 1980, the average age of first menstruation has advanced by 3 to 5 months, and the average age of breast development has advanced by 1 to 2 years.[244] In a 1997 study of tens of thousands of girls visiting pediatricians, even at three years of age, 3 percent of African-American and 1 percent of Caucasian girls showed breast and/or pubic hair development. By seven years of age, the numbers increased to 27.2 percent and 6.7 percent, respectively.[245] The data for boys is less reliable, but suggests that boys may be maturing earlier as well.[246]

The trend also appears to be happening in other industrialized countries. For example, for children born in Denmark in 1969 were 4 to 6 months younger when they hit the peak growth spurt during puberty than children born in 1930.[247] Similarly, the age of puberty onset in Danish boys dropped about 3-4 months from the early 1990s to the mid 2000s.[248]

The younger girls are when they enter puberty, the greater their risk of breast cancer later in life.[249] Scientists conclude that "earlier development may not be healthy and may indicate environmental problems that need to be further researched and addressed." [250]

Chemical Exposures and the Timing of Reproductive Development

The cause of the trend toward earlier puberty is unknown, but exposure to toxic chemicals could be an important

factor.[251] A 2005 review of the scientific evidence found that a variety of compounds had the potential to affect puberty timing – with some pulling in opposite directions.[252] People are constantly exposed to a complex mixture of these substances.

A tragic accident exposing thousands of Michigan residents in the 1970s to polybrominated biphenyl (PBB), a now banned flame retardant chemical, proves that chemical exposures can cause earlier menstruation and pubic hair development in humans.[253] Girls exposed *in utero* to meat and dairy products contaminated with PBB, which was accidentally added to cattle feed in the place of a nutritional supplement, started menstruating a year earlier than normal. Other chemicals in wide use today may also have this effect.

Bisphenol A

Bisphenol A can alter the timing of puberty in experimental animals.

- When pregnant mice are fed very small doses of bisphenol A, their female offspring tend to grow larger and menstruate earlier.[254]
- Mice fed doses as low as 20 ppb bisphenol A during the third week of pregnancy give birth to daughters that had earlier vaginal opening (a developmental marker of sexual maturity in rodents), lower body weight at this point in maturity, and earlier menstruation than unexposed rats. A lower 2 ppb dose also causes significant difference in body weight at this point in maturity.[255]
- Rats exposed to bisphenol A after birth develop long-lasting changes to reproductive hormone levels which contribute to early puberty and aberrant ovulation patterns.[256]

Phthalates

One study of male rats and the phthalate DEHP suggests that the chemical can delay puberty development. Rats fed relatively high levels of DEHP from weaning to adulthood reached puberty later, showed inhibited testicle and reproductive tract development, and lowered testosterone production. Some types of rats appeared to be more genetically susceptible to these effects.[257]

No firm links have been made between phthalate exposures and changes in puberty timing in humans, because of the large number of variables and difficulty of sound experiment design. However, one study of Puerto Rican girls suggests that phthalates may be playing a role in trends toward earlier sexual maturity.

- Puerto Rican girls experience the highest rates of premature breast development ever recorded. Dr. Ivelisse Colon at the University of Puerto Rico and her colleagues searched for a link between chemical exposures and this phenomenon. They looked for foreign chemicals in blood samples from a group of very young girls with premature breast development (average age of 31 months). They found high levels of phthalates in these girls compared to controls in the

study.[258] In particular, the phthalate DEHP was seven times higher in girls with premature breast development than in the control group, suggesting exposure to food and drink contaminated by contact with plastic wrappings and containers and chewing or mouthing of plastic toys and pacifiers.

Flame Retardants

Flame retardant chemicals could be another piece in the puzzle of what could be causing altered puberty timing.

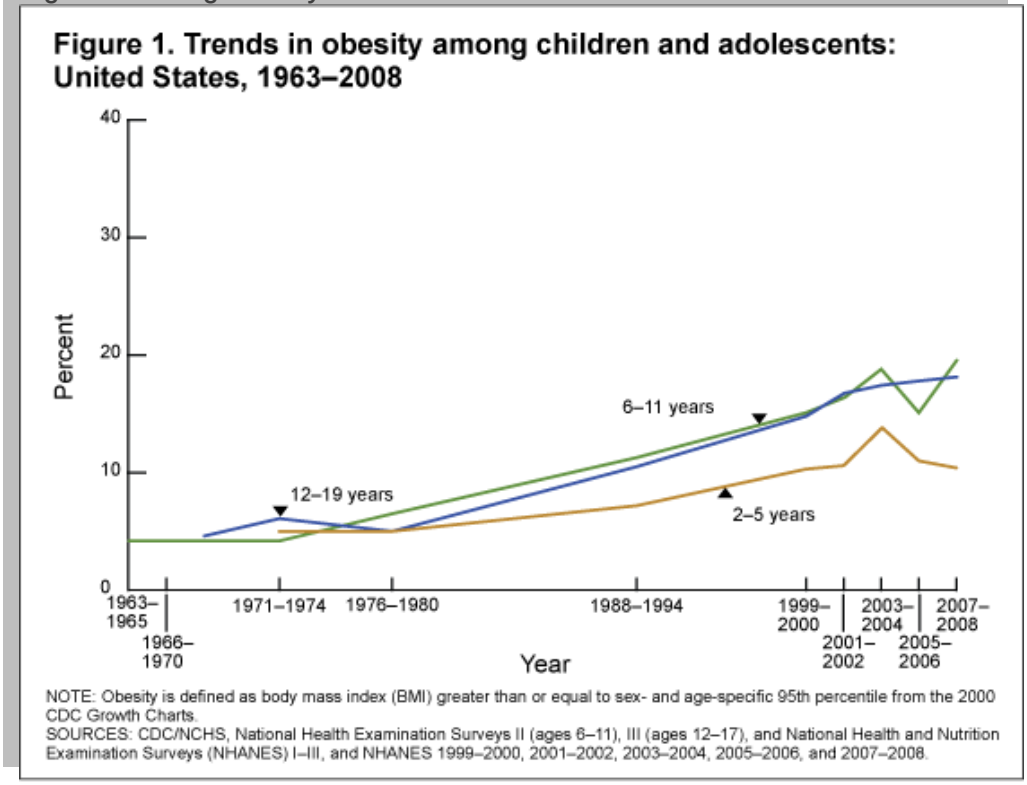
- In one experiment, male rats exposed to a common PBDE flame retardant mixture showed delayed puberty and reduced growth of the prostate gland and the seminal vesicles. The chemicals appear to inhibit the function of important male reproductive hormones and interfere with gene expression.[259]

OBESITY AND DIABETES

More American children are becoming obese, and growing up into obese adults. This trend has been ongoing for at least 100 years, and has accelerated since the 1970s.[260]

Even children less than four years of age are becoming overweight at higher rates.[261] In the United States overall, the number of overweight children between 2 and 5 years of age grew from 5.0 percent in the 1970s to 10.4 percent in 2007. The overall prevalence of this condition in children and adolescents quadrupled in the past four decades.[262] (See figure 8.)

Figure 8: Rising Obesity Trend in Adolescents[263]



Diseases associated with obesity are rising as well, especially type II diabetes.[264] In 1980 the age-adjusted incidence of diagnosed diabetes was 3.5 per 1,000 people. By 2008, that number had increased 131 percent to 8.1 per 1,000.[265]

In the United States., 34 percent of adults have metabolic abnormalities associated with insulin resistance.[266] Typical symptoms of insulin resistance are fatigue, obesity, accumulation of fat around the belly and difficulty regulating the blood levels of fat and sugar. Insulin resistance is the underlying cause of type 2 diabetes, cardiovascular problems and liver disease.

Evidence Tying Chemicals to Obesity

The causes of obesity are probably complex and varied. Decreased exercise and changes in diet – factors that get much attention – are likely candidates. However, the change in obesity patterns is happening faster than these factors can fully explain.[267] Scientists have uncovered hints that a range of other factors could be at play – including reduced sleep, air conditioning, less tobacco smoking, pharmaceutical prescription patterns, and the increasing average age of parents at birth.[268] And importantly, scientists are increasingly discovering that chemicals to which humans are widely exposed can influence the growth and development of their offspring in ways that could

increase the odds of developing metabolic problems that lead to obesity and diabetes.[269]

The fact that obesity is increasing in very young people as well as adults points to events in child development that could predispose people towards obesity. Starting in the womb, hormonal signals direct the development of fat tissues that take up and store energy in the body. Chemicals that interfere with these signals could influence the development of these tissues in ways that could increase the odds of developing metabolic diseases later in life. This idea is supported by studies demonstrating that both low and high birth weights are associated with a roughly one-third greater chance of developing diabetes in adulthood.[270]

Researchers call toxic chemicals with this effect "obesogens." A 2009 review of the science concluded that "these obesogens derail the homeostatic mechanisms important for weight control, such that exposed individuals are predisposed to weight gain, despite normal diet and exercise."[271]

DDT, PCBs and Dioxin

Banned chemicals to which humans are still exposed, such as DDT and PCBs, appear to affect the development and function of the metabolic system in both experimental animals and humans in ways that could contribute to obesity, diabetes and heart disease. For example:

- A team of researchers in Europe showed in 2009 that bioaccumulative pollutants found at levels in fish oil could cause insulin resistance in adult rats – a key symptom on the road to type 2 diabetes. The researchers fed unrefined fish oil from farmed Atlantic salmon – which contains pollutants such as DDT, dioxin and PCBs – or purified fish oil as a control, to adult male rats. The rats fed the pollutants accumulated more fat tissue and developed insulin resistance and liver disease.[272] The levels of contaminants in the rat's bodies where similar to those found in people today.
- A survey of people in Japan found that those with the highest levels of dioxin and PCBs in their bodies were five times more likely to have metabolic problems including obesity, glucose intolerance, or high blood pressure – symptoms connected with diabetes and heart disease.[273]
- In 2007, a group of researchers from Korea, the United States and Norway found that Americans with higher levels of persistent pollutants – including many organochlorine pesticides and PCBs – were more likely to have insulin resistance thus a higher risk of developing type 2 diabetes.[274] This same team found in 2006 a striking link between diabetes and blood levels of six persistent pollutants, including dioxin. The 20 percent of the study population with the most exposure was almost 40 times more likely to have diabetes

– and the association was even stronger in obese individuals.[275]

Bisphenol A

Drugs that mimic the function of the estrogen hormone can alter the development of the metabolic system in experimental animals, predisposing them toward obesity. For example, a team of researchers from the U.S. National Institutes of Health found in 2005 that mice exposed to a potent estrogen-like drug called DES while in the womb became "programmed" to develop obesity later in life.[276] *(See photo below)*

Bisphenol A has estrogen-like abilities and scientists are accumulating evidence that exposure to this ubiquitous chemical could be playing a role in obesity and diabetes prevalence. For example:

- In 2001, Dr. Beverly Rubin at Tufts University Medical School in Boston and her colleagues showed that bisphenol A makes rodents become fatter after they are exposed in the womb, confirming similar findings from Frederick vom Saal's laboratory.[277] When pregnant rats were fed 100 ppb bisphenol A during pregnancy through lactation, their offspring were notably heavier after birth and into adulthood.
- In 2002, a team of researchers at the Ehime College of Health Science in Japan first discovered that bisphenol A can trigger the conversion of fiber cells into fat storage cells.[278] In the body, this effect could result in larger numbers of fat cells developing. In addition to converting to fat cells, treated cells increased their fat content by 150 percent over 11 days. Combined with insulin, bisphenol A increased the fat content of cells by 1,300 percent. In 2004, another Japanese laboratory confirmed these findings, showing that bisphenol A alone and with insulin increased the uptake of sugar into fat cells.[279]
- In 2005, a group of Japanese researchers showed that long-term exposure to bisphenol A can cause pancreatic cells to release more insulin. The researchers concluded that if this effect happened in the body, it could "induce long-term hyperinsulinemia, resulting in obesity, exhaustion of pancreatic b-cells and diabetes."[280]
- Later that year, researchers in Spain and Mexico showed that in mice, bisphenol A exposure (at levels close to what humans are now exposed to) causes insulin resistance. The researchers concluded that bisphenol A exposure increases the risk of developing type 2 diabetes and high blood pressure.[281]
- In 2008, a group of researchers at the University of Cincinnati and several local hospitals found that bisphenol A interferes with the function of a fat-cell hormone that increases insulin sensitivity and reduces inflammation in human tissue. They tested fat cells obtained from people undergoing surgical procedures, adding bisphenol A at levels commonly

found in the average population. The results support the idea that bisphenol A exposure "could lead to insulin resistance and increased susceptibility to obesity-associated diseases."[282]

Pesticides

Exposure to a variety of toxic pesticides appears to contribute to metabolic disorders, obesity and diabetes. For example:

- Researchers in Spain found that mothers who had high levels of the persistent pesticide hexachlorobenzene in their blood gave birth to children who were significantly more likely to become overweight or obese in their first six years of life.[283]
- Mice exposed in the womb to tributyltin, a commonly encountered persistent chemical, accumulate excess fat in their livers and testes at birth, and grow obese into adulthood. A similar effect occurs in frogs exposed to the compound.[284] A 2010 follow-up study showed that pre-birth exposure to tributyltin causes human and mouse stem cells (which are flexible and have the ability to develop into many different tissue types) to become fat cells.[285]
- A group of researchers in Korea found that chronic exposure to low doses of the pesticide atrazine caused rats to develop insulin resistance and gain weight, particularly in rats fed a high-fat diet.[286] Interpreting the study, analysts at the non-profit Environmental Health Sciences concluded that "a 150 pound person exposed to low doses of atrazine eating a high fat diet would gain nearly 15 more pounds than someone else who was not exposed to atrazine but who ate the exact same foods."[287] This effect may in part explain observations that obesity is more prevalent in parts of the United States where atrazine use is high.[288]

The Developing Brain Is Vulnerable

The brain is the most complicated and delicate organ in the human body. Nestled within the skull, the brain consists of a vast collection of nerve cells designed to pass messages to one another, with more complexity and adaptability than any computer.

The development of the brain is a complex and lengthy process. Starting in the third week of pregnancy, the tissue destined to become the brain and spinal cord begins to differentiate from the rest of the embryo. This tissue curls into a tube during the fourth week. By the fifth week, this tube begins to divide into the different regions of the brain. Beginning in the eighth week, the brain tissue develops rapidly into the complicated structures that give children the capabilities to perceive and organize information, learn, remember, and grow into fully functional people. Most of the cognitive capability of the brain develops between the eighth week of pregnancy and the second year of life.[289] During this period, the developing brain is most vulnerable.

During this intensive period of development, nerve cells replicate, grow, and even die in response to chemical signals. These signals tell cells when and where to connect to other cells, what proteins to put on their surface, and when to die when their function is complete. Many types of chemical signals, including those provided by the thyroid hormone system, help direct brain development.[290]

Thyroid hormone signals are particularly important. Scientists know that disruptions in thyroid levels as early as week eight in the womb through the second year of life can disrupt children's normal brain development and impair their intelligence and coordination. Too much or too little thyroid hormone during brain development can decrease the number of cells in the mature brain, impairing neurological development, with consequences including learning disabilities, speech and memory problems, poor coordination and balance, or – in severe cases – mental retardation. Mothers with thyroid problems during pregnancy give birth to children suffering from varying degrees of these defects.[291] Reduced thyroid levels in the first few weeks of life for pre-term and low birth-weight babies are associated with increased risk of neurological disorders, including the need for special education by age nine.[292]

Scientists have shown that exposure to certain industrial chemicals and pollutants can disrupt thyroid hormone levels and interfere with brain development in experimental animals – and in humans – with life-long consequences for brain function and behavior.[293]

ADULTHOOD

By the time a child has become an adult, most growth and development is complete. The child is now fully developed, with bones that have stopped growing. All of the adult's organs are fully functional, including the reproductive system.

When adults begin to bear children the process of child development begins all over again. However, the influence of chemical exposures, beginning perhaps even before they themselves were born, may extend to their ability to reproduce.

Parents in the modern industrial world may now face more obstacles when attempting to have children. Over the past century, sperm production has declined in the average U.S. or European male. Regional differences in sperm health suggest an environmental influence may be responsible.

At the same time, adults begin to develop debilitating diseases, such as cancer. Scientists have uncovered a great deal of evidence that exposure to toxic chemicals – beginning in the womb – can influence the development of cancer later on in life.

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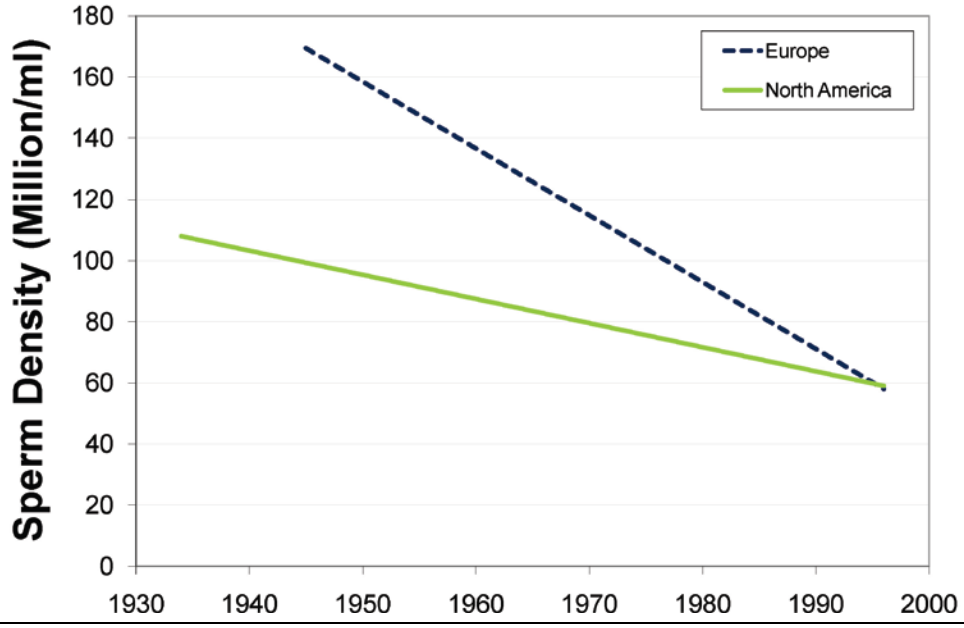
DECLINING FERTILITY

Roughly 10 to 15 percent of the population experiences infertility – although the cause of an individual's infertility is rarely known.[294] Some scientists have concluded that "decreasing trends in fertility rates in many industrialized countries are now so dramatic that they deserve much more scientific attention."[295]

According to the U.S. Centers for Disease Control and Prevention, the number of women reporting difficulty in becoming pregnant is climbing. In 1998, an estimated 4.9 million American women reported infertility. In 1995, the number was 6.1 million. In 2002, the number was 7.3 million.[296] The survey found the trend in younger women as well, suggesting that increasing numbers of women waiting to have children cannot fully explain the phenomenon.

Possibly contributing to reduced fertility, semen quality has apparently declined in industrialized nations over the latter half of the 20th century. In 2000, Dr. Shanna Swan at the University of Missouri found, based on studies published between 1934 and 1996, a statistically significant decline in mean sperm concentration in U.S. and Europe.[297] In the U.S., data showed an average decline in sperm density of about 1 percent per year during this period. (See figure 9.)

Figure 9: Average Decline in Sperm Density Across North America and Europe in the 20th Century



By 1996, the average trend in sperm density had fallen to 60 million per milliliter (ml). This raises the possibility that impaired sperm quality is leading to infertility problems in parts of the U.S. population. When sperm density falls below 40 million per ml, couples begin to have difficulty in becoming pregnant.[298] (The authors are unaware of updates to this research within the United States.)

One study in Scotland found a trend toward lower sperm quality in younger men.[299] This suggests that deficiencies in sperm production could be caused during the development of the reproductive system, in addition to being influenced by external factors later in life. It also suggests that growing exposure to an environmental contaminant during this period could be responsible for the decline in sperm quality. A related study of men in Massachusetts found that testosterone hormone levels declined in both the population and in individuals by an average of 17 percent from 1987 to 2004.[300]

Dr. Swan notes that while interpretation of the data on sperm quality trends remains controversial, there are clear links between certain pesticides and phthalates and reduced sperm concentration in individual men that adds plausibility.[301]

Infertility and Links to Chemical Exposures

Scientists have carried out dozens of experiments with animals that suggest that toxic chemicals at levels to which people are commonly exposed, either before or after birth, could affect adult fertility.[302] Both sperm and egg

development could be targets.[303] Moreover, toxicants that affect egg development could affect the fertility of children, grandchildren, or even great-grandchildren – because females develop all their eggs while in their mother's womb, and because some toxicants cause changes in gene expression that can be inherited across multiple generations. In one experiment, scientists showed that 90 percent of even the great-great grandsons of mice exposed to the pesticides vinclozolin and methoxychlor had reduced sperm counts, and 10 percent were infertile.[304]

DDT, PCBs, Dioxin and Flame Retardants

Some scientific studies have found links between DDT, PCBs, dioxin and changes in the reproductive systems of males and females that could contribute to infertility. For example:

- Studying men in an area of Mexico where DDT was used for malaria control, one research team found that men with higher DDT exposure had sperm that were less mobile and had more tail defects.[305]
- A research group at the University of Texas found that PCB exposure in rats caused changes in the reproductive system of granddaughters that could lead to reduced fertility.[306]
- A review of epidemiological studies found that higher PCB exposures were consistently associated with reduced sperm mobility.[307]
- Dr. Brenda Eskenazi at the University of California and her colleagues found that women exposed to high levels of dioxin when a chemical plant in Italy exploded in 1976 took longer to conceive. The women with the highest blood levels of the chemical after the accident were twice as likely to be infertile.[308] In 2010, Dr. Eskenazi and her team found that women in California with high levels of PBDE flame retardant chemicals in their bodies suffered a similar effect. For every 10-fold increase in PBDE levels, the women were 30 percent less likely to become pregnant in a given month.[309]

Pesticides

During the course of her research, Dr. Shanna Swan found that there are regional differences in sperm quality across the United States. These regional differences could offer clues as to why sperm quality overall has shown a decline, and could be related to differences in pesticide exposure.

- Dr. Swan demonstrated in the spring of 2003 that men from Columbia, Missouri, have lower sperm counts than men from Minneapolis, New York or Los Angeles.[310] She wondered if this could be due to higher levels of agricultural pesticide use in Missouri, with exposure potentially resulting from drinking contaminated groundwater.
- Dr. Swan subsequently showed that in fact, men with high exposure to pesticides, especially alachlor, diazinon, and atrazine, were much more likely to have

poor semen quality than men with lower levels of these pesticides in their urine.[311]

- In 2004, Dr. Russ Hauser and his team published a study linking exposure to the commonly used pesticide carbaryl to semen defects.[312] In 2005, Dr. Hauser's team found that carbaryl, in addition to the insecticide chlorpyrifos, correlated with reduced levels of the testosterone hormone in adult men visiting an infertility clinic.[313]\
- In 2007, a research team from Japan found that the widely used household insecticide permethrin can reduce testosterone levels and sperm production in adult male mice.[314] The herbicide atrazine shows a similar effect, acting by affecting the genes responsible for hormone production in testicular cells.[315]

Phthalates, Bisphenol A, Non-Stick Chemicals and Flame Retardants

Scientists have found evidence linking phthalates, bisphenol A, non-stick chemicals and flame retardants to altered hormone levels and sperm defects. For example:

- In 1998, Dr. Frederick vom Saal at the University of Missouri at Columbia and his colleagues discovered that male rats exposed to bisphenol A in the womb produced 20 percent less sperm after they matured, and showed physical changes in hormone-secreting glands.[316]
- In 2001, Dr. Motoharu Sakaue and his colleagues in Japan discovered that bisphenol A reduces the number of sperm in rats, even when given doses after puberty.[317] Dr. Sakaue concluded that bisphenol A retarded the development of germ cells that normally takes place as the male rat reproductive system matures from week 14 to week 18. In 2003, another Japanese lab demonstrated that fetal exposure to bisphenol A at concentrations found in humans causes reduced testes weight.[318]
- In 2003, Dr. Russ Hauser and Dr. Susan Duty of the Harvard School of Public Health found that men in the Boston area who had higher levels of two phthalates in their urine tended to have lower sperm counts.[319] In a 2006 follow up study, Dr. Hauser and his colleagues found more evidence linking exposure to the phthalate DBP at levels common in the American public to reduced sperm quality.[320]
- In 2004, a team of researchers in Germany showed that a single dose of PBDE flame retardants in the womb – at levels found in human breast milk – could cause male rats to develop with lower sperm counts after maturity.[321]
- Studying a group of men from an infertility clinic, Dr. Hauser's team linked phthalate exposure to damage to the genetic material (DNA) in sperm, and bisphenol A, phthalate and PBDE flame retardant exposure to reduced

levels of hormones necessary for healthy sperm production.[322]

- In 2009, a research team in India found that exposure to bisphenol A can reduce sperm quality in rats exposed in the womb and early in life – with effects persisting through the next two generations.[323] Another team from Canada found that low-level bisphenol A exposure causes human placenta cells to undergo programmed cell death – an effect that could have adverse effects for pregnancy, including "preeclampsia, intrauterine growth restriction, prematurity and pregnancy loss."[324]
- Also in 2009, a research team from Denmark found that men with higher levels of non-stick chemicals in their blood were more likely to have deteriorated sperm quality.[325]

ADULT CANCERS

Some scientists are uncovering evidence that the genesis of even adult cancers could begin early in development, when people are more vulnerable to damage from exposure to hazardous substances. Chemical exposures at an early age could cause genetic damage that could lead to cancer, or increase sensitivity to cancer-causing agents, later in life. Once cancer has developed, chemical exposures could also promote further growth and development of the tumor.[326]

The causes of most cancers are complex and largely unknown. Scientists estimate that genetic vulnerabilities make only a "small to moderate contribution to the incidence of prostate, breast and colorectal cancer," which typically develop in adulthood.[327] Exposure to the hundreds of chemicals in use today with the ability to cause or promote these diseases is a likely additional factor.[328]

Breast Cancer

Breast cancer is the most common form of cancer in U.S. women. For women in their late 30s to early 50s, breast cancer is the leading cause of death.[329]

While breast cancer incidence rates have mostly remained steady over the last 30 years, the Silent Spring Institute notes that breast cancer incidence rates are 5-fold different across the globe, with people living in developed countries facing a higher risk.[330]

Evidence Tying Chemicals to the Effect

Chemicals could be part of the explanation. In animal experiments, scientists have linked exposure to more than 200 different chemicals with increases in the incidence of mammary gland tumors.[331] U.S. chemical companies manufacture 29 of these chemicals at volumes exceeding one million pounds per year, and 73 have been used in consumer products or have contaminated food.[332] Most of these chemicals have not been studied in people.[333]

Legacy Pollutants

- A study of blood samples taken in the 1950s and 1960s showed that women exposed to relatively high levels of DDT before mid-adolescence were 5 times more likely to develop breast cancer

than women with lower exposures – and exposures later in life appeared to not increase risk. This study supports the idea that exposure to toxic chemicals during critical windows of vulnerability early in life can increase the odds of cancer at older age.[334] The authors noted that since many U.S. women exposed to DDT have not yet reached 50 years of age, "the public health significance of DDT exposure in early life may be large."[335]

- Scientists have observed similar effects with dioxin. Rats exposed to dioxin before birth developed changes in mammary cell function that could increase the vulnerability of breast tissue to other cancer-causing agents.[336]

Bisphenol-A

Multiple lines of evidence suggest that exposure to bisphenol-A in critical stages of development can increase breast cancer risk. For example:

- The research team of Dr. Coral Lamartiniere at the University of Alabama found that rats exposed to low doses of bisphenol-A through mothers' milk at a young age developed increased susceptibility to breast cancer later in life.[337] Exposure to bisphenol-A even in the womb caused persistent changes in the mammary gland that are consistent with cancer transformation.[338] The levels of exposure were similar to what people commonly experience today.
- Multiple additional rodent studies link exposure to very low and environmentally relevant levels of bisphenol A before birth to effects that persist long after exposure has ended, including early breast development and structural changes to breast tissues consistent with cancer formation, and greater susceptibility to cancer-causing chemicals.[339]

Prostate Cancer

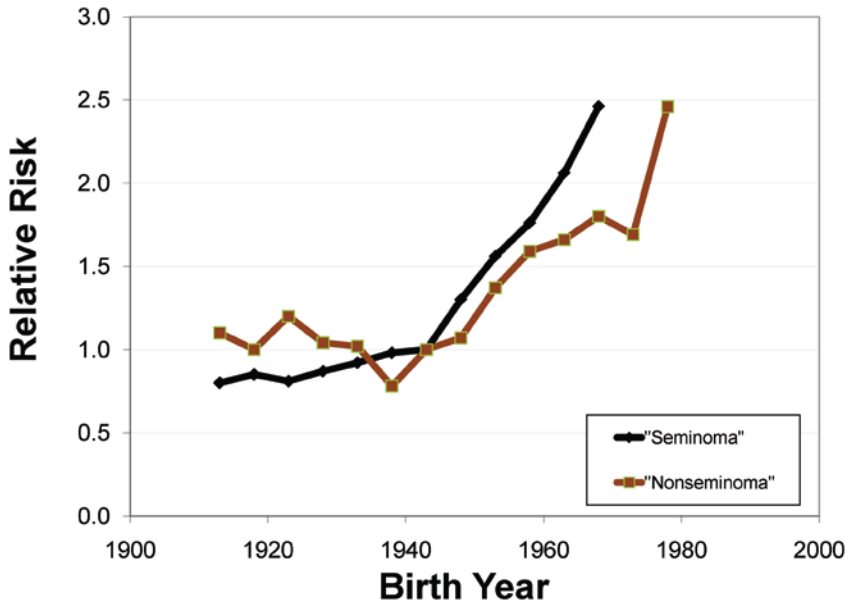
Prostate cancer is a disease that typically develops in adults. However, the prostate gland forms before birth. Exposure to biologically active chemicals during this critical window of vulnerability can alter prostate tissue in ways that increase the odds of developing prostate cancer later in life.

As of 2007, prostate cancer affects about 165 men out of every 100,000 of all ages. From 1975 to 2007, prostate cancer incidence climbed more than 75 percent.[340] In the early 1990s, incidence rates spiked dramatically. (See Figure 11.)

Evidence Tying Chemicals to the Effect

Scientists have tied exposure to a variety of chemicals with estrogenic hormone-like effects – including bisphenol-A, persistent organic pollutants and pesticides – to changes in prostate development that could be linked to cancer formation.[341]

Figure 10: Rising Risk of Two Types of Testicular Cancer in the U.S. by Time of Birth



Legacy Pollutants

In one experiment, men with prostate cancer or elevated levels of a protein associated with prostate disorders were likely to also have elevated amounts of several types of persistent organic pollutants, including PCBs, hexachlorobenzene, DDT metabolites, and chlordanes in their bodies.[342]orkers exposed to PCBs at two manufacturing plants in Massachusetts and New York showed higher likelihood of developing prostate cancer, as well as liver and stomach cancers.[343]

- Mice exposed to dioxin before birth develop prostate abnormalities that could lead to disease, including cancer, later in life.[344]

Bisphenol-A

Bisphenol-A exposure before birth causes changes to the development of the mouse and rat prostate gland in ways that can increase the risk of an enlarged prostate and future susceptibility to cancer.[345] In human prostate tumors implanted into mice, bisphenol-A interferes with common treatment procedures and accelerates the rate at which the cancer cells become more dangerous.[346]

Pesticides

- Men with a higher blood level of three (now banned) organochlorine pesticides – Beta HCH, trans-nonachlor and dieldrin – have a higher risk of prostate cancer.[347]

- Rats exposed to the fungicide vinclozolin before birth suffered from prostate inflammation later in life – a condition that can harm reproductive function and lead to prostate cancer.[348] These effects can be transmitted across multiple generations, long after exposure has ended.[349]

Testicular Cancer

Testicular cancer typically affects men early in adulthood – striking about 11 in every 100,000 men between the ages of 20 and 49.[350] Reproductive abnormalities, including cryptorchidism, poor sperm quality and infertility, are a significant risk factor.[351] Men with infertility problems and abnormal semen are almost 20 times more likely to develop testicular cancer than the average population.[352]

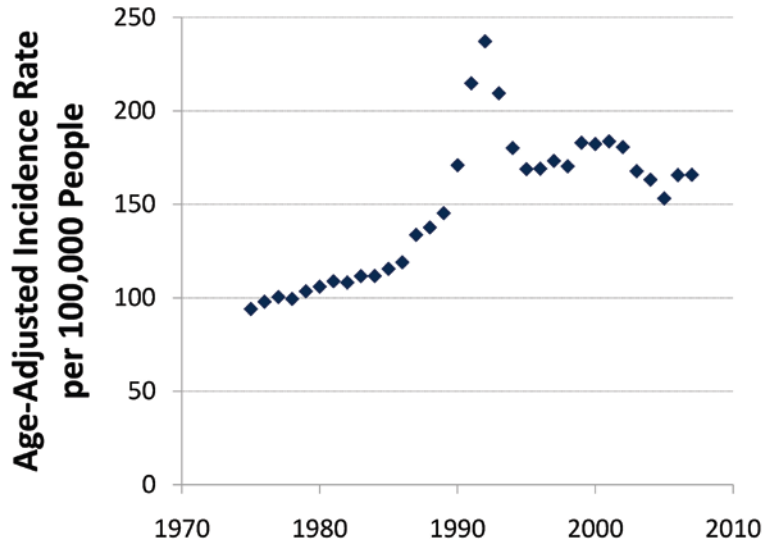
From 1975 to 2007, incidence of testicular cancer in the United States increased by 65 percent.[353] Additionally, the increase is correlated to year of birth – in other words, people who share a common time period of birth share a common risk of disease – suggesting that some early developmental event or prolonged exposure to an environmental contaminant may be the trigger for developing disease.[354] (See Figure 10).

Evidence Tying Chemicals to Adult Cancer Development

Impacts on reproductive health – from declining sperm counts to increased male birth defects to testicular cancer – may all result from exposure to improper signals during key windows of vulnerability during early development. Chemicals that could contribute to these diseases include phthalates, organochlorine pesticides, and PCBs. For example:

- Rats exposed to phthalates early in development develop cryptorchidism (undescended testicles), which is a risk factor

Figure 11: Prostate Cancer Incidence Spiked in the Early 1990s



for testicular cancer.[355] Phthalate exposure could also act after development to promote the growth of latent cancer cells. For example, one study of men exposed in the workplace to PVC plastics (which contain phthalates) showed significantly increased risk for one type of testicular cancer.[356]

- Organochlorine pesticides and PCBs could be linked to testicular cancer as well. One study showed that mothers with high levels of PCBs, hexachlorobenzene, and chlordanes were about 4 times more likely to give birth to sons that developed testicular cancer.[357]

SUCCESS STORIES: REDUCING CHEMICAL EXPOSURES CAN PROTECT OUR HEALTH

In the last four decades, regulatory agencies have occasionally taken action to reduce or eliminate exposure to a toxic substance after evidence of harm was discovered. Many of these efforts have successfully reduced human contamination and produced real improvements in human health.

Most recently, the U.S. EPA banned household uses of two pesticides, chlorpyrifos and diazinon. As these products were phased out of residential use in Manhattan, exposures in pregnant women declined and they gave birth to larger and healthier babies. In the 1970s, the EPA phased out leaded gasoline. As a result, the number of children in the U.S. with lead levels higher than the EPA health target of 10 micrograms per deciliter of blood has fallen by more than 85 percentage points since the 1970s. Finally, the bans on DDT and PCBs in the 1970s are yielding lower exposures to the chemicals that some scientists associate with a slowing of the incidence of non-Hodgkin's lymphoma.

Unfortunately, however, in all of these cases human exposures were allowed to reach the point where harm was unavoidable before action was taken.

Declining Lead Levels in Children after the Phase-Out of Leaded Gasoline

The story of lead in the United States is one of success, but also one of profound failure.

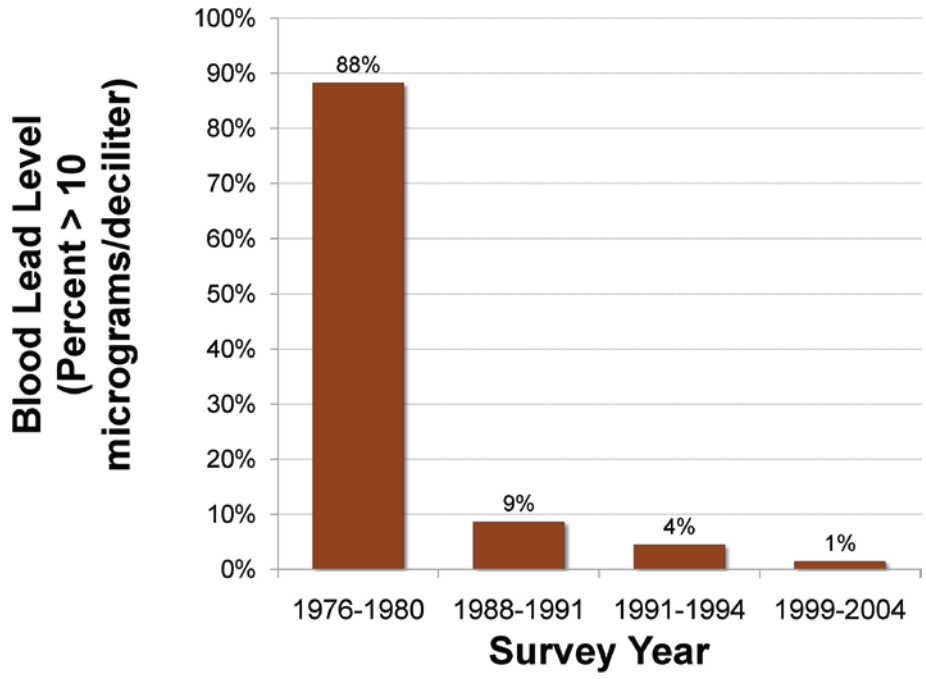
In the 1920s, oil companies decided to put tetraethyl lead into gasoline to keep car engines from "knocking." Emitted from the tailpipes of millions of cars, lead contaminated the blood of millions of mothers and children to the point where developmental damage, including brain damage, was unavoidable. Industry continued to promote the use of lead for decades, opposing efforts by the public health community and regulatory agency staff to ban lead in gasoline. Finally in the 1970s, advocates were successful in overriding industry concerns and winning a phase-out. The U.S. EPA began with mandated reductions of lead in gasoline and enforced a total ban in 1986. Other EPA actions eliminated lead from house paint. As a result, average blood lead levels for both children and adults have dropped more than 80 percent since the late 1970s.[358]

In 1997, then EPA administrator Carol Browner said, "The ongoing reduction in blood lead levels is a great American success story of environmental and public health protection. Years of aggressive action against lead exposure, particularly EPA's banning of lead in gasoline two decades ago, is yielding a brighter future for our children."[359]

Researchers estimate that the reduced exposure to lead between 1976 and 1999 produced more than $300 billion in benefits for the United States' economy.[360]

Although exposure is much lower today than in 1970, toxic lead levels still persist in close to half a million children – far too many to claim victory over this pervasive health threat. And even current standards for lead exposure are not fully protective. The researchers who estimated the economic benefits of U.S. action against lead also found that the current lead action level "fails to protect against most damage and economic cost attributable to lead exposure." [361]

Figure 12: **Declining Lead Levels in Children after the Phase-Out of Leaded Gasoline**



INCREASED BIRTH WEIGHT AFTER BAN OF TWO PESTICIDES

After the U.S. EPA banned household uses of two pesticides, chlorpyrifos and diazinon, in 2001, women in New York City gave birth to larger babies.

Until 2001, the pesticides chlorpyrifos and diazinon were commonly used to kill insects in homes, schools, gardens and agricultural crops. The EPA banned chlorpyrifos at the end of 2001 and diazinon at the end of 2002, due to significant evidence of harm to children. Products containing these ingredients began to dwindle on shelves while commercial applicators switched to new pesticides. (The products are still used in agriculture and can still be found on some produce, except for certain crops that kids often eat, such as tomatoes and apples).

In March of 2004, Dr. Frederica Perera, Dr. Robin Whyatt, and their colleagues at Columbia University studied the connection between exposure to these two pesticides and birth weight.

The researchers reported that pregnant women in upper Manhattan who had higher exposure to two common pesticides had smaller babies than women with less exposure.[362] Women with the highest pesticide exposures had babies that were more than 0.4 lb lighter and 0.33 inch shorter than babies from women with the least exposure. These findings suggested harm to the health of exposed children not just in the womb, but later in life as well. Interviewed in the *New York Times*, Dr. Perera noted that "Birth weight is a very good predictor of later health and development of children, including physical development, mental development, and school performance." But the most striking finding of the work was the immediate benefit of the phase-out of chlorpyrifos and diazinon from household uses. The scientists noted that after the ban, women had much less chlorpyrifos in their blood. Before the ban, one third of children fell into the high exposure group. From 2001 on, just one in 77 fell into that group. Remarkably, as pesticide levels fell, birth weight and body length rose.

The scientists were astounded that such an effect was visible so soon, since the phase-out of the pesticide products was not immediate. Surveyors still found remaining stocks of products containing chlorpyrifos and diazinon on the shelves of some stores in Manhattan as late as mid-2003. Accordingly, exposure levels should continue to decline as the products become scarcer. In the *New York Times*, Dr. Whyatt noted that "the exposure levels are still going down… We may continue to see added benefits of this ban over time."[363]

Declining Levels of Persistent Chemicals After Ban

Scientists are finding that the amounts of toxic chemicals that have been banned, such as PCBs, are declining in the average human body over time – although they are still present. In one study of women in Sweden, the levels of PCBs in breast milk fell by 4 to 9 percent per year from 1996 to 2006.[364] Dioxins and furans, byproducts of industrial activity and incineration, decreased as well.[365] In another study of pregnant women in the United States, PCB levels fell 17-fold over 40 years from the early 1960s to the early 2000s.[366] The United States discontinued PCB production in 1979 , but the general population is still being exposed to them at low levels, predominantly through diet.[367]

Scientists have some evidence that bans of dangerous persistent chemicals are yielding health benefits. For example, as exposure to the banned pesticides heptachlor epoxide and dieldrin decline, the incidence rate of non-Hodgkin's lymphoma (a disease to which these chemicals have been linked), appears to be slowing or holding steady in the United States and northern Europe.[368] Researchers have proposed that "The change in incidence of non-Hodgkin's lymphoma […] may serve as a good example of how prohibition and limitation of exposure may be reflected in cancer statistics some decades later."[369]

Flame Retardants – Declining In Europe, Still High in the U.S.

In Sweden, levels of certain PBDE flame retardants are also falling.[370] Sweden, along with Germany, was one of the first countries in the world to scale back the use of these toxic chemicals. Germany banned PBDEs in 1989 because of concern that they could form dioxins when burned. Sweden scaled back the use of one type of flame retardant in the mid 1990s.

Sweden took action after Dr. Ake Bergman and his colleagues at the University of Stockholm took advantage of Sweden's breast milk monitoring program, which enabled them to look back in time and document rising levels of toxic flame retardants in the breast milk of Swedish mothers.[371] The group discovered that concentrations of PBDEs in samples of milk from Swedish mothers had increased about sixty-fold from 1972 to 1997, doubling every 5 years.

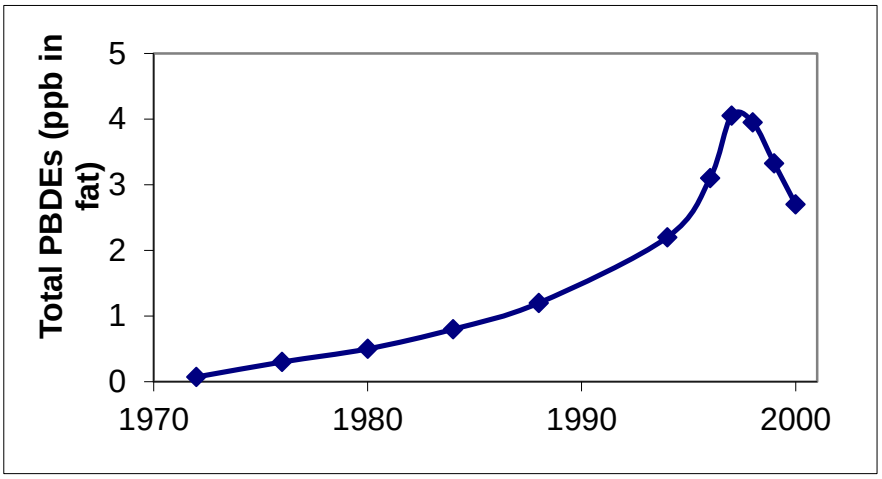
This finding caused a stir in the scientific community, especially since the flame retardants were not readily leaving the body and showed similarities to PCBs. Public concern about the potential health consequences of this trend led to sharply decreased usage of products treated with PBDEs in European countries. In addition, from 1997 to 1998, the European Union cut down on PBDE use by two thirds, or 180,000 pounds. Afterward, levels of contamination in the breast milk of Swedish mothers began to decline (Figure 13).

Levels of flame retardant contamination are higher in the U.S. citizens than in Europe or Asia.[372]

In 2003, California enacted a ban of two types of PBDEs mainly used in furniture foam. One manufacturer of these chemicals made an agreement with the EPA shortly thereafter to phase out national production of the two chemicals. As these actions take effect, the United States should see a similar gradual decline in human contamination levels.

Lingering questions over a third type of flame retardant (known as "deca"), used in high volumes and shown to degrade in the environment to form the banned substances, could delay or reduce the response.[373] As of 2011, deca has been banned for some uses in Maine, Maryland, Vermont and Washington states, and U.S. manufacturers have agreed to phase it out – although it could still be manufactured in other countries and imported.

Figure 13: Recently Declining Toxic Flame Retardant Levels in Breast Milk from Swedish Mothers.



[374]

POLICY RECOMMENDATIONS

Americans expect that the government will protect them from chemicals that can cause harm, or, at the very least, issue warnings about those chemicals so that consumers can make informed decisions. However, in reality, regulators have few effective tools to protect public health from chemical hazards or address the broad impacts of the way companies design and manufacture goods.

First, existing policies do not ensure access to information. When Congress passed the Toxic Substances Control Act 35 years ago, the chemical industry succeeded in making sure there were no new testing requirements placed on the tens of thousands of chemicals already in use. For new chemicals, the law required only a rapid pre-market screening based on existing information, and did not require toxicity testing for health effects.

As a result, very little is known about most chemicals in commerce. The health effects of almost half of the major industrial chemicals have not been studied at all.[375] Manufacturers can sell a chemical or product without studying or sharing information about its potential health or environmental hazards. And consumers and businesses have difficulty knowing what ingredients are in a product, whether those ingredients are safe – or even knowing whether an alternative to a hazardous chemical is actually better.

Second, current policy places the burden of proving that a chemical is unsafe on the EPA and the scientific community. And the burden of proof is impossibly high. Approximately 1,400 chemicals with known or probable links to cancer, birth defects, reproductive impacts and other health problems are still in use today.[376] Even in the case of asbestos, EPA was unable to successfully ban the use of the substance despite decades of evidence that inhalation of asbestos causes cancer.[377] This approach is far less stringent than the process for approving drugs, where the U.S. Food and Drug Administration requires manufacturers to demonstrate safety and effectiveness before a new drug can be placed on the market.

As a result, U.S. chemical regulation stumbles blindly, using an "innocent until proven guilty" model, allowing widespread exposure to toxic chemicals before they have been tested for safety. Moreover, where significant evidence of harm to public health already exists, inadequate resources and legal authority often prevent regulatory agencies from taking protective action. The system allows manufacturers to become tied to the profits chemical sales can generate, and exposure to offending substances continues.

This situation – which allows human lives to become a giant, uncontrolled health experiment – is unacceptable.

In September 2009, federal EPA Administrator Lisa Jackson made the case for reforming the Toxic Substances Control Act (TSCA), the primary federal law governing chemicals. She acknowledged that "over the years, not

only has TSCA fallen behind the industry it's supposed to regulate – it's been proven an inadequate tool for providing the protection against chemical risks that the public rightfully expects."[378]

More than 100 scientific experts on chemical exposures and health agree that we should take action against possible threats, even without the benefit of 100 percent certainty.[379] With better policies, America can reduce our exposure to toxic substances, promote innovation in fields like green chemistry, create green jobs, and protect public health.

CHEMICAL POLICY REFORM

The United States should reform its chemical regulatory policies to require manufacturers to assess chemical safety and then to restrict or phase out the use of the most dangerous substances. Reform should:

Require chemical manufacturers to prove that a chemical is safe before allowing it on the market.

- Regulators should require companies to provide comprehensive data on the intrinsic hazards of chemicals that they produce or import. Such data should include information on a chemical's ability to persist in the environment, accumulate in living organisms, be metabolized into other hazardous compounds, cause genetic damage, mimic important hormone signals, interfere with human development or reproduction, weaken the immune system, damage the nervous system, cause respiratory disease, or otherwise harm human health.
- Chemical testing should include specific consideration of potential impacts on vulnerable populations including infants, children, and pregnant women; potential impacts of low-dose exposures; and potential interactions with other toxic chemicals.
- The reliability and adequacy of the information should be validated by government scientists and/or an independent third party free of conflicts of interest.
- Allowances for ingredient secrecy based on claims of "confidential business information" should be limited.

Empower regulatory agencies to restrict or ban the manufacture and use of chemicals that pose potential dangers to human health or the environment.

- Where chemicals show evidence of intrinsic hazard – such as a tendency to persist in the environment, accumulate in living organisms, or cause toxic effects – regulators should restrict or prohibit the use of these chemicals and require the substitution of safer alternatives, particularly in consumer products or other applications that lead to human exposure. In addition, regulators should consider possible adverse impacts to ecosystems.

- Federal and state agencies should lead the effort to identify and prioritize chemicals of concern and direct an appropriate regulatory response, based on a chemical's ability to cause harm.
- Where there is uncertainty in the evidence, regulators should err on the side of protecting health and the environment. In other words, "no data, no market."

Ensure public access to information on chemicals and their uses.

- The public has a right to know about chemicals currently on the market, including their specific uses, potential hazards to health and the environment, and potential routes of exposure. Information should enable businesses and consumers to compare the safety of chemicals, identify missing data, and create demand for safer alternatives.
- Until health and safety data are available for a particular chemical, there should be mandatory labeling for consumer products indicating the presence of a chemical that has not been tested for its impact on human health.

NOTES

[i] U.S. National Cancer Institute, President's Cancer Panel, *Reducing Environmental Cancer Risk: What We Can Do Now*, April 2010.
[ii] Ruth Rudel et al, Silent Spring Institute and Harvard School of Public Health, "Phthalates, Alkylphenols, Pesticides, Polybrominated Diphenyl Ethers, and Other Endocrine-Disrupting Compounds in Indoor Air and Dust," *Environmental Science and Technology* 37: 4543-4553, 15 October 2003.
[iii] U.S. Centers for Disease Control and Prevention, *Fourth National Study on Human Exposure to Environmental Chemicals*, December 2009; Environmental Working Group, *Body Burden: The Pollution in People*, January 2003.
[iv] U.S. Environmental Protection Agency, *What is the TSCA Chemical Substance Inventory?*, (factsheet), 19 August 2009; available at www.epa.gov/opptintr/newchems/pubs/invntory.htm.
[v] U.S. Environmental Protection Agency, *Chemical Hazard Data Availability Study,* 1998. Major chemicals are defined as those produced or imported in amounts exceeding one million pounds per year.
[vi] Philip H. Howard and Derek C.G. Muir, "Identifying New Persistent and Bioaccumulative Organics Among Chemicals in Commerce," *Environmental Science and Technology* 44: 2277–2285, doi: 10.1021/es903383a, 17 February 2010.
[vii] Commission of the European Communities, *White Paper: Strategy for a Future Chemicals Policy*, COM(2001) 88 final, 27 February 2001; Carcinogenic, mutagenic, and reprotoxic chemicals, plus chemicals defined as category 1 or 2 in EU Directive 67/548, plus persistent organic pollutants.
[viii] U.S. National Cancer Institute, President's Cancer Panel, *Reducing Environmental Cancer Risk: What We Can Do Now*, April 2010.
[9] U.S. National Academies of Science, National Research Council, *Scientific Frontiers in Developmental Toxicology and Risk Assessment*, (National Academy Press, Washington DC) 2000.
[10] Joyce A. Martin, Michelle J.K. Osterman and Paul D. Sutton, U.S. Centers for Disease Control and Prevention, *Are Preterm Births on the Decline in the United States? Recent Data From the National Vital Statistics System*, NCHS Data Brief No. 39, May 2010.
[11] U.S. Centers for Disease Control and Prevention, "Trends in Infant Mortality Attributable to Birth Defects--United States, 1980-1995," *Morbidity and Mortality Weekly Report* 47: 773-778, 25 September 1998
[12] Leonard J. Paulozzi, National Center for Environmental Health, Centers for Disease Control and Prevention, "International Trends in Rates of Hypospadias and Cryptorchidism," *Environmental Health Perspectives* 107: 297-302, March 1999; Marla Cone, "Boys' Birth Defect Is Not Increasing, Raising Questions about Phthalate Syndrome," *Environmental Health News*, 10 July 2009.
[13] KA Kavale , SR Forness, and CT Ramey, "Co-variants in learning disability and behavior disorders: An examination of classification and placement issues," *Advances in Learning and Behavioral Disabilities* 12:1-42, 1998; as cited in: Ted Schettler et al., Physicians for Social Responsibility and the Clean Water Fund, *In Harm's Way: Toxic Threats to Child Development*, May 2000.
[14] Laura Kaloi et al, National Center for Learning Disabilities, *The State of Learning Disabilities 2009*, January 2010.
[15] SN Visser et al, U.S. Centers for Disease Control and Prevention, "Increasing Prevalence of Parent-Reported Attention-Deficit/Hyperactivity Disorder Among Children --- United States, 2003 and 2007," *Morbidity and Mortality Weekly Report* 59; 1439-1443, 12 November 2010.
[16] CDC Surveillance SummariesPrevalence of Autism Spectrum Disorders --- Autism and Developmental Disabilities Monitoring Network, United States, 2006, December 18, 2009 / 58(SS10);1-20

[17] Tracey Woodruff et al, U.S. Environmental Protection Agency, "Trends in Environmentally Related Childhood Illnesses," *Pediatrics* 113: 1133-1140, April 2004; Lara J. Akinbami, U.S. Centers for Disease Control and Prevention, "The State of Childhood Asthma, United States, 1980–2005," *Advance Data from Vital Health and Statistics* 381, 12 December 2006.
[18] U.S. Environmental Protection Agency, *Asthma Prevalence*, 10 March 2010, downloaded from cfpub.epa.gov.
[19] U.S. Centers for Disease Control and Prevention, "Summary Health Statisticsfor U.S. Children: National Health Interview Survey, 2009," *Vital and Health Statistics* Series 10, Number 247, August 2010.
[20] U.S. National Cancer Institute, *Surveillance Epidemiology and End Results*, Age-Adjusted Incidence Rates from 1975 to 2007 for individuals less than 20 years old (the youngest window available), downloaded from seer.cancer.gov on 24 Feburary 2011. The percentage change reported here represents the difference between the value of a linear regression trend line through the data in 2007 compared to 1975. For example, see the trend line in figure XX.
[21] Steingraber Sandra. *The Falling Age of Puberty in US Girls: What We Know, What We Need to Know.* San Francisco, CA: Breast Cancer Fund, 2007.

[22] Marcia Herman-Giddens, "Recent data on pubertal milestones in United States children: the secular trend toward earlier development," *International Journal of Andrology* 29 Issue 1, Pages 241 – 246, 11 October 2005.
[23] Cynthia Ogden and Margaret Carroll, U.S. Centers for Disease Control and Prevention, *Prevalence of Obesity Among Children and Adolescents: United States, Trends 1963–1965 Through 2007–2008*, Health E-Stat factsheet, June 2010; CL Ogden et al, "Prevalence and Trends in Overweight Among US Children and Adolescents, 1999-2000," *Journal of the American Medical Association* 288: 1728-1732, 2002.
[24] U.S. National Cancer Institute, *Surveillance Epidemiology and End Results*, Age-Adjusted Incidence Rates for prostate cancer from 1975 to 2007 for males of all ages, downloaded from seer.cancer.gov on 24 Feburary 2011. The percentage change reported here represents the difference between the incidence rate in 2007 vs. 1975, since the trend over time is not linear.
[25] Autism: California Department of Developmental Services, *Changes in the Population of Persons with Autism and Pervasive Developmental Disorders in California's Developmental Services System: 1987 through 1998*, Report to the Legislature, 1 March 1999; Prostate and testicular cancer: U.S. National Cancer Institute, *Surveillance Epidemiology and End Results*, Age-Adjusted Incidence Rates for prostate cancer from 1975 to 2007 for males of all ages, and for testicular cancer for males below age 20, downloaded from seer.cancer.gov on 24 Feburary 2011; Cryptorchidism: Leonard J. Paulozzi, National Center for Environmental Health, Centers for Disease Control and Prevention, "International Trends in Rates of Hypospadias and Cryptorchidism," *Environmental Health Perspectives* 107: 297-302, March 1999; Sperm density: Shanna H. Swan, EP Elkin, and L Fenster, "The Question of Declining Sperm Density Revisited: An Analysis of 101 Studies Published 1934-1996," *Environmental Health Perspectives* 108: 961-966, 2000; Diabetes incidence: U.S. Centers for Disease Control and Prevention, *Crude and Age-Adjusted Incidence of Diagnosed Diabetes per 1,000 Population Aged 18–79 Years, United States, 1980–2009*, data from the National Health Interview Survey, computed by personnel in CDC's Division of Diabetes Translation, National Center for Chronic Disease Prevention and Health Promotion, 5 January 2011.
[26] TJ Woodruff , AR Zota, and JM Schwart" Environmental chemicals in pregnant women in the US: NHANES 2003-2004." *Environmental Health Perspectives* , available at dx.doi.org/10.1289/ehp.1002727. January 2011
[27] Andrea Gore et al, "Endocrine Disruption for Endocrinologists (and Others)," *Endocrinology* 147(6 Suppl):S1-3, 11 May 2006.
[28] Federal Reserve Board. *G.17 - Industrial Production and Capacity Utilization, Industrial Production for Chemicals (NAICS=325) 2008*, 14 August 2009.
[29] Energy Information Administration, U.S. Department of Energy, *Chemicals Industry Analysis Brief*, 2 February 2004.
[30] Jiang-Ping Wu et al, "Residues of Polybrominated Diphenyl Ethers in Frogs (*Rana limnocharis*) from a Contaminated Site, South China: Tissue Distribution, Biomagnification, and Maternal Transfer," *Environmental Science and Technology* 43: 5212–5217, doi: 10.1021/es901103y, 15 June 2009.
[31] Kyunghee Ji et al, "Influence of a Five-Day Vegetarian Diet on Urinary Levels of Antibiotics and Phthalate Metabolites: A Pilot Study with "Temple Stay" Participants," *Environmental Research* 110: 375-382, dx.doi.org/10.1016/j.envres.2010.02.008, May 2010; Alicia J. Fraser et al, "Diet Contributes Significantly to the Body Burden of PBDEs in the General U.S. Population," *Environmental Health Perspectives* 117: 1520-1525, doi:10.1289/ehp.0900817, 18 June 2009; Nerissa Wu et al, "Human Exposure to PBDEs: Associations of PBDE Body Burdens with Food Consumption and House Dust Concentrations," *Environmental Science and Technology* 41: 1584-1589, doi: 10.1021/es0620282, 17 January 2007.
[32] American Plastics Council, *Questions and Answers About BPA*, downloaded from www.bisphenol-a.org on 14 April 2004; Wilding et al, The National Workgroup for Safe Markets. *No Silver Lining: An Investigation Into Bisphenol A in Canned Foods,* May 2010. Available at ej4all.org/contaminatedwithoutconsent/downloads/NoSilverLining-Report.pdf
[33] Jenny L. Carwile et al, "Polycarbonate Bottle Use and Urinary Bisphenol A Concentrations," *Environmental Health Perspectives* 117: 1368-1372, doi:10.1289/ehp.0900604, 12 May 2009.
[34] Pamela Imm et al, "Household Exposures to Polybrominated Diphenyl Ethers (PBDEs) in a Wisconsin Cohort," *Environmental Health Perspectives* 117: 1890-1895, doi:10.1289/ehp.0900839, 4 August 2009; Anthony F. Lagalante et al, "Polybrominated Diphenyl Ether (PBDE) Levels in Dust from Previously Owned Automobiles at United States Dealerships," *Environment International* 35: 539-544, April 2009.
[35] National Cancer Institute, Formaldehyde and Cancer Risk, 11/15/2010 http://www.cancer.gov/cancertopics/factsheet/Risk/formaldehyde
[36] CG Bornehag et al, Phthalates in Indoor Dust and Their Association with Building Characteristics," *Environmental Health Perspectives* 113: 1399-404, October 2005.
[37] Ruth Rudel et al, Silent Spring Institute and Harvard School of Public Health, "Phthalates, Alkylphenols, Pesticides, Polybrominated Diphenyl Ethers, and Other Endocrine-Disrupting Compounds in Indoor Air and Dust," *Environmental Science and Technology* 37: 4543-4553, 15 October 2003.

[38] Paula I. Johnson et al, "Relationships between Polybrominated Diphenyl Ether Concentrations in House Dust and Serum," doi: *Environmental Science and Technology* 10.1021/es100697q, 3 June 2010; Nerissa Wu et al, "Human Exposure to PBDEs: Associations of PBDE Body Burdens with Food Consumption and House Dust Concentrations," *Environmental Science and Technology* 41: 1584-1589, doi: 10.1021/es0620282, 17 January 2007.
[39] Heather M. Stapleton et al, "Measurement of Polybrominated Diphenyl Ethers on Hand Wipes: Estimating Exposure from Hand-to-Mouth Contact," *Environmental Science and Technology* 42: 3329–3334, doi: 10.1021/es7029625, 19 March 2008.
[40] Robert W. Gale et al, "Semivolatile Organic Compounds in Residential Air along the Arizona−Mexico Border," *Environmental Science and Technology* 43: 3054–3060, doi: 10.1021/es803482u, 26 March 2009.
[41] Robert W. Gale et al, "Semivolatile Organic Compounds in Residential Air along the Arizona−Mexico Border," *Environmental Science and Technology* 43: 3054–3060, doi: 10.1021/es803482u, 26 March 2009; Daniel M. Stout et al, "American Healthy Homes Survey: A National Study of Residential Pesticides Measured from Floor Wipes," *Environmental Science and Technology* 43: 4294-4300, doi: 10.1021/es8030243, 6 May 2009.
[42] California Department of Toxic Substances Control, *California Green Chemistry Initiative: Questions and Answers*, 26 June 2007.
[43] L. Geranio et al, "The Behavior of Silver Nanotextiles During Washing," *Environmental Science and Technology* 43: 8113–8118, doi: 10.1021/es9018332, 24 September 2009.
[44] Susan Duty et al, "Personal Care Product Use Predicts Urinary Concentrations of Some Phthalate Monoesters," *Environmental Health Perspectives* 113: 1530-1535, doi:10.1289/ehp.8083, 18 July 2005.
[45] Sheela Sathyanarayana et al, "Baby Care Products: Possible Sources of Infant Phthalate Exposure," *Pediatrics* 121: e260-e268, doi:10.1542/peds.2006-3766, 1 February 2008.
[46] Antonia M. Calafat et al, "Exposure to Bisphenol A and Other Phenols in Neonatal Intensive Care Unit Premature Infants," *Environmental Health Perspectives* 117: 639-644, doi:10.1289/ehp.0800265, 10 December 2008.
[47] Elcim Seckin et al, "Determination of Total and Free Mono-n-Butyl Phthalate in Human Urine Samples After Medication of a Di-n-Butyl Phthalate Containing Capsule," *Toxicology Letters* 188: 33-37, 10 July 2009.
[48] Dana Barr et al, "Concentrations of Xenobiotic Chemicals in the Maternal-Fetal Unit," *Reproductive Toxicology* 23(3): 260-266, April-May 2007.
[49] M. Nishikawa et al. "Placental Transfer of Conjugated Bisphenol A and Subsequent Reactivation in the Rat Fetus," *Environmental Health Perspectives,* available at dx.doi.org/10.1289/ehp.0901575, 9 April 2010; B. Balakrishnan et al, "Transfer of Bisphenol A Across the Human Placenta," *American Journal of Obstetrics and Gynecology* 202: 393e1-e7, 2010; TJ Woodruff, AR Zota, JM Schwartz, "Environmental Chemicals in Pregnant Women in the US: NHANES 2003-2004." *Environmental Health Perspectives,* doi:10.1289/ehp.1002727, 2011.
[50] S. Sathyanarayana et al, "Maternal and Infant Urinary Phthalate Metabolite Concentrations: Are They Related?," *Environmental Research* 108: 413-418, November 2008.
[51] Anna Kärrman et al., "Exposure of Perfluorinated Chemicals through Lactation: Levels of Matched Human Milk and Serum and a Temporal Trend, 1996–2004, in Sweden," *Environmental Health Perspectives* 115: 226-230. doi:10.1289/ehp.9491, 28 November 2006.
[52] Julie L. Daniels et al, "Individual Characteristics Associated with PBDE Levels in U.S. Human Milk Samples," *Environmental Health Perspectives* 118:155-160. doi:10.1289/ehp.0900759, 14 September 2009; A. Schecter et al, "Congener Specific Measurement of Polybrominated Diphenyl Ethers in 47 Individual Milk Samples From Nursing Mothers in the U.S.A.," *Organohalogen Compounds 61*, 13-16, 2003; Sonia Lunder and Renee Sharp, Environmental Working Group, *Mothers' Milk: Record Levels of Toxic Fire Retardants Found in American Mothers' Breast Milk*, September 2003.
[53] Josée Doucet et al, "Persistent Organic Pollutant Residues in Human Fetal Liver and Placenta from Greater Montreal, Quebec: A Longitudinal Study from 1998 through 2006," *Environmental Health Perspectives* 117: 605-610. doi:10.1289/ehp.0800205, 10 December 2008.
[54] U.S. Centers for Disease Control and Prevention, *Fourth National Study on Human Exposure to Environmental Chemicals*, December 2009; Environmental Working Group, *Body Burden: The Pollution in People*, January 2003.
[55] TJ Woodruff, AR Zota, JM Schwartz, "Environmental Chemicals in Pregnant Women in the US: NHANES 2003-2004." *Environmental Health Perspectives,* doi:10.1289/ehp.1002727, 2011
[56] As documented in: Kristin S. Schafer, Margaret Reeves, Skip Spitzer, and Susan E. Kegley, Pesticide Action Network North America, *Chemical Trespass: Pesticides in Our Bodies and Corporate Accountability*, May 2004.
[57] U.S. Centers for Disease Control and Prevention, *Fourth National Study on Human Exposure to Environmental Chemicals*, December 2009.

[58] Ronald A. Hites, "Polybrominated Diphenyl Ethers in the Environment and in People: A Meta-Analysis of Concentrations," *Environmental Science and Technology* 38: 945–956, doi: 10.1021/es035082g, 8 January 2004.

[59] Ronald A. Hites, "Polybrominated Diphenyl Ethers in the Environment and in People: A Meta-Analysis of Concentrations," *Environmental Science and Technology* 38: 945–956, doi: 10.1021/es035082g, 8 January 2004; Andreas Sjödin et al, "Serum Concentrations of Polybrominated Diphenyl Ethers (PBDEs) and Polybrominated Biphenyl (PBB) in the United States Population: 2003–2004," *Environmental Science and Technology* 42: 1377-1384, doi: 10.1021/es702451p, 8 January 2008.

[60] Melissa Rose et al, "PBDEs in 2−5 Year-Old Children from California and Associations with Diet and Indoor Environment," *Environmental Science and Technology* 44: 2648–2653, doi: 10.1021/es903240g, 2 March 2010; Gayle C. Windham et al, "Body Burdens of Brominated Flame Retardants and Other Persistent Organo-Halogenated Compounds and Their Descriptors in US Girls," *Environmental Research* 110: 251-257, April 2010.

[61] Benjamin J. Apelberg et al, "Determinants of Fetal Exposure to Polyfluoroalkyl Compounds in Baltimore, Maryland," *Environmental Science and Technology* 41: 3891–3897, doi: 10.1021/es0700911, 20 April 2007.

[62] Kurunthachalam Kannan et al, "Perfluorooctanesulfonate and Related Fluorochemicals in Human Blood from Several Countries," *Environmental Science and Technology* 38: 4489–4495, doi: 10.1021/es0493446, 24 July 2004.

[63] Antonia M. Calafat et al, "Exposure of the U.S. Population to Bisphenol A and 4-tertiary-Octylphenol: 2003–2004," *Environmental Health Perspectives* 116:39-44. doi:10.1289/ehp.10753, 24 October 2007; Antonia M. Calafat et al, "Urinary Concentrations of Bisphenol A and 4-Nonylphenol in a Human Reference Population," *Environmental Health Perspectives* 113: 391-395, doi:10.1289/ehp.7534, 20 December 2004; U.S. Centers for Disease Control and Prevention, *Fourth National Study on Human Exposure to Environmental Chemicals*, Bisphenol A, December 2009.

[64] Andrea N. Edginton and Len Ritter, "Predicting Plasma Concentrations of Bisphenol A in Children Younger Than 2 Years of Age after Typical Feeding Schedules, using a Physiologically Based Toxicokinetic Model," *Environmental Health Perspectives* 117: 645-652, doi:10.1289/ehp.0800073, 14 November 2008.

[65] O. Tsutsumi, "Assessment of Human Contamination of Estrogenic Endocrine-Disrupting Chemicals and their Risk for Human Reproduction," *Journal of Steroid Biochemistry and Molecular Biology* 93: 325-30, 26 January 2005.

[66] U.S. Centers for Disease Control and Prevention, *Fourth National Study on Human Exposure to Environmental Chemicals*, Phthalates, December 2009.

[67] Phthalate Esters Panel of the American Chemistry Council, *What are Phthalates?,* downloaded from www.phthalates.org on 14 April 2004; Catherine Dorey, Greenpeace, *Chemical Legacy: Contamination of the Child*, October 2003.

[68] Anne Platt McGinn, Worldwatch Institute, *Why Poison Ourselves? A Precautionary Approach to Synthetic Chemicals*, Worldwatch Paper 153, ISBN: 1-878071-55-6, November 2000.

[69] Anne Platt McGinn, Worldwatch Institute, *Why Poison Ourselves? A Precautionary Approach to Synthetic Chemicals*, Worldwatch Paper 153, ISBN: 1-878071-55-6, November 2000.

[70] WV Welshons, KA Thayer, BM Judy, JA Taylor, EM Curran and FS vom Saal. "Large Effects from Small Exposures. I. Mechanisms for Endocrine Disrupting Chemicals with Estrogenic Activity," *Environmental Health Perspectives* 111:994-1006, June 2003.

[71] WV Welshons, KA Thayer, BM Judy, JA Taylor, EM Curran and FS vom Saal. "Large Effects from Small Exposures. I. Mechanisms for Endocrine Disrupting Chemicals with Estrogenic Activity," *Environmental Health Perspectives* 111:994-1006, June 2003.

[72] Frederick S. vom Saal et al, "Chapel Hill Bisphenol A Expert Panel Consensus Statement: Integration of Mechanisms, Effects in Animals and Potential to Impact Human Health at Current Levels of Exposure," *Reproductive Toxicology* 24: 131-138, August-September 2007; Wade V. Welshons et al, "Large Effects from Small Exposures. III. Endocrine Mechanisms Mediating Effects of Bisphenol A at Levels of Human Exposure," *Endocrinology* 147: s56-s69, doi: 10.1210/en.2005-1159, 2006.

[73] W. Foster, S. Chan, L. Platt, and C. Hughes, "Detection of Endocrine-Disrupting Chemicals in Samples of Second Trimester Human Amniotic Fluid," *The Journal of Clinical Endocrinology and Metabolism* 85, 1-1, 2000.

[74] Jerrold Heindel, "Role of Exposure to Environmental Chemicals in the Developmental Basis of Reproductive Disease and Dysfunction," *Seminars in Reproductive Medicine* 24: 168-177, doi: 10.1055/s-2006-944423, 2006.
[75] Philippe Grandjean et al, "The Faroes Statement: Human Health Effects of Developmental Exposure to Chemicals in Our Environment," *Basic & Clinical Pharmacology & Toxicology* 102: 73-75, doi: 10.1111/j.1742-7843.2007.00114.x, 30 July 2007.
[76] Paul Foster and Martha Harris, "Changes In Androgen-Mediated Reproductive Development In Male Rat Offspring Following Exposure To A Single Oral Dose Of Flutamide At Different Gestational Ages," *Toxicological Sciences* 85: 1024-1032, doi:10.1093/toxsci/kfi159, 23 March 2005.
[77] Lina Xing et al, "Embryotoxic and Teratogenic Effects of the Combination of Bisphenol A and Genistein on In Vitro Cultured Postimplantation Rat Embryos," *Toxicological Sciences* 115: 577-588, doi:10.1093/toxsci/kfq081, 18 March 2010.
[78] Ingrid Stavenes Andersen et al, "Effects of Methyl Mercury in Combination with Polychlorinated Biphenyls and Brominated Flame Retardants on the Uptake of Glutamate in Rat Brain Synaptosomes: A Mathematical Approach for the Study of Mixtures," *Toxicological Sciences* 112: 175-184, doi:10.1093/toxsci/kfp178, 21 August 2009.
[79] Sofie Christiansen et al, "Synergistic Disruption of External Male Sex Organ Development by a Mixture of Four Antiandrogens," *Environmental Health Perspectives* 117: 1839-1846, doi:10.1289/ehp.0900689, 15 July 2009; Stine Broeng Metzdorff et al, "Dysgenesis and Histological Changes of Genitals and Perturbations of Gene Expression in Male Rats after In Utero Exposure to Antiandrogen Mixtures," *Toxicological Sciences* 98: 87-98, doi:10.1093/toxsci/kfm079, 9 April 2007.
[80] Cathy A. Laetz et al, "The Synergistic Toxicity of Pesticide Mixtures: Implications for Risk Assessment and the Conservation of Endangered Pacific Salmon," *Environmental Health Perspectives* 117:348-353, doi:10.1289/ehp.0800096, 14 November 2008.
[81] Tyrone B. Hayes et al, "Pesticide Mixtures, Endocrine Disruption, and Amphibian Declines: Are We Underestimating the Impact?," *Environmental Health Perspectives* 114: 40-50, doi:10.1289/ehp.8051, 24 January 2006.
[82] Kevin Crofton et al, "Thyroid-Hormone–Disrupting Chemicals: Evidence for Dose-Dependent Additivity or Synergism," *Environmental Health Perspectives* 113: 1549-1554, doi:10.1289/ehp.8195, 21 July 2005.
[83] V.C. Moser et al, "Neurotoxicological and Statistical Analyses of a Mixture of Five Organophosphorus Pesticides Using a Ray Design," *Toxicological Sciences*, doi:10.1093/toxsci/kfi163, 30 March 2005.
[84] Nigel J. Walker et al, "Dose-Additive Carcinogenicity of a Defined Mixture of "Dioxin-like Compounds," *Environmental Health Perspectives* 113: 43-48, doi:10.1289/ehp.7351, 19 October 2004.
[85] EC Dodds and W Lawson, "Molecular Structure in Relation to Estrogenic Activity: Compounds Without a Phenanthrene Nucleus," *Proceedings of the Royal Society of London B* 125: 222-232, 1938.
[86] Elvira Greiner, Thomas Kaelin and Goro Toki, SRI Consulting, *Chemical Economics Handbook Report: Bisphenol A*, February 2001.
[87] Global Industry Analysts, *Global Bisphenol A Market to Exceed 6.3 Million Metric Tons by 2015, According to New Report by Global Industry Analysts, Inc.*.(press release), 24 March 2010.
[88] SourceWatch, *Bisphenol-A: Efforts to Ban Bisphenol-A*, 9 November 2010, available at www.sourcewatch.org.
[89] For example: As revealed in documents made public as a result of the major tobacco lawsuits, Philip Morris launched an effort called "The Whitecoat Project to: "Resist and roll back smoking restrictions" "Restore smoker confidence," and "address product liability concerns." The company planned to "Reverse scientific and popular misconception that [second-hand smoke] is harmful" "generate a body of scientific and technical knowledge in the field of [environmental tobacco smoke]… undertaken by whitecoats, contract laboratories and commercial organizations…" "disseminate and exploit such knowledge within specific communication programmes…" and to use "scientific and technical resources to challenge existing laws; to counter specific legislative and regulatory threats; and to respond to specific mis-information and bias as it arises…" See: Philip Morris, *Proposal for the Organization of the Whitecoat Project*, February 1988, memo obtained from the Legacy Tobacco Document Archive at the University of California, San Francisco, Document number 2501474262.
[90] Frederick S. vom Saal and Claude Hughes, "An Extensive New Literature Concerning Low-Dose Effects of Bisphenol A Shows the Need for a New Risk Assessment," *Environmental Health Perspectives* 113: 926-933, doi:10.1289/ehp.7713, 13 April 2005.
[91] Jennifer Beth Sass, Barry Castleman and David Wallinga, "Vinyl Chloride: A Case Study of Data Suppression and Misrepresentation," Environmental Health Perspectives 113: 809-812, doi:10.1289/ehp.7716, 24 March 2005.
[92] Tyrone B. Hayes, "There Is No Denying This: Defusing the Confusion about Atrazine," *BioScience* 54: 1138-1149, doi: 10.1641/0006-3568(2004)054[1138:TINDTD]2.0.CO;2, December 2004.
[93] [93] Hunt, PA, KE Koehler, M Susiarjo, CA Hodges, A Ilagan, RC Voigt, S Thomas, BF Thomas and TJ Hassold. 2003. Bisphenol A exposure causes meiotic aneuploidy in the female mouse. Current Biology 13: 546-553.

[93] U.S. National Academies of Science, National Researc h Council, *Scientific Frontiers in Developmental Toxicology and Risk Assessment*, (National Academy Press, Washington DC) 2000
[94] Travis Madsen, Susan Lee, and Teri Olle, Environment California Research and Policy Center, *Growing Threats: Toxic Flame Retardants and Children's Health*, April 2003; Marla Cone, "Cause for Alarm Over Chemicals; Levels of Common Fire Retardants in Humans are Rising Rapidly, Especially in the U.S. Animal Tests Show Effects on the Brain," *Los Angeles Times*, 20 April 2003.
[95] Sonya Lunder and Anila Jacob, Environmental Working Group, *Fire Retardants in Toddlers and Their Mothers: Gov't and Industry Actions to Phase Out PBDEs*, September 2008.
[96] U.S. Environmental Protection Agency, DecaBDE Phase-Out Initiative, 17 December 2009, downloaded from http://www.epa.gov/oppt/existingchemicals/pubs/actionplans/deccadbe.html
[97] Cameron Scott, "Feds Get Serious About Chemicals," *The Thin Green Line (Blog), San Francisco Chronicle*, 2 October 2009.
[98] Kellyn Betts. *Environmental Science & Technology* / January 15, 2009 10.1021/es8032154 2009 American Chemical Society Published on Web 12/03/2008.

[102] U.S. National Academies of Science, National Research h Council, *Scientific Frontiers in Developmental Toxicology and Risk Assessment*, (National Academy Press, Washington DC) 2000
[101] Mayumi Sugiura-Ogasawara, "Exposure to Bisphenol A Is Associated with Recurrent Miscarriage," *Human Reproduction* 20: 2325-2329, doi:10.1093/humrep/deh888, 9 June 2005.
[102] EM Bell, I Hertz-Picciotto, and JJ Beaumont, "A Case-Control Study of Pesticides and Fetal Death Due to Congenital Anomalies," *Epidemiology* 12: 148-156, 2001.
[103] MF Cavieres, J Jaeger, and W Porter, "Developmental Toxicity of a Commercial Herbicide Mixture in Mice: I. Effects on Embryo Implantation and Litter Size," *Environmental Health Perspectives* 110: 1081-1085, 2002.
[104] Matthew P. Longnecker et al, "Maternal Serum Level of the DDT Metabolite DDE in Relation to Fetal Loss in Previous Pregnancies," *Environmental Research* 97: 127-133, February 2005.
[105] S.A. Venners et al, "Preconception Serum DDT and Pregnancy Loss: A Prospective Study Using A Biomarker of Pregnancy," *Epidemiology* 16, S21-S22, September 2005.
[106] Cande Ananth et al, "Rates of Preterm Delivery among Black Women and White Women in the United States over Two Decades: An Age-Period-Cohort Analysis," *American Journal of Epidemiology* 154: 657-665, 2001.
[107] AM Branum and KC Schoendorf, "Changing Patterns of Low Birthweight and Preterm Birth in the United States, 1981-98, *Paediatric and Perinatal Epidemiology,* 16: 8-15, January 2002; Joyce A. Martin, Michelle J.K. Osterman and Paul D. Sutton, U.S. Centers for Disease Control and Prevention, *Are Preterm Births on the Decline in the United States? Recent Data From the National Vital Statistics System*, NCHS Data Brief No. 39, May 2010.
[108] Anders Hviid and Mads Melbye et al, "The Impact of Birth Weight on Infectious Disease Hospitalization in Childhood," *American Journal of Epidemiology* 2007 165: 756-761; doi:10.1093/aje/kwk064, 22 December 2006; AT Bhutta et al, "Cognitive and Behavioral Outcomes of School-Aged Children Who Were Born Preterm: a Meta-Analysis," *Journal of the American Medical Association* 288: 728-737, 2002.
[109] MP Longnecker et al, "Association Between Maternal Serum Concentration of the DDT Metabolite DDE and Preterm and Small-for-Gestational-Age Babies at Birth," *Lancet* 358: 110-114, July 2001.
[110] Thorhallur Ingi Halldorsson et al, "Linking Exposure to Polychlorinated Biphenyls With Fatty Fish Consumption and Reduced Fetal Growth Among Danish Pregnant Women: A Cause for Concern?" *American Journal of Epidemiology* 168: 958-965; doi:10.1093/aje/kwn204, 21 August 2008.
[111] G Latini et al, "In-Utero Exposure to Di-(2-ethylhexyl)-phthalate and Human Pregnancy Duration," *Environmental Health Perspectives* 111:1783-1785, 2003.
[112] John Meeker et al, "Urinary Phthalate Metabolites in Relation to Preterm Birth in Mexico City." *Environmental Health Perspectives* 117: 1587-1592, doi:10.1289/ehp.0800522, 16 June 2009.
[113] Giuseppe Latini et al, "Prenatal Exposure to Phthalates and Intrauterine Inflammation: A Unifying Hypothesis," *Toxicological Sciences* 85: 743, doi:10.1093/toxsci/kfi131, 23 February 2005.
[114] Dana Barr et al, "Pesticide Concentrations in Maternal and Umbilical Cord Sera and Their Relation to Birth Outcomes in a Population of Pregnant Women and Newborns in New Jersey," *Science of the Total Environment* 408: 790-795, doi:10.1016/j.scitotenv.2009.10.007, 15 January 2010.
[115] Mary Wolff et al, "Prenatal Pesticide and PCB Exposures and Birth Outcomes," Pediatric Research 61: 243-250, doi: 10.1203/pdr.0b013e31802d77f0, February 2007.
[116] Kendall Morgan, Duke University Medical Center, *Pre-Term Labor Drug Sensitizes Brain to Pesticide Injury,* (Press Release) 30 March 2004.

[117] MC Rhodes et al, "Terbutaline is a Developmental Neurotoxicant: Effects on Neuroproteins and Morphology in Cerebellum, Hippocampus, and Somatosensory Cortex," *Journal of Pharmacology and Experimental Therapeutics* 308: 529-537, February 2004.
[118] Cheryl Stein et al, "Serum Levels of Perfluorooctanoic Acid and Perfluorooctane Sulfonate and Pregnancy Outcome," *American Journal of Epidemiology* 170: 837-846; doi:10.1093/aje/kwp212, 19 August 2009.
[119] Benjamin J. Apelberg et al, "Cord Serum Concentrations of Perfluorooctane Sulfonate (PFOS) and Perfluorooctanoate (PFOA) in Relation to Weight and Size at Birth," *Environmental Health Perspectives* 115:1670-1676, doi:10.1289/ehp.10334, 31 July 2007.
[120] Leonard J. Paulozzi, National Center for Environmental Health, Centers for Disease Control and Prevention, "International Trends in Rates of Hypospadias and Cryptorchidism," *Environmental Health Perspectives* 107: 297-302, March 1999.
[121] Marla Cone, "Boys' Birth Defect Is Not Increasing, Raising Questions about Phthalate Syndrome," *Environmental Health News*, 10 July 2009.
[122] H.E. Virtanen and J. Toppari, "Epidemiology and pathogenesis of cryptorchidism," *Human Reproduction Update* 14: 49-58, doi:10.1093/humupd/dmm027, 21 November 2007.
[123] Helen Dolk et al, "Toward the effective surveillance of hypospadias," *Environmental Health Perspectives* 112: 398–402, March 2004.
[124] Shanna Swan, University of Rochester, "Trends in disease don't always reveal environmental causes," *Environmental Health News*, 24 July 2009.
[125] NE Skakkebaek et al., "Testicular Dysgenesis Syndrome: An Increasingly Common Developmental Disorder with Environmental Aspects," *Human Reproduction* 16: 972-978, 2001.
[126] Carlo Foresta et al, "Role of Hormones, Genes, and Environment in Human Cryptorchidism," *Endocrine Reviews* 29: 560-580, doi:10.1210/er.2007-0042, 2008.
[127] Irva Hertz-Picciotto et al, "A Cohort Study of *in Utero* Polychlorinated Biphenyl (PCB) Exposures in Relation to Secondary Sex Ratio," *Environmental Health* 7: 37, doi:10.1186/1476-069X-7-37, 15 July 2008.
[128] Françoise Brucker-Davis et al, "Cryptorchidism at Birth in Nice Area (France) Is Associated with Higher Prenatal Exposure to PCBs and DDE, as Assessed by Colostrum Concentrations," *Human Reproduction* 23: 1708-1718; doi:10.1093/humrep/den186, 24 May 2008.
[129] Matthew P. Longnecker et al, "In Utero Exposure to the Antiandrogen 1,1-Dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE) in Relation to Anogenital Distance in Male Newborns from Chiapas, México," *American Journal of Epidemiology* 165: 1015-1022; doi:10.1093/aje/kwk109, 31 January 2007; Katherine A. McGlynn et al, "Maternal Pregnancy Levels of Polychlorinated Biphenyls and Risk of Hypospadias and Cryptorchidism in Male Offspring," *Environmental Health Perspectives* 117: 1472–1476, September 2009.
[130] D.N.R. Veeramachaneni et al, "Sequelae in Male Rabbits Following Developmental Exposure to p,p'-DDT or a Mixture of p,p'-DDT and Vinclozolin: Cryptorchidism, Germ Cell Atypia, and Sexual Dysfunction," *Reproductive Toxicology* 23: 353-365, April-May 2007.
[131] Risheng Ma and David A. Sassoon, "PCBs Exert an Estrogenic Effect through Repression of the Wnt7a Signaling Pathway in the Female Reproductive Tract," *Environmental Health Perspectives* 114: 898-904, doi:10.1289/ehp.8748, 2 February 2006.
[132] LE Gray et al, "Perinatal Exposure to the Phthalates DEHP, BBP, and DINP, but not DEP, DMP, or DOTP, Alters Sexual Differentiation of the Male Rat," *Toxicological Science* 58: 350-365, December 2000.
[133] Louise Parks et al, U.S. EPA, "The Plasticizer Diethylhexyl Phthalate Induces Malformations by Decreasing Fetal Testosterone Synthesis during Sexual Differentiation in the Male Rat," *Toxicological Sciences* 58, 339-349, 2000.
[134] Vickie Wilson et al, "Phthalate Ester-Induced Gubernacular Lesions are Associated with Reduced Insl3 Gene Expression in the Fetal Rat Testis," *Toxicology Letters* 146: 207-215, 2 February 2004; Ren-Shan Ge et al, "Phthalate Ester Toxicity in Leydig Cells: Developmental Timing and Dosage Considerations," *Reproductive Toxicology* 23: 366-373, April-May 2007.
[135] JS Fisher et al, "Human 'Testicular Dysgenesis Syndrome': A Possible Model Using *in-utero* Exposure of the Rat to Dibutyl Phthalate," *Human Reproduction* 18: 1383-1394, 2003; Anne-Marie Saillenfait et al, "Diisobutyl Phthalate Impairs the Androgen-Dependent Reproductive Development of the Male Rat," *Reproductive Toxicology* 26: 107-115, October 2008.
[136] Kim P. Lehmann et al, "Dose-Dependent Alterations in Gene Expression and Testosterone Synthesis in the Fetal Testes of Male Rats Exposed to Di (n-butyl) Phthalate," *Toxicological Sciences* 81: 60-68, doi:10.1093/toxsci/kfh169, 12 May 2004.
[137] Kembra L. Howdeshell, "Cumulative Effects of Dibutyl Phthalate and Diethylhexyl Phthalate on Male Rat Reproductive Tract Development: Altered Fetal Steroid Hormones and Genes," *Toxicological Sciences* 99: 190-202, doi:10.1093/toxsci/kfm069, 30 March 2007.

[138] Jane Fisher, "Environmental Anti-Androgens and Male Reproductive Health: Focus on Phthalates and Testicular Dysgenesis Syndrome," *Reproduction* 127: 305-315, 2004.
[139] Shanna H. Swan et al, "Decrease in Anogenital Distance among Male Infants with Prenatal Phthalate Exposure," *Environmental Health Perspectives* 113: 1056-1061, doi:10.1289/ehp.8100, 27 May 2005.
[140] Gillian Ormond et al, "Endocrine Disruptors in the Workplace, Hair Spray, Folate Supplementation, and Risk of Hypospadias: Case–Control Study," *Environmental Health Perspectives* 117: 303-307, doi:10.1289/ehp.11933, 20 November 2008.
[141] Romain Lambrot et al, "Phthalates Impair Germ Cell Development in the Human Fetal Testis in Vitro without Change in Testosterone Production," *Environmental Health Perspectives* 117: 32-37, doi:10.1289/ehp.11146, 9 September 2008.
[142] Frances Orton et al., "Widely Used Pesticides with Previously Unknown Endocrine Activity Revealed as *in Vitro* Anti-Androgens," *Environmental Health Perspectives,* doi:10.1289/ehp.1002895, published online 10 February 2011.
[143] TB Hayes et al, "Hermaphroditic, Demasculinized Frogs After Exposure to the Herbicide Atrazine at Low, Ecologically Relevant Doses," *Proceedings of the National Academy of Sciences* (US) 99: 5476-5480, 2002.
[144] US Geological Survey, *NAWQA National Water Quality Data Warehouse*.
[145] Neil M. Dubrovsky et al, "Pesticide Occurrence as a Function of Land Use, Application, and Hydrology, San Joaquin River, California," *Society of Environmental Toxicology and Chemistry, SETAC 17th Annual Meeting,* Washington, D.C., November 17-21, 1996, Abstract Book, p. 69
[146] TB Hayes et al, "Hermaphroditic, Demasculinized Frogs After Exposure to the Herbicide Atrazine at Low, Ecologically Relevant Doses," *Proceedings of the National Academy of Sciences* (US) 99: 5476-5480, 2002.
[147] Helle R. Andersen et al, "Impaired Reproductive Development in Sons of Women Occupationally Exposed to Pesticides during Pregnancy," *Environmental Health Perspectives* 116: 566-572, doi:10.1289/ehp.10790, 22 January 2008.
[148] Ida N. Damgaard et al, "Persistent Pesticides in Human Breast Milk and Cryptorchidism," *Environmental Health Perspectives* 114: 1133-1138, doi:10.1289/ehp.8741, 27 February 2006.
[149] Xiaolan Fei et al, "Methoxychlor Disrupts Uterine Hoxa10 Gene Expression," *Endocrinology* 146: 3445-3451, doi:10.1210/en.2005-0341, 2005.
[150] Chris Talsness, et al., "Ultrastructural Changes in the Ovaries of Adult Offspring Following a Single Maternal Exposure to Lowdose 2,2', 4,4', 5-Pentabromodiphenyl Ether," *Organohalogen Compounds,* 61: 88-91, 2003; Hellmuth Lilienthal et al, "Effects of Developmental Exposure to 2,2',4,4',5-Pentabromodiphenyl Ether (PBDE-99) on Sex Steroids, Sexual Development, and Sexually Dimorphic Behavior in Rats," *Environmental Health Perspectives* 114: 194-201, doi:10.1289/ehp.8391, 6 February 2006.
[151] Hellmuth Lilienthal et al, "Effects of Developmental Exposure to 2,2',4,4',5-Pentabromodiphenyl Ether (PBDE-99) on Sex Steroids, Sexual Development, and Sexually Dimorphic Behavior in Rats," *Environmental Health Perspectives* 114: 194-201, doi:10.1289/ehp.8391, 6 February 2006.
[152] G Schonfelder et al, "In Utero Exposure to Low Doses of Bisphenol A Lead to Long-Term Deleterious Effects in the Vagina," *Neoplasia* 4:98-102, 2002;
[153] Caroline M. Markey et al, "
[154] Zhimin Shi et al, "Alterations in Gene Expression and Testosterone Synthesis in the Testes of Male Rats Exposed to Perfluorododecanoic Acid," *Toxicological Sciences* 98: 206-215, doi:10.1093/toxsci/kfm070, 30 March 2007.
[155] U.S. Centers for Disease Control and Prevention, "Surveillance Summaries Temporal Trends in the Incidence of Birth Defects -- United States," *Morbidity and Mortality Weekly Report* 46: 1171-1176, 12 December 1997.
[156] U.S. Centers for Disease Control and Prevention, "Trends in Infant Mortality Attributable to Birth Defects--United States, 1980-1995," *Morbidity and Mortality Weekly Report* 47: 773-778, 25 September 1998.
[157] DM Schreinemachers, "Birth Malformations and Other Adverse Perinatal Outcomes in Four U.S. Wheat-Producing States," *Environmental Health Perspectives* 111: 1259-1264, 2003.
[158] National Library of Medicine, U.S. National Institutes of Health, *Household Products Database*, accessed at hpd.nlm.nih.gov on 12 May 2004.
[159] E. Courchesne, R. Carper, and N. Akshoomoff, "Evidence of Brain Overgrowth in the First Year of Life in Autism," *Journal of the American Medical Association* 290: 337-344, 2003.
[160] JW Gilger and BJ Kaplan, "Atypical Brain Development: A Conceptual Framework for Understanding Developmental Learning Disabilities," *Developmental Neuropsychology* 20: 465-481, 2001.
[161] FX Castellanos et al, "Developmental Trajectories of Brain Volume Abnormalities in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder," *Journal of the American Medical Association* 288: 1740-1748, 2002.
[162] Shari Roan, "A Different View of Attention Deficit," *Los Angeles Times*, 14 October 2002.
[163] Peter Hauser et al, National Institutes of Health, "Attention Deficit-Hyperactivity Disorder in People with Generalized Resistance to Thyroid Hormone," *The New England Journal of Medicine* 328: 997-1001, 1993.

[164] Michael P McDonald et al, National Institute of Mental Health, "Hyperactivity and Learning Deficits in Transgenic Mice Bearing a Human Mutant Thyroid Hormone beta 1 Receptor Gene," *Learning and Memory* 5: 289-301, 1998.
[165] P. Grandjean and P. Landrigan, "Developmental Neurotoxicity of Industrial Chemicals," *The Lancet* 368: 2167 - 2178, 16 December 2006.
[166] KA Kavale , SR Forness, and CT Ramey, "Co-variants in learning disability and behavior disorders: An examination of classification and placement issues," *Advances in Learning and Behavioral Disabilities* 12:1-42, 1998; as cited in: Ted Schettler et al., Physicians for Social Responsibility and the Clean Water Fund, *In Harm's Way: Toxic Threats to Child Development*, May 2000.
[167] Laura Kaloi et al, National Center for Learning Disabilities, *The State of Learning Disabilities 2009*, January 2010.
[168] Rich Mayes, University of Richmond VA, *Rise of ADHD Prevalence and Psychostimulant Use: A Historical Perspective,* Presented at the 130th Annual Meeting of the American Public Health Association, 11 November 2002.
[169] SN Visser et al, U.S. Centers for Disease Control and Prevention, "Increasing Prevalence of Parent-Reported Attention-Deficit/Hyperactivity Disorder Among Children --- United States, 2003 and 2007," *Morbidity and Mortality Weekly Report* 59; 1439-1443, 12 November 2010.
[170] CDC Surveillance Summaries, Prevalence of Autism Spectrum Disorders --- Autism and Developmental Disabilities Monitoring Network, United States, 2006, December 18, 2009 / 58(SS10);1-20
[171] California Health and Human Services Agency, Department of Developmental Services, *Autistic Spectrum Disorders: Changes in the California Caseload, An Update: June 1987 – June 2007*, April 2009.
[172] R.S. Byrd et al., MIND Institute, University of California, Davis, *Report to the Legislature on the Principle Findings from The Epidemiology of Autism in California: A Comprehensive Pilot Study*, 17 October 2002.
[173] W.J. Rogan, *et al, Congenital poisoning by polychlorinated biphenyls and their contaminants in Taiwan.* Science 241, 334-338, 1988; Y.C. Chen, Y.L. Guo, and W.J. Rogan, *Cognitive Development of Yu-Cheng (Oil-Disease) Children Prenatally Exposed to Heat Degraded PCBs*. Journal of the American Medical Association 268, 3213-8, 1992.
[174] J.L. Jacobson and S.W. Jacobson, "Effects of in utero exposure to PCBs and related contaminants on cognitive functioning in young children." *Journal of Pediatrics* 116, 38-45, 1990; J.L. Jacobson and S.W. Jacobson, "Intellectual impairment in children exposed to polychlorinated biphenyls in utero." *New England Journal of Medicine* 335, 783-789, 1996.
[175] Deborah C. Rice, "Parallels Between Attention Deficit Hyperactivity Disorder and Behavioral Deficits Produced by Neurotoxic Exposure in Monkeys," *Environmental Health Perspectives* 108, Supplement 3: 405-408, 2000.
[176] C. Koopman-Esseboom, et al, "Effects of Dioxins and Polychlorinated Biphenyls on Thyroid Hormone Status of Pregnant Women and Their Infants," *Pediatric Research* 36, 468-473, 1994.
[177] Sharon K. Sagiv et al, "Prenatal Organochlorine Exposure and Behaviors Associated with Attention Deficit Hyperactivity Disorder in School-Aged Children," *American Journal of Epidemiology* 171: 593-601, doi:10.1093/aje/kwp427, 27 January 2010.
[178] Paul Stewart et al, "The Relationship between Prenatal PCB Exposure and Intelligence (IQ) in 9-Year-Old Children," *Environmental Health Perspectives* 116: 1416-1422, doi:10.1289/ehp.11058, 28 May 2008.
[179] Luisa Torres-Sánchez et al, "*In Utero* p,p'-DDE Exposure and Infant Neurodevelopment: A Perinatal Cohort in Mexico," *Environmental Health Perspectives* 115: 435-439, doi:10.1289/ehp.9566, 16 January 2007; Núria Ribas-Fitó et al, "*In Utero* Exposure to Background Concentrations of DDT and Cognitive Functioning among Preschoolers," *American Journal of Epidemiology* 164: 955-962; doi:10.1093/aje/kwj299, 12 September 2006; Brenda Eskenazi et al, "*In Utero* Exposure to Dichlorodiphenyltrichloroethane (DDT) and Dichlorodiphenyldichloroethylene (DDE) and Neurodevelopment Among Young Mexican American Children," *Pediatrics* 118: 233-241, doi:10.1542/peds.2005-3117, July 2006.
[180] Maria-Jose Lopez-Espinosa, "Association between thyroid hormone levels and 4,4'-DDE concentrations in pregnant women (Valencia, Spain)," *Environmental Research* 109: 479-485, May 2009; Dongren Yang et al, "Developmental Exposure to Polychlorinated Biphenyls Interferes with Experience-Dependent Dendritic Plasticity and Ryanodine Receptor Expression in Weanling Rats" *Environmental Health Perspectives* 117: 426-435, doi:10.1289/ehp.11771, 12 September 2008.
[181] Dongren Yang et al, "Developmental Exposure to Polychlorinated Biphenyls Interferes with Experience-Dependent Dendritic Plasticity and Ryanodine Receptor Expression in Weanling Rats" *Environmental Health Perspectives* 117: 426-435, doi:10.1289/ehp.11771, 12 September 2008.
[182] I Quesada et al, "Low Doses of the Endocrine Disruptor Bisphenol-A and the Native Hormone 17□Estradiol Rapidly Activate Transcription Factor CREB," *Federation of American Societies for Experimental Biology (FASEB) Journal* 16: 1671-1673, 2002.
[183] Dana C. Dolinoy et al, "Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development," *Proceedings of the National Academies of Science* 104: 13056-13061, 7 August 2007.
[184] M Ishido et al, "Bisphenol A Causes Hyperactivity in the Rat Concomitantly with Impairment of Tyrosine Hydroxylase Immunoreactivity," *Journal of Neuroscience Research* 76: 423-433, PubMed ID 15079872, 1 May 2004.

[185] Keisuke Kawai et al, "Aggressive Behavior and Serum Testosterone Concentration during the Maturation Process of Male Mice: The Effects of Fetal Exposure to Bisphenol A," *Environmental Health Perspectives* 111: 175-178, 2003; H Kabuto, M Amakawa, and T Shishibori, "Exposure to Bisphenol-A During Embryonic/Fetal Life and Infancy Increases Oxidative Injury and Causes Underdevelopoment of the Brain and Testes in Mice," *Life Sciences* 74: 2931-2940, 30 April 2004.
[186] Akiko Nakagami et al, "Alterations in male infant behaviors towards its mother by prenatal exposure to bisphenol A in cynomolgus monkeys (Macaca fascicularis) during early suckling period," *Psychoneuroendocrinology* 34: 1189-1197, September 2009.
[187] Yu-Hua Tian et al, "Prenatal and postnatal exposure to bisphenol a induces anxiolytic behaviors and cognitive deficits in mice," *Synapse* 64: 432 – 439, February 2010.
[188] J.M. Braun, K.,Yolton, K.N. Dietrich, R. Hornung, X.,Ye et al. "Prenatal Bisphenol A Exposure and Early Childhood Behavior." *Environmental Health Perspectives* 117(12): doi:10.1289/ehp.0900979, 2009.
[189] A Ilonka et al., "Potent Competitive Interactions of Some Brominated Flame Retardants and Related Compounds with Human Transthyretin in Vitro," *Toxicological Sciences* 56: 95-104, 2000.
[190] Zhou et al, "Effects of Short Term *in vivo E*xposure to Polybrominated Diphenyl Ethers on Thyroid Hormones and Hepatic Enzyme Activities in Weanling Rats," *Toxicological Science* 61, 76-82, 2001.
[191] S. Hallgren and P.O. Darnerud, "Effects of Polybrominated Diphenyl Ethers (PBDEs), Polychlorinated Biphenyls (PCBs), and Chlorinated Paraffins (CPs) on Thyroid Hormone Levels and Enzyme Activities in Rats," *Organohalogen Compounds* 35, 391-394, 1998.
[192] P Eriksson et al, "Brominated Flame Retardants: A Novel Class of Developmental Neurotoxicants in Our Environment?" *Environmental Health Perspectives* 109, 903-8, 2001; P Eriksson et al, "A Brominated Flame Retardant, 2,2',4,4',5-Pentabromodiphenyl Ether: Uptake, Retention, and Induction of Neurobehavioral Alterations in Mice During a Critical Phase of Neonatal Brain Development," *Toxicological Science* 67, 98-103, 2002; H Viberg et al, "Neonatal Exposure to the Brominated Flame Retardant 2,2',4,4',5- Pentabromodiphenyl Ether Causes Altered Susceptibility in the Cholinergic Transmitter System in the Adult Mouse," *Toxicological Science* 67, 104-7, 2002; H. Viberg, A. Fredriksson, and E. Jakobsson, "Developmental Neurotoxic Effects of 2,2,4,4,5-Pentabromodiphenyl Ether in the Neonatal Mouse," *Toxicologist* 54, 1360, 2000; H. Viberg, A. Fredriksson, E. Jakobsson, U. Ohrn, and P. Eriksson, "Brominated Flame Retardant: Uptake, Retention, and Developmental Neurotoxic Effects of Decabromodiphenyl Ether in the Neonatal Mouse," *Toxicologist* 61, 1034, 2001; I. Branchi et al, "Effects of Perinatal Exposure to a Polybrominated Diphenyl Ether (PBDE 99) on Mouse Neurobehavioural Development," *Neurotoxicology* 23, 375-84, 2002; J.L. Jacobson., S.W. Jacobson, H.B. Humphrey, "Effects of in Utero Exposure to Polychlorinated-Biphenyls and Related Contaminants on Cognitive-Functioning in Young Children" *Journal of Pediatrics*, 116:38-45, 1990; Sergio N. Kuriyam, "Developmental Exposure to Low Dose PBDE 99: Effects on Male Fertility and Neurobehavior in Rat Offspring," Environmental Health Perspectives Volume 113: 149-154, February 2005;
[193] N. Johansson et al, "Neonatal exposure to deca-brominated diphenyl ether (PBDE 209) causes dose–response changes in spontaneous behaviour and cholinergic susceptibility in adult mice," *NeuroToxicology* 29: 911-919, November 2008.
[194] J.B. Herbstman, M. Kurzon, S.A. Lederman, V. Rauh, D. Tang, F. Perera. "Prenatal PBDEs and Neurodevelopment: Herbstman et al. Respond to Goodman et al. and to Banasik and Strosznajde," *Environmental Health Perspectives* 118:a469-a470. doi:10.1289/ehp.1002748R, 2010.
[195] DC Rice et al, "Lessons for Neurotoxicology from Selected Model Compounds: SGOMSEC Joint Report," *Environmental Health Perspectives* 104, Supplement 2:205-15, 1996.
[196] Julie Herbstman et al, "Birth Delivery Mode Modifies the Associations between Prenatal Polychlorinated Biphenyl (PCB) and Polybrominated Diphenyl Ether (PBDE) and Neonatal Thyroid Hormone Levels," *Environmental Health Perspectives* 116: 1376-1382, doi:10.1289/ehp.11379, 27 May 2008.
[197] Stephanie Engel et al, "Prenatal Phthalate Exposure Is Associated with Childhood Behavior and Executive Functioning," *Environmental Health Perspectives* 118: 565-571, doi:10.1289/ehp.0901470, 28 January 2010.
[198] Stephanie Engel et al, "Prenatal phthalate exposure and performance on the Neonatal Behavioral Assessment Scale in a multiethnic birth cohort," *Neurotoxicology* 30:522-528, July 2009.
[199] Bung-Nyun Kim et al, "Phthalates Exposure and Attention-Deficit/Hyperactivity Disorder in School-Age Children," *Biological Psychiatry* 66: 958-963, 15 November 2009.
[200] S.H. Swan et al, "Prenatal phthalate exposure and reduced masculine play in boys," *International Journal of Andrology* 33: 259 -269, 16 November 2009.
[201] Anderson J.M. Andrade et al, "A dose–response study following in utero and lactational exposure to di-(2-ethylhexyl)-phthalate (DEHP): Non-monotonic dose–response and low dose effects on rat brain aromatase activity," *Toxicology* 227: 185-192, 29 October 2006.

[202] J Ahlbom, A Fredriksson, and Per Eriksson, "Exposure to an Organophosphate (DFP) During a Defined Period in Neonatal Life Induces Permanent Changes in Brain Muscarinic Receptors and Behaviour in Adult Mice," *Brain Research* 677:13-19, 1995; Per Eriksson and A Fredriksson, "Neurotoxic Effects of Two Different Pyrethroids, Bioallethrin and Deltamethrin, on Immature and Adult Mice: Changes in Behavioural and Muscarinic Receptor Variables," *Toxicology and Applied Pharmacology* 108:78-85, 1991; Veronica M. Rodriguez, "Sustained Exposure to the Widely Used Herbicide Atrazine: Altered Function and Loss of Neurons in Brain Monoamine Systems" *Environmental Health Perspectives* 113: 708-715, doi:10.1289/ehp.7783, 24 February 2005; Nathan K.W. Colbert et al, "Perinatal Exposure to Low Levels of the Environmental Antiandrogen Vinclozolin Alters Sex-Differentiated Social Play and Sexual Behaviors in the Rat," *Environmental Health Perspectives* 113: 700-707, doi:10.1289/ehp.7509, 16 March 2005.
[203] Raul Harari et al, "Neurobehavioral Deficits and Increased Blood Pressure in School-Age Children Prenatally Exposed to Pesticides," *Environmental Health Perspectives* 118: 890-896, doi:10.1289/ehp.0901582, 25 February 2010.
[204] Virginia A. Rauh et al, "Impact of Prenatal Chlorpyrifos Exposure on Neurodevelopment in the First 3 Years of Life Among Inner-City Children," *Pediatrics*, doi:10.1542/peds.2006-0338, 20 November 2006; Núria Ribas-Fitó et al, "Exposure to Hexachlorobenzene during Pregnancy and Children's Social Behavior at 4 Years of Age," *Environmental Health Perspectives* 115: 447-450, doi:10.1289/ehp.9314, 6 November 2006.
[205] Niclas Johansson et al, "Neonatal Exposure to PFOS and PFOA in Mice Results in Changes in Proteins which are Important for Neuronal Growth and Synaptogenesis in the Developing Brain," *Toxicological Sciences* 108: 412-418; doi:10.1093/toxsci/kfp029, 11 February 2009.
[206] Niclas Johansson et al, "Neonatal exposure to perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) causes neurobehavioural defects in adult mice," *Neurotoxicology* 29: 160-169, January 2008.
[207] Renée Dallaire et al, "Thyroid Function and Plasma Concentrations of Polyhalogenated Compounds in Inuit Adults," *Environmental Health Perspectives* 117: 1380-1386, doi:10.1289/ehp.0900633, 12 May 2009.
[208] Kate Hoffman et al, "Exposure to Polyfluoroalkyl Chemicals and Attention Deficit Hyperactivity Disorder in U.S. Children Aged 12-15 Years. *Environmental Health Perspectives*, doi:10.1289/ehp.1001898, 15 June 2010.
[209] U.S. Centers for Disease Control and Prevention, *Childhood Lead Poisoning Prevention Factsheet*, downloaded from www.cdc.gov on 24 March 2011; Pamela Meyer et al, CDC, *Surveillance for Elevated Blood Lead Levels Among Children --- United States, 1997—2001*, 12 September 2003.
[210] Joan Lowy, "EPA Raises Estimate of Newborns Exposed to Mercury," *Scripps Howard News Service*, 04 February 2004.
[211] J.B. Adams et al, "The Severity of Autism Is Associated with Toxic Metal Body Burden and Red Blood Cell Glutathione Levels," *Journal of Toxicology* 2009, doi:10.1155/2009/532640, 12 July 2009.
[212] Todd A. Jusko et al, "Blood Lead Concentrations < 10 µg/dL and Child Intelligence at 6 Years of Age. *Environmental Health Perspectives* 116: 243-248, doi:10.1289/ehp.10424, 20 November 2007.
[213] Christopher Brubaker et al, "Altered myelination and axonal integrity in adults with childhood lead exposure: A diffusion tensor imaging study," *NeuroToxicology* 30: 867-875, November 2009.
[214] Christina M. Powers et al, "Silver Impairs Neurodevelopment: Studies in PC12 Cells," *Environmental Health Perspectives* 118: 73-79, doi:10.1289/ehp.0901149, 31 August 2009.
[215] Yaginuma-Sakurai, K, K Murata, M Shimada, N Kunihiko, N Kurokawa, S Kameo and H Satoh, "Intervention study on cardiac autonomic nervous system effects of methylmercury from seafood," *Neurotoxicology and Teratology*, doi.10.1016/j.ntt.2009.08.009, March-April 2010.
[216] Jeanne E. Moorman, M.S., et al, Division of Environmental Hazards and Health Effects, National Center for Environmental Health, CDC, National Surveillance for Asthma --- United States, 1980—2004, 56(SS08);1-14;18-54, October 19, 2007;Tracey Woodruff et al, U.S. Environmental Protection Agency, "Trends in Environmentally Related Childhood Illnesses," *Pediatrics* 113: 1133-1140, April 2004; Lara J. Akinbami, U.S. Centers for Disease Control and Prevention, "The State of Childhood Asthma, United States, 1980–2005," *Advance Data from Vital Health and Statistics* 381, 12 December 2006.
[217] U.S. Environmental Protection Agency, *Asthma Prevalence*, 10 March 2010, downloaded from cfpub.epa.gov.
[218] Ben Shaberman, American Academy of Dermatology, "Severe Eczema Strikes Hard at Children," *Dermatology Insights*, Spring 2001.
[219] U.S. Centers for Disease Control and Prevention, "Summary Health Statisticsfor U.S. Children: National Health Interview Survey, 2009," *Vital and Health Statistics* Series 10, Number 247, August 2010.
[220] Shin-ichiro Narita et al, "Environmental Estrogens Induce Mast Cell Degranulation and Enhance IgE-Mediated Release of Allergic Mediators," *Environmental Health Perspectives* 115: 48-52, doi:10.1289/ehp.9378, 3 October 2006.
[221] Anders Glynn et al, "Immune cell counts and risks of respiratory infections among infants exposed pre- and postnatally to organochlorine compounds: a prospective study," *Environmental Health* 7: 62, doi:10.1186/1476-069X-7-62, 4 December 2008.

[222] Tomomi Shigeno et al, "Phthalate ester-induced thymic stromal lymphopoietin mediates allergic dermatitis in mice," *Immunology* 128: e849-e857, doi:10.1111/j.1365-2567.2009.03094.x, 23 March 2009.
[223] Rie Yanagisawa et al, "Effects of Maternal Exposure to Di-(2-ethylhexyl) Phthalate during Fetal and/or Neonatal Periods on Atopic Dermatitis in Male Offspring. *Environmental Health Perspectives* 116: 1136-1141, doi:10.1289/ehp.11191, 9 April 2008.
[224] Hirohisa Takano et al, "Di-(2-ethylhexyl) Phthalate Enhances Atopic Dermatitis-Like Skin Lesions in Mice. *Environmental Health Perspectives* 114: 1266-1269, doi:10.1289/ehp.8985, 15 May 2006.
[225] Barbara Kolarik et al, "The Association between Phthalates in Dust and Allergic Diseases among Bulgarian Children. *Environmental Health Perspectives* 116:98-103, doi:10.1289/ehp.10498, 15 October 2007.
[226] Carl-Gustaf Bornehag et al, "The Association between Asthma and Allergic Symptoms in Children and Phthalates in House Dust: A Nested Case-Control Study," *Environmental Health Perspectives* 112: 1393-1397, doi:10.1289/ehp.7187, 15 July 2004.
[227] Jouni J. K. Jaakkola et al, "Interior Surface Materials and Asthma in Adults: A Population-based Incident Case-Control Study," *American Journal of Epidemiology* 164: 742-749, doi:10.1093/aje/kwj249, 28 July 2006.
[228] Jason P. Hogaboam et al, "The Aryl Hydrocarbon Receptor Affects Distinct Tissue Compartments during Ontogeny of the Immune System," *Toxicological Sciences* 102: 160-170, doi:10.1093/toxsci/kfm283, 17 November 2007.
[229] KJ Fairley et al, "Exposure to the Immunosuppresant, Perfluorooctanoic Acid, Enhances the Murine Ige and Airway Hyperreactivity Response to Ovalbumin," *Toxicological Sciences* 97: 375-383, doi:10.1093/toxsci/kfm053, 15 March 2007.
[230] Donghong Gao et al, "Lead effects on development and function of bone marrow-derived dendritic cells promote Th2 immune responses," *Toxicology and Applied Pharmacology* 222: 69-79, 16 April 2007.
[231] Defined as children up to age 14. U.S. National Cancer Institute, *A Snapshot of Pediatric Cancers*, September 2010, available at www.cancer.gov.
[232] U.S. National Cancer Institute, *A Snapshot of Pediatric Cancers*, September 2010, downloaded from www.cancer.gov.
[233] Dr. Philip Landrigan, Director, Children's Environmental Health Center at the Mount Sinai School of Medicine, *Childhood Cancer and the Environment: Testimony before the President's Cancer Panel*, East Brunswick, New Jersey, 16 September 2008.
[234] U.S. National Cancer Institute, *Surveillance Epidemiology and End Results*, Age-Adjusted Incidence Rates from 1975 to 2007 for individuals less than 20 years old (the youngest window available), downloaded from seer.cancer.gov on 24 Feburary 2011. The percentage change reported here represents the difference between the value of a linear regression trend line through the data in 2007 compared to 1975. For example, see the trend line in figure XX.
[235] Dr. Philip Landrigan, Director, Children's Environmental Health Center at the Mount Sinai School of Medicine, *Childhood Cancer and the Environment: Testimony before the President's Cancer Panel*, East Brunswick, New Jersey, 16 September 2008.
[236] U.S. Department of Health and Human Services, National Toxicology Program, *Report on Carcinogens, Eleventh Edition*, 2005.
[237] Dr. Philip Landrigan, Director, Children's Environmental Health Center at the Mount Sinai School of Medicine, *Childhood Cancer and the Environment: Testimony before the President's Cancer Panel*, East Brunswick, New Jersey, 16 September 2008.
[238] Dr. Philip Landrigan, Director, Children's Environmental Health Center at the Mount Sinai School of Medicine, *Childhood Cancer and the Environment: Testimony before the President's Cancer Panel*, East Brunswick, New Jersey, 16 September 2008; Ghislaine Scélo et al, "Household Exposure to Paint and Petroleum Solvents, Chromosomal Translocations, and the Risk of Childhood Leukemia," Environmental Health Perspectives 117: 133–139, January 2009; Patricia Buffler et al., "Environmental and Genetic Risk Factors for Childhood Leukemia: Appraising the Evidence," *Informa Healthcare* 23: 60-75, 2005.
[239] Donald Wigle, Michelle Turner MC and Daniel Krewski, "A Systematic Review and Meta-analysis of Childhood Leukemia and Parental Occupational Pesticide Exposure," *Environmental Health Perspectives* 117: 1505-1513, doi:10.1289/ehp.0900582, 2009.
[240] Youn K. Shim, Steven P. Mlynarek and Edwin van Wijngaarden, "Parental Exposure to Pesticides and Childhood Brain Cancer: US Atlantic Coast Childhood Brain Cancer Study," *Environmental Health Perspectives* 117:1002-1006, 2009.
[241] Youn K. Shim, Steven P. Mlynarek and Edwin van Wijngaarden, "Parental Exposure to Pesticides and Childhood Brain Cancer: US Atlantic Coast Childhood Brain Cancer Study," *Environmental Health Perspectives* 117:1002-1006, 2009.
[242] Jérémie Rudant et al, "Household Exposure to Pesticides and Risk of Childhood Hematopoietic Malignancies: The ESCALE Study (SFCE)," *Environmental Health Perspectives* 115: 1787-1793, doi:10.1289/ehp.10596, 25 September 2007.

[243] Kori B. Flower et al, "Cancer Risk and Parental Pesticide Application in Children of Agricultural Health Study Participants," *Environmental Health Perspectives* 112: 631-635, doi:10.1289/ehp.6586, 22 December 2003.
[244] Marcia Herman-Giddens, "Recent data on pubertal milestones in United States children: the secular trend toward earlier development," *International Journal of Andrology* 29 Issue 1, Pages 241 – 246, 11 October 2005.
[245] ME Herman-Giddens et al, "Secondary Sexual Characteristics and Menses in Young Girls Seen in Office Practice: A Study From the Pediatric Research in Office Settings Network," *Pediatrics* 99(4): 505-512, 1997.
[246] Marcia Herman-Giddens, "Recent data on pubertal milestones in United States children: the secular trend toward earlier development," *International Journal of Andrology* 29 Issue 1, Pages 241 – 246, 11 October 2005.
[247] Lise Aksglaede et al, "Forty Years Trends in Timing of Pubertal Growth Spurt in 157,000 Danish School Children," *PLoS ONE* 3(7): e2728. doi:10.1371/journal.pone.0002728, 2008.
[248] Kaspar Sørensen et al, "Recent Changes in Pubertal Timing in Healthy Danish Boys: Associations with Body Mass Index," *J. Clin. Endocrinol. Metab.* 95: 263-270, doi: 10.1210/jc.2009-1478, 19 November 2009.
[249] Sandra Steingraber, T*he Falling Age of Puberty in US Girls: What We Know, What We Need to Know.* San Francisco, CA: Breast Cancer Fund. (2007).
[250] Marcia Herman-Giddens, "Recent data on pubertal milestones in United States children: the secular trend toward earlier development," *International Journal of Andrology* 29 Issue 1, Pages 241 – 246, 11 October 2005.
[251] Anne-Simone Parent et al, "The Timing of Normal Puberty and the Age Limits of Sexual Precocity: Variations Around the World, Secular Trends, and Changes After Migration," *Endocrine Reviews* 24: 668-693, 2003.
[252] E. Den Hond and G. Schoeters, "Endocrine disrupters and human puberty," *International Journal of Andrology* 29: 264 – 271, 28 July 2005.
[253] HM Blanck et al, "Age at Menarche and Tanner Stage in Girls Exposed *In-Utero* and Postnatally to Polybrominated Biphenyl," *Epidemiology* 11: 641-647, 2000.
[254] K Howdeshell et al, "Exposure to Bisphenol A Advances Puberty," *Nature* 401, 763-764, 1999.
[255] S Honma et al, "Low Dose Effect of in utero Exposure to Bisphenol-A and Diethylstilbestrol on Female Mouse Reproduction," *Reproductive Toxicology* 16: 117-122, 2002.
[256] Marina Fernández et al, "Neonatal Exposure to Bisphenol A Alters Reproductive Parameters and Gonadotropin Releasing Hormone Signaling in Female Rats," *Environmental Health Perspectives* 117: 757-762, doi:10.1289/ehp.0800267, 7 January 2009.
[257] Nigel C. Noriega et al, "Pubertal Administration of DEHP Delays Puberty, Suppresses Testosterone Production, and Inhibits Reproductive Tract Development in Male Sprague-Dawley and Long-Evans Rats," *Toxicological Sciences* 111: 163-178, doi:10.1093/toxsci/kfp129, 15 June 2009.
[258] I. Colón, D Caro, CJ Bourdony and O Rosario, "Identification of Phthalate Esters in the Serum of Young Puerto Rican Girls with Premature Breast Development," *Environmental Health Perspectives* 108: 895-900, 2000.
[259] T.E. Stoker et al, "In vivo and in vitro anti-androgenic effects of DE-71, a commercial polybrominated diphenyl ether (PBDE) mixture," *Toxicology and Applied Pharmacology* 207: 78-88, 22 August 2005.
[260] S.W. Keith et al, "Putative contributors to the secular increase in obesity: exploring the roads less traveled," *International Journal of Obesity* 30: 1585–1594, doi:10.1038/sj.ijo.0803326, 27 June 2006.
[261] P Bundred, D Kitchiner, and I Buchan, "Prevalence of Overweight and Obese Children Between 1989 and 1998: Population Based Series of Cross Sectiona l Studies," *British Medical Journal* 322:326 –328, 2001.
[262] Cynthia Ogden and Margaret Carroll, U.S. Centers for Disease Control and Prevention, *Prevalence of Obesity Among Children and Adolescents: United States, Trends 1963–1965 Through 2007–2008*, Health E-Stat factsheet, June 2010; CL Ogden et al, "Prevalence and Trends in Overweight Among US Children and Adolescents, 1999-2000," *Journal of the American Medical Association* 288: 1728-1732, 2002.
[263][263] http://www.cdc.gov/nchs/data/hestat/obesity_child_07_08/Figures1.png
[264] AP Rocchini, "Childhood Obesity and a Diabetes Epidemic," *New England Journal of Medicine* 346: 854-855, 2002; American Academy of Pediatrics, "Prevention of Pediatric Overweight and Obesity," *Pediatrics* 112:424-430, 2003.
[265] U.S. Centers for Disease Control and Prevention, *Crude and Age-Adjusted Incidence of Diagnosed Diabetes per 1,000 Population Aged 18–79 Years, United States, 1980–2009*, data from the National Health Interview Survey, computed by personnel in CDC's Division of Diabetes Translation, National Center for Chronic Disease Prevention and Health Promotion, 5 January 2011.
[266] Ervin RB. *Prevalence of metabolic syndrome among adults 20 years of age and over, by sex, age, race and ethnicity, and body mass index: United States, 2003–2006*. National Health Statistics Reports; No 13. Hyattsville, MD: National Center for Health Statistics. 2009.
[267] K Clement and P Ferre, "Genetics and the Pathophysiology of Obesity," *Pediatric Research* 53: 721-725, 2003.
[268] S.W. Keith et al, "Putative contributors to the secular increase in obesity: exploring the roads less traveled," *International Journal of Obesity* 30: 1585–1594, doi:10.1038/sj.ijo.0803326, 27 June 2006.

[269] S.W. Keith et al, "Putative contributors to the secular increase in obesity: exploring the roads less traveled," *International Journal of Obesity* 30: 1585–1594, doi:10.1038/sj.ijo.0803326, 27 June 2006.
[270] Thomas Harder et al, "Birth Weight and Subsequent Risk of Type 2 Diabetes: A Meta-Analysis," *American Journal of Epidemiology*165: 849-857, doi:10.1093/aje/kwk07, 10 January 2007.
[271] Felix Grün and Bruce Blumberg, "Minireview: The Case for Obesogens," Molecular Endocrinology 23:1127-1134, doi:10.1210/me.2008-0485, 2009.
[272] Jérôme Ruzzin et al, "Persistent Organic Pollutant Exposure Leads to Insulin Resistance Syndrome" *Environmental Health Perspectives* 118: 465-471, doi:10.1289/ehp.0901321, 19 November 2009.
[273] Hirokazu Uemura et al, "Prevalence of Metabolic Syndrome Associated with Body Burden Levels of Dioxin and Related Compounds among Japan's General Population," *Environmental Health Perspectives* 117:568-573, doi:10.1289/ehp.0800012, 10 October 2008.
[274] Duk-Hee Lee et al, "Association Between Serum Concentrations of Persistent Organic Pollutants and Insulin Resistance Among Nondiabetic Adults: Results from the National Health and Nutrition Examination Survey 1999–2002," *Diabetes Care* 30: 622-628, doi: 10.2337/dc06-2190, March 2007.
[275] Duk-Hee Lee et al, "A Strong Dose-Response Relation Between Serum Concentrations of Persistent Organic Pollutants and Diabetes: Results from the National Health and Examination Survey 1999–2002," *Diabetes Care* 29: 1638-1644, doi: 10.2337/dc06-0543, July 2006.
[276] Retha Newbold et al, "Developmental exposure to endocrine disruptors and the obesity epidemic," *Reproductive Toxicology* 23: 290-296, April-May 2007; Retha R. Newbold et al, "Developmental exposure to estrogenic compounds and obesity," *Birth Defects Research Part A: Clinical and Molecular Teratology* 73: 478- 480, doi: 10.1002/bdra.20147, 15 June 2005.
[277] BS Rubin et al, "Perinatal Exposure to Low Doses of Bisphenol A Affects Body Weight, Patterns of Estrous Cyclicity, and Plasma LH Levels," *Environmental Health Perspectives* 109: 675-680, 2001; K Howdeshell et al, "Exposure to Bisphenol-A Advances Puberty," *Nature* 401, 763-764, 1999.
[278] H Masuno et al, "Bisphenol A in Combination with Insulin Can Accelerate the Conversion of 3T3-L1 Fibroblasts to Adipocytes," *Journal of Lipid Research* 43: 676-684, May 2002.
[279] K Sakurai et al, "Bisphenol A Affects Glucose Transport in Mouse 3T3-F442A Adipocytes," *British Journal of Pharmacology* 141: 209-214, 2004.
[280] Tetsuya Adachi et al, "Promoting insulin secretion in pancreatic islets by means of bisphenol A and nonylphenol via intracellular estrogen receptors," *Food and Chemical Toxicology* 43: 713-719, May 2005.
[281] Paloma Alonso-Magdalena et al, "The Estrogenic Effect of Bisphenol A Disrupts Pancreatic β-Cell Function *In Vivo* and Induces Insulin Resistance," *Environmental Health Perspectives* 114: 106-112, doi:10.1289/ehp.8451, 20 September 2005.
[282] Eric R. Hugo et al, "Bisphenol A at Environmentally Relevant Doses Inhibits Adiponectin Release from Human Adipose Tissue Explants and Adipocytes," *Environmental Health Perspectives* 116:1642-1647, doi:10.1289/ehp.11537, 14 August 2008.
[283] Agnes Smink et al, "Exposure to hexachlorobenzene during pregnancy increases the risk of overweight in children aged 6 years," *Acta Pædiatrica* 97: 1465 – 1469, 28 Jul 2008.
[284] Felix Grün et al, "Endocrine-Disrupting Organotin Compounds Are Potent Inducers of Adipogenesis in Vertebrates," *Molecular Endocrinology* 20: 2141-2155, doi:10.1210/me.2005-0367, 2006.
[285] Séverine Kirchner et al, "Prenatal Exposure to the Environmental Obesogen Tributyltin Predisposes Multipotent Stem Cells to Become Adipocytes," Molecular Endocrinology 24: 526-539, doi:10.1210/me.2009-0261, 2010
[286] Soo Lim et al, "Chronic Exposure to the Herbicide, Atrazine, Causes Mitochondrial Dysfunction and Insulin Resistance," *PLoS ONE* 4: e5186, doi:10.1371/journal.pone.0005186, 13 April 2009.
[287] Heather Hamlin, "Rats are fat after long-term exposure to lower levels of atrazine," *Environmental Health News*, 23 April 2009.
[288] Soo Lim et al, "Chronic Exposure to the Herbicide, Atrazine, Causes Mitochondrial Dysfunction and Insulin Resistance," *PLoS ONE* 4: e5186, doi:10.1371/journal.pone.0005186, 13 April 2009.
[289] G. Koren, *Maternal-Fetal Toxicology (2nd Ed.)*, Marcel Dekker, Inc. 1994.
[290] S.P. Porterfield, C.E. Hendrich, "The Role of Thyroid Hormones in Prenatal and Neonatal Neurological Development-Current Perspectives," *Endocrinology Review* 14:94-106, 1993.
[291] V.J. Pop et al, "Low Maternal Free Thyroxine Concentrations During Early Pregnancy are Associated with Impaired Psychomotor Development in Infancy," *Clinical Endocrinology* 50, 149-155, 1999; J.E. Haddow et al, "Maternal Thyroid Deficiency During Pregnancy and Subsequent Neuropsychological Development of the Child," *New England Journal of Medicine* 341, 549-555, 1999; G. Morreale de Escobar et al, "Is Neuropsychological Development Related to Maternal Hypothyroidism or to Maternal Hypothyroxinemia?" Journal of Clinical Endocrinology and Metabolism 85, 3975-3987,

2000; K. Howdeshell, "A Model of the Development of the Brain as a Construct of the Thyroid Hormone System," *Environmental Health Perspectives* 110, 337-348, 2002.

[292] AL den Ouden et al, "The Relation Between Neonatal Thyroxine Levels and Neurodevelopmental Outcome at Age 5 and 9 Years in a National Cohort of Very Preterm and/or Very Low Birth Weight Infants," *Pediatric Research* 39, 142-145, 1996.

[293] Reviewed in F Brucker-Davis, "Effect of Environmental Synthetic Chemicals on Thyroid Function," *Thyroid* 8: 827-855, 1998.

[294] Linda C. Giudice, "Infertility and the Environment: The Medical Context," *Seminars in Reproductive Medicine* 24: 129-133, doi:10.1055/s-2006-944418, 2006; Jacky Boivin et al, "International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care," *Human Reproduction* 22: 1506-1512, doi:10.1093/humrep/dem046, 21 March 2007.

[295] Niels E. Skakkebæk et al, "Is human fecundity declining?," *International Journal of Andrology* 29: 2 – 11, doi: 10.1111/j.1365-2605.2005.00573.x, 7 February 2006.

[296] A. Chandra et al, "Fertility, family planning, and reproductive health of U.S. women: data from the 2002 National Survey of Family Growth.," *Vital Health Statistics* 23:1-160, December 2005.

[297] Shanna H. Swan, EP Elkin, and L Fenster, "The Question of Declining Sperm Density Revisited: An Analysis of 101 Studies Published 1934-1996," *Environmental Health Perspectives* 108: 961-966, 2000.

[298] JPE Bonde et al, "Relation Between Semen Quality and Fertility: A Population-Based Study of 430 First-Pregnancy Planners," *Lancet* 352: 1172-1177, 1998.

[299] S Irvine et al, "Evidence of Deteriorating Semen Quality in the United Kingdom: Birth Cohort Study in 577 Men in Scotland Over 11 Years," *British Medical Journal* 312: 467-471, 1996.

[300] Thomas G. Travison et al, "A Population-Level Decline in Serum Testosterone Levels in American Men," *The Journal of Clinical Endocrinology & Metabolism* 92: 196-202, doi:10.1210/jc.2006-1375, 2007.

[301] Shanna H. Swan, "Does Our Environment Affect Our Fertility? Some Examples to Help Reframe the Question," *Seminars in Reproductive Medicine* 24: 142-146 doi:10.1055/s-2006-944420, 2006.

[302] Stanford University School of Medicine and Collaborative on Health and the Environment, *Vallombrosa Consensus Statement on Environmental Contaminants and Human Fertility Compromise,* October 2005.

[303] Louis J. Guillette Jr. and Brandon C. Moore, "Environmental Contaminants, Fertility, and Multioocytic Follicles: A Lesson from Wildlife?," *Seminars in Reproductive Medicine* 24: 134-141, doi:10.1055/s-2006-944419, 2006.

[304] Matthew D. Anway et al, "Epigenetic Transgenerational Actions of Endocrine Disruptors and Male Fertility," *Science* 308: 1466 – 1469, doi: 10.1126/science.1108190, 3 June 2005.

[305] Christiaan de Jaeger et al, "Reduced Seminal Parameters Associated With Environmental DDT Exposure and p,p'-DDE Concentrations in Men in Chiapas, Mexico: A Cross-Sectional Study," *Journal of Andrology* 27, doi:10.2164/jandrol.0512, January/February 2006.

[306] Rebecca M. Steinberg et al, "Effects of Perinatal Polychlorinated Biphenyls on Adult Female Rat Reproduction: Development, Reproductive Physiology, and Second Generational Effects," *Biology of Reproduction* 78: 1091-1101, doi: 10.1095/ biolreprod.107.067249, 27 February 2008.

[307] Russ Hauser, "The Environment and Male Fertility: Recent Research on Emerging Chemicals and Semen Quality," *Seminars in Reproductive Medicine* 24: 156-167, 2006.
DOI: 10.1055/s-2006-944422

[308] "Infertile" in this sentence means unable to achieve pregnancy despite trying for 12 months. Brenda Eskenazi et al, "Serum Dioxin Concentrations and Time to Pregnancy," *Epidemiology* 21: 224-231, doi: 10.1097/EDE.0b013e3181cb8b95, March 2010.

[309] Kim G. Harley et al, "PBDE Concentrations in Women's Serum and Fecundability," *Environmental Health Perspectives* 118: 699-704, doi:10.1289/ehp.0901450, 26 January 2010.

[310] Shanna H Swan et al, "Geographic Differences in Semen Quality of Fertile U.S. Males," *Environmental Health Perspectives* 111: 414-420, April 2003.

[311] Shanna H Swan et al, "Semen Quality in Relation to Biomarkers of Pesticide Exposure," *Environmental Health Perspectives* 111, 1478-1484, June 2003; Shanna Swan, "Semen quality in fertile US men in relation to geographical area and pesticide exposure," *International Journal of Andrology* 29: 62-68, 7 February 2006.

[312] John D. Meeker et al, "The Relationship of Urinary Metabolites of Carbaryl/Naphthalene and Chlorpyrifos with Human Semen Quality," *Environmental Health Perspectives* 112: 1665-1670 , doi:10.1289/ehp.7234, 7 September 2004.

[313] John D. Meeker et al, "Exposure to Nonpersistent Insecticides and Male Reproductive Hormones," *Epidemiology* 17: 61-68, doi: 10.1097/01.ede.0000190602.14691.70, January 2006.

[314] Shu-Yun Zhang et al, "Permethrin May Disrupt Testosterone Biosynthesis via Mitochondrial Membrane Damage of Leydig Cells in Adult Male Mouse," *Endocrinology* 148: 3941-3949, doi:10.1210/en.2006-1497, 26 April 2007.

[315] Kristina Pogrmic et al, "Atrazine Oral Exposure of Peripubertal Male Rats Downregulates Steroidogenesis Gene Expression in Leydig Cells," *Toxicological Sciences* 111: 189-197, doi:10.1093/toxsci/kfp135, 18 June 2009.
[316] Frederick vom Saal et al, "A Physiologically Based Approach to the Study of Bisphenol-A and Other Estrogenic Chemicals on the Size of Reproductive Organs, Daily Sperm Production, and Behavior," *Toxicology & Industrial Health* 14:239-60, 1998.
[317] Motoharu Sakaue et al, "Bisphenol-A Affects Spermatogenesis in the Adult Rat Even at a Low Dose," *Journal of Occupational Health* 43:185-190, 2001.
[318] Keisuke Kawai et al, "Aggressive Behavior and Serum Testosterone Concentration during the Maturation Process of Male Mice: The Effects of Fetal Exposure to Bisphenol A," *Environmental Health Perspectives* 111: 175-178, 2003.
[319] SM Duty et al, "Phthalate Exposure and Human Semen Parameters," *Epidemiology* 14: 269-277, 2003.
[320] Russ Hauser et al, "Altered Semen Quality in Relation to Urinary Concentrations of Phthalate Monoester and Oxidative Metabolites," *Epidemiology* 17: 682-691, doi: 10.1097/01.ede.0000235996.89953.d7, November 2006.
[321] Sergio N. Kuriyama et al, "Developmental Exposure to Low Dose PBDE 99: Effects on Male Fertility and Neurobehavior in Rat Offspring," *Environmental Health Perspectives* 113: 149-154 , doi:10.1289/ehp.7421, February 2005.
[322] Russ Hauser et al, "DNA damage in human sperm is related to urinary levels of phthalate monoester and oxidative metabolites," *Human Reproduction* 22: 688-695, doi:10.1093/humrep/del428, 7 November 2006; John D. Meeker et al, "Urinary Metabolites of di(2-ethylhexyl) phthalate Are Associated with Decreased Steroid Hormone Levels in Adult Men," *Journal of Andrology* 30, doi:10.2164/jandrol.108.006403, May/June 2009; John D. Meeker et al, "Polybrominated diphenyl ether (PBDE) concentrations in house dust are related to hormone levels in men," *Science of the Total Environment* 407: 3425-3429, 1 May 2009; John D. Meeker et al, "Urinary Bisphenol A Concentrations in Relation to Serum Thyroid and Reproductive Hormone Levels in Men from an Infertility Clinic," *Environmental Science and Technology* 44: 1458–1463, doi: 10.1021/es9028292, 23 December 2009.
[323] Smita Salian et al, "Perinatal exposure of rats to Bisphenol A affects the fertility of male offspring," *Life Sciences* 85: 742-752, 18 November 2009.
[324] Nora Benachour and Aziz Aris, "Toxic effects of low doses of Bisphenol-A on human placental cells," *Toxicology and Applied Pharmacology* 241: 322-328, 15 December 2009.
[325] Ulla Nordström Joensen et al, "Do Perfluoroalkyl Compounds Impair Human Semen Quality?" *Environmental Health Perspectives* 117:923-927. doi:10.1289/ehp.0800517, 2 March 2009.
[326] Linda Birnbaum and Suzanne Fenton, "Cancer and Developmental Exposure to Endocrine Disruptors," *Environmental Health Perspectives* 111:389-394. doi:10.1289/ehp.5686, 1 November 2002.
[327] S.G. Baker et al, "Genetic Susceptibility to Prostate, Breast, and Colorectal Cancer among Nordic Twins," *Biometrics* 61: 55-63, March 2005.
[328] Ruthann A. Rudel et al, "Chemicals Causing Mammary Gland Tumors in Animals Signal New Directions for Epidemiology, Chemicals Testing, and Risk Assessment for Breast Cancer Prevention," *Cancer* 109: 2635-2666, doi: 10.1002/cncr.22653, 14 May 2007.
[329] Ruthann A. Rudel et al, "Chemicals Causing Mammary Gland Tumors in Animals Signal New Directions for Epidemiology, Chemicals Testing, and Risk Assessment for Breast Cancer Prevention," *Cancer* 109: 2635-2666, doi: 10.1002/cncr.22653, 14 May 2007.
[330] Silent Spring Institute, *Environment and Breast Cancer: Science Review*, downloaded from sciencereview.silentspring.org/ on 3 March 2011.
[331] Ruthann A. Rudel et al, "Chemicals Causing Mammary Gland Tumors in Animals Signal New Directions for Epidemiology, Chemicals Testing, and Risk Assessment for Breast Cancer Prevention," *Cancer* 109: 2635-2666, doi: 10.1002/cncr.22653, 14 May 2007.
[332] Ruthann A. Rudel et al, "Chemicals Causing Mammary Gland Tumors in Animals Signal New Directions for Epidemiology, Chemicals Testing, and Risk Assessment for Breast Cancer Prevention," *Cancer* 109: 2635-2666, doi: 10.1002/cncr.22653, 14 May 2007.
[333] Julia Green Brody et al, "Environmental Pollutants and Breast Cancer," *Cancer* 109: 2667–2711, 15 June 2007.
[334] Barbara A. Cohn et al, "DDT and Breast Cancer in Young Women: New Data on the Significance of Age at Exposure," *Environmental Health Perspectives* 115: 1406-1414, doi:10.1289/ehp.10260, 2007.
[335] Barbara A. Cohn et al, "DDT and Breast Cancer in Young Women: New Data on the Significance of Age at Exposure," *Environmental Health Perspectives* 115: 1406-1414, doi:10.1289/ehp.10260, 2007.
[336] Sarah Jenkins et al, "Prenatal TCDD Exposure Predisposes for Mammary Cancer in Rats," *Reproductive Toxicology* 23: 391-396, April-May 2007.
[337] Sarah Jenkins et al., "Oral Exposure to Bisphenol A Increases Dimethylbenzanthracene-Induced Mammary Cancer in Rats," *Environmental Health Perspectives* 117: 910-915, doi:10.1289/ehp.11751, 7 January 2009.

[338] Angela Betancourt et al, "Proteomic Analysis in Mammary Glands of Rat Offspring Exposed *in utero* to Bisphenol A," *Journal of Proteomics* 73: 1241-1253, 18 April 2010.
[339] Laura N. Vandenberg et al, "Exposure to Environmentally Relevant Doses of the Xenoestrogen Bisphenol-A Alters Development of the Fetal Mouse Mammary Gland," *Endocrinology* 148: 116-127, doi:10.1210/en.2006-0561, 2007; Tessa Murray et al, "Induction of Mammary Gland Ductal Hyperplasias and Carcinoma *in situ* Following Fetal Bisphenol A Exposure," *Reproductive Toxicology* 23: 383-390, April-May 2007; Milena Durando et al, "Prenatal Bisphenol A Exposure Induces Preneoplastic Lesions in the Mammary Gland in Wistar Rats," *Environmental Health Perspectives* 115: 80-86, doi:10.1289/ehp.9282, 2007; Monica Munoz-de-Toro et al, "Perinatal Exposure to Bisphenol A Alters Peripubertal Mammary Gland Development in Mice," *Endocrinology*, doi:10.1210/en.2005-0340, 26 May 2005; Raquel Moral et al, "Effect of Prenatal Exposure to the Endocrine Disruptor Bisphenol A on Mammary Gland Morphology and Gene Expression Signature," *Journal of Endocrinology* 196: 101-112, doi: 10.1677/JOE-07-0056, 2008.
[340] U.S. National Cancer Institute, *Surveillance Epidemiology and End Results*, Age-Adjusted Incidence Rates for prostate cancer from 1975 to 2007 for males of all ages, downloaded from seer.cancer.gov on 24 Feburary 2011. The percentage change reported here represents the difference between the incidence rate in 2007 vs. 1975, since the trend over time is not linear.
[341] Gail S. Prins et al, "Developmental Estrogen Exposures Predispose to Prostate Carcinogenesis with Aging," *Reproductive Toxicology* 23: 374-382, April-May 2007.
[342] Lennart Hardell et al, "Adipose Tissue Concentrations of Persistent Organic Pollutants and the Risk of Prostate Cancer," *Journal of Occupational & Environmental Medicine* 48: 700-707, July 2006.
[343] Mary Prince et al, "Mortality and Exposure Response among 14,458 Electrical Capacitor Manufacturing Workers Exposed to Polychlorinated Biphenyls (PCBs)," *Environmental Health Perspectives* 114: 1508-1514., doi:10.1289/ehp.9175, 22 June 2006.
[344] Chad Vezina et al, "Dioxin Causes Ventral Prostate Agenesis by Disrupting Dorsoventral Patterning in Developing Mouse Prostate," *Toxicological Sciences* 106 : 488-496, doi: 10.1093/toxsci/kfn183, 8 September 2008.
[345] Catherine Richter et al, "Estradiol and Bisphenol A Stimulate Androgen Receptor and Estrogen Receptor Gene Expression in Fetal Mouse Prostate Mesenchyme Cells," *Environmental Health Perspectives* 115: 902-908, doi:10.1289/ehp.9804, 27 February 2007; Shuk-Mei Ho et al, "Developmental Exposure to Estradiol and Bisphenol A Increases Susceptibility to Prostate Carcinogenesis and Epigenetically Regulates Phosphodiesterase Type 4 Variant 4," *Cancer Research* 66: 5624, doi: 10.1158/0008-5472.CAN-06-0516, 1 June 2006; Barry Timms et al, Estrogenic Chemicals in Plastic and Oral Contraceptives Disrupt Development of the Fetal Mouse Prostate and Urethra," *Proceedings of the National Academy of Sciences* 102: 7014-7019, 10 May 2005.
[346] Yelena Wetherill et al, "Bisphenol A Facilitates Bypass of Androgen Ablation Therapy in Prostate Cancer," *Molecular Cancer Therapeutics*, doi: 10.1158/1535-7163.MCT-06-0272, December 2006.
[347] Xiaohui Xu et al, "Associations of Serum Concentrations of Organochlorine Pesticides with Breast Cancer and Prostate Cancer in U.S. Adults," *Environmental Health Perspectives* 118: 60-66. doi:10.1289/ehp.0900919, 3 September 2009.
[348] Prue Cowin et al, "Early-Onset Endocrine Disruptor–Induced Prostatitis in the Rat," *Environmental Health Perspectives* 116: 923-929, doi:10.1289/ehp.11239, 26 March 2008.
[349] Matthew D. Anway et al, "Endocrine Disruptor Vinclozolin Induced Epigenetic Transgenerational Adult Onset Disease," *Endocrinology*, doi:10.1210/en.2006-0640, 14 September 2006.
[350] U.S. National Cancer Institute, *Surveillance Epidemiology and End Results*, Age-Adjusted Incidence Rates for testicular cancer from 1975 to 2007 for males between the ages of 20 and 49, downloaded from seer.cancer.gov on 24 Feburary 2011. The percentage change reported here represents the difference between the incidence rate in 2007 vs. 1975, since the trend over time is not linear.
[351] Michael Garner et al, "Epidemiology of Testicular Cancer: An Overview," *International Journal of Cancer* 116: 331–339, 1 September 2005.
[352] JD Raman et al, "Increased Incidence of Testicular Cancer in Men Presenting with Infertility and Abnormal Semen Analysis," *Journal of Urology* 174: 1819-22, November 2005.
[353] U.S. National Cancer Institute, *Surveillance Epidemiology and End Results*, Age-Adjusted Incidence Rates for testicular cancer from 1975 to 2007 for males between the ages of 20 and 49, downloaded from seer.cancer.gov on 24 Feburary 2011. The percentage change reported here represents the difference between the incidence rate in 2007 vs. 1975, which is nearly the same as the difference between the two years on a linear regression trend line through the data points.
[354] R Bergstrom et al, "Increase in Testicular Cancer Incidence in Six European Countries: A Birth Cohort Phenomenon," *Journal of the National Cancer Institute* 88: 727–733, 1996.
[355] As cited in: CG Ohlson and L Hardell, "Testicular Cancer and Occupational Exposures with a Focus on Xenoestrogens in Polyvinyl Chloride Plastics," *Chemosphere* 40: 1277-1282, May–June 2000.

[356] As cited in: CG Ohlson and L Hardell, "Testicular Cancer and Occupational Exposures with a Focus on Xenoestrogens in Polyvinyl Chloride Plastics," *Chemosphere* 40: 1277-1282, May–June 2000.
[357] Lennart Hardell et al, "Increased Concentrations of Polychlorinated Biphenyls, Hexachlorobenzene, and Chlordanes in Mothers of Men with Testicular Cancer," *Environmental Health Perspectives* 111: 930-934, 2003.
[358] U.S. Centers for Disease Control and Prevention, "Blood Lead Levels Keep Dropping; New Guidelines Proposed for Those Most Vulnerable," (*Press Release*), 20 February 1997.
[359] U.S. Centers for Disease Control and Prevention, "Blood Lead Levels Keep Dropping; New Guidelines Proposed for Those Most Vulnerable," (*Press Release*), 20 February 1997.
[360] Stephen J. Rothenberg et al, "Testing the Dose–Response Specification in Epidemiology: Public Health and Policy Consequences for Lead," *Environmental Health Perspectives* 113: 1190-1195, doi:10.1289/ehp.7691, 10 May 2005.
[361] Stephen J. Rothenberg et al, "Testing the Dose–Response Specification in Epidemiology: Public Health and Policy Consequences for Lead," *Environmental Health Perspectives* 113: 1190-1195, doi:10.1289/ehp.7691, 10 May 2005.
[362] R.M. Whyatt et al, "Prenatal Insecticide Exposures, Birth Weight and Length Among an Urban Minority Cohort," *Environmental Health Perspectives*, doi:10.1289/ehp.6641, 22 March 2004.
[363] Richard Perez-Pena, "Babies are Larger After Ban on Two Pesticides, Study Finds," *New York Times*, 22 March 2004.
[364] Sanna Lignell et al, "Persistent organochlorine and organobromine compounds in mother's milk from Sweden 1996–2006: Compound-specific temporal trends," *Environmental Research* 109: 760-767, August 2009.
[365] Sanna Lignell et al, "Persistent organochlorine and organobromine compounds in mother's milk from Sweden 1996–2006: Compound-specific temporal trends," *Environmental Research* 109: 760-767, August 2009.
[366] Richard Y. Wang et al, "Serum Concentrations of Selected Persistent Organic Pollutants in a Sample of Pregnant Females and Changes in Their Concentrations during Gestation," *Environmental Health Perspectives* 117: 1244-1249, doi:10.1289/ehp.0800105, 12 March 2009.
[367] CDC, Third National Report on Human Exposure to Environmental Chemicals. Atlanta, GA: Centers for Disease Control and Prevention. 2005a
[368] Linked: Penelope J.E. Quintana et al, "Adipose Tissue Levels of Organochlorine Pesticides and Polychlorinated Biphenyls and Risk of Non-Hodgkin's Lymphoma," *Environmental Health Perspectives* 112: 854-861, doi:10.1289/ehp.6726, 2 March 2004. United States: The Collaborative on Health and the Environment, *Protecting Our Health: Non-Hodgkin's Lymphoma in the United States*, downloaded from protectingourhealth.net/newscience/nonhodgkins/2004/2004-0830nhlrate.htm on 29 June 2010. Europe: Lennart Hardell and Mikael Eriksson, "Is the Decline of the Increasing Incidence of Non-Hodgkin Lymphoma in Sweden and Other Countries a Result of Cancer Preventive Measures?," *Environmental Health Perspectives* 111: 1704–1706, doi:10.1289/ehp.6270, 2 July 2003.
[369] Lennart Hardell and Mikael Eriksson, "Is the Decline of the Increasing Incidence of Non-Hodgkin Lymphoma in Sweden and Other Countries a Result of Cancer Preventive Measures?," *Environmental Health Perspectives* 111: 1704–1706, doi:10.1289/ehp.6270, 2 July 2003.
[370] Sanna Lignell et al, "Persistent organochlorine and organobromine compounds in mother's milk from Sweden 1996–2006: Compound-specific temporal trends," *Environmental Research* 109: 760-767, August 2009.
[371] D Meironyte, K Noren and A Bergman, "Analysis of Polybrominated Diphenyl Ethers in Swedish Human Milk. A Time-Related Trend Study, 1972-1997," *Journal of Toxicology and Environmental Health*, 58(6), 329-41, 26 November 1999; K Noren and D Meironyte, "Certain Organochlorine and Organobromine Contaminants in Swedish Human Milk in Perspective of Past 20-30 Years" *Chemosphere* 40, 1111-1123, 2000.
[372] JLDaniels, I-J Pan, R Jones, S Anderson, DG Patterson Jr, et al. 2009 Individual Characteristics Associated with PBDE Levels in U.S. Human Milk Samples. Environmental Health Perspectives 118(1): doi:10.1289/ehp.0900759 2009
[373] Reviewed in Y Kucher and M Purvis, Environment California and the State Public Interest Research Groups, *Body of Evidence: New Science in the Debate over Toxic Flame Retardants and Our Health*, 18 February 2004.
[374] K Noren., D Meironyte., *Certain Organochlorine and Organobromine Contaminants in Swedish Human Milk in Perspective of Past 20-30 Years.* Chemosphere 40, 1111-1123, 2000.
[375] U.S. Environmental Protection Agency, *Chemical Hazard Data Availability Study,* 1998. Major chemicals are defined as those produced or imported in amounts exceeding one million pounds per year.
[376] Commission of the European Communities, *White Paper: Strategy for a Future Chemicals Policy*, COM(2001) 88 final, 27 February 2001; Carcinogenic, mutagenic, and reprotoxic chemicals, plus chemicals defined as category 1 or 2 in EU Directive 67/548, plus persistent organic pollutants.
[377] Richard Wiles, Environmental Working Group, *Asbestos: Think Again*, 4 March 2004.
[378] U.S. Environmental Protection Agency, *EPA Administrator Jackson Unveils New Administration Framework for Chemical Management Reform in the United States* (press release), 29 September 2009.
[379] Dr. Ronny van Aerle et al, *The Prague Declaration on Endocrine Disruption*, 4 May 2006.