GIRL, DISRUPTED

Hormone Disruptors and Women's Reproductive Health

A REPORT ON THE WOMEN'S REPRODUCTIVE HEALTH AND THE ENVIRONMENT WORKSHOP

Girl,

This report was produced by the Collaborative on Health and the Environment (CHE). CHE's administrative headquarters are located at Commonweal, a health and environmental research institute in Bolinas, California.

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Hormone Disruptors and Women's Reproductive Health

A Report on the Women's Reproductive Health and the Environment Workshop

This report summarizes the key outcomes of the Women's Reproductive Health and the Environment Workshop, held in January 2008 at Commonweal, a health and environmental research institute in Bolinas, California. The scientific results of the workshop were written by Crain et al. and are published in "Female reproductive disorders: The roles of endocrine disrupting compounds and developmental timing." The article can be found online at www.fertstert.org in the October 2008 issue of the journal *Fertility and Sterility*.[1] See References for full citation.

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For more information about the workshop, please visit: www.healthandenvironment.org/reprohealthworkshop.

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Introduction

Imagine you are building a house. What would happen if you left a brick out of the foundation, or added a few bricks where they did not belong? The house may seem fine, but the hidden fault might impair the structure or make the house more vulnerable to other stressors. The house may stand for years without trouble, slowly crumble over time, or suddenly collapse in an earthquake or hurricane. Like bricks in the foundation of a house, hormone-controlled prenatal (before birth) development of the reproductive system lays the foundation for a person's lifelong reproductive health. Small hormone disruptions during this critical time — or at another hormone-driven stage of development like early life or puberty — can lead to reproductive health problems or an increased vulnerability to reproductive disorders later in life.

The Problem

Chemicals can impact female reproductive health by interfering with hormones that regulate reproductive system development.

A woman's body goes through a wide range of changes throughout her lifetime. Each stage of her life, from fetal development through her post-menopause years, involves a direct relationship between her hormones and how her body develops and functions. When this relationship is in balance, it helps create the conditions for good health. When this relationship is out of balance, it can lead to a range of health problems that can be painful and devastating.

Scientific evidence increasingly shows that some industrial chemicals, known as endocrine-disrupting compounds (EDCs), or **hormone disruptors**, can throw off this balance, particularly if exposure occurs during fetal development. Other stages of rapid development are also vulnerable to hormone disruption. With exposure, women and girls are at greater risk for developing reproductive health problems such as early puberty, infertility, and breast cancer.[1]

Hormone disruptors have come under increased scrutiny as industrial chemical production has proliferated. Over the last 70 years, more than 80,000 chemicals have been registered for use in commerce. More than 3,000 of these are produced or imported in amounts over one million pounds per year. An EPA analysis finds that 43 percent of these high production chemicals have no testing data on basic toxicity, and only seven percent have a full set of basic test data.[2] Many of these chemicals may not harm human health, but without testing we have no way to know. Additionally, a significant number of compounds already tested are now believed to increase risk for serious health problems, and these health problems can be passed on from generation to generation. Although many different chemicals can increase a woman's risk for health problems, hormone disruptors are of particular concern because they can alter the critical hormonal balances required for proper health and development at all stages of a woman's life.

Building Consensus: The Women's Reproductive Health and the Environment Workshop

Historically, most hormone disruptor research has focused on males. Compelled by reports of declining sperm counts, increased incidence of male birth defects, and rising rates of adult testicular cancer, leading researchers gathered in Copenhagen in 1996 to discuss and debate the state of the science on male reproductive health and the environment. The group concluded that hormone disruptors might be contributing to rising rates of male reproductive health problems.[3]

The meeting also led to the development of the "testicular dysgenesis syndrome" hypothesis, which states that hormone disruption during a key period of fetal testis development might be a common origin for multiple male reproductive disorders. These findings have since stimulated a new generation of research and increased the dialogue around hormone disruptors and male reproductive health among governments, healthcare providers, and the public.[1]

What is the state of the scientific evidence on hormone disruptors and women's reproductive health? In January 2008, 18 leading researchers specializing in issues related to hormone disruption and women's reproductive health convened at Commonweal, a nonprofit health and environmental research institute in Bolinas, California, to address this question. They agreed on five main activities, including:

1. **Mapping what is known** about female reproductive health problems.
2. **Evaluating the possible role of hormone disruptors** in female reproductive health disorders.
3. **Summarizing critical gaps in research** that prevent us from fully understanding the contributions of hormone disruptors to female reproductive health problems.
4. **Identifying a common origin of female reproductive health problems** in prenatal development, similar to the testicular dysgenesis syndrome hypothesis for males.
5. **Writing a scientific review paper** summarizing their findings, and disseminating the information to a broader audience.

Like the influential paper from the male reproductive health and the environment meeting, the resulting scientific review paper from the women's environmental reproductive health workshop was published in a respected journal. The review was written by Crain et al. and is titled "Female reproductive disorders: The roles of endocrine-disrupting compounds and developmental timing." It can be found online at www.fertstert.org in the October 2008 issue of *Fertility and Sterility*.[1] The authors of the paper hope their findings and analysis will catalyze a new wave of research on hormone disruptors and, ultimately, lead to greater protections from chemicals that affect the reproductive health of women and girls. The goal of this report is to translate the complex research findings from the scientific paper for key stakeholders and advocates working to support these same efforts.

The Basics

Before we examine the relationship between hormone disruptors and women's reproductive health and development, we should consider some basic but important questions and concerns.

Are Female Reproductive Disorders on the Rise?

Do women today suffer a higher rate of reproductive problems than their grandmothers did? It is difficult to know for certain. Historical data and on-going records that could definitively indicate a trend generally do not exist. But the limited data we do have is troubling. Conception rates fell by 44 percent in the United States between 1960 and 2002,[4] and the number of couples reporting fertility problems has increased over the last two decades. Some of the increase is likely due to people starting families later in life — we know that fertility decreases with age. But that does not explain why the sharpest increase in reported infertility was seen in younger women, under age 25.[5-7]

Improvements in health tracking are vital for better understanding female reproductive health trends. We do know that millions of women are affected by reproductive disorders, including early puberty, uterine fibroids, endometriosis, polycystic ovarian syndrome (PCOS), and breast cancer.[1] These health problems can be devastating to a woman's fertility, overall health and quality of life. In the United States alone, women's reproductive health disorders cost billions of dollars in healthcare and loss of productivity. Many

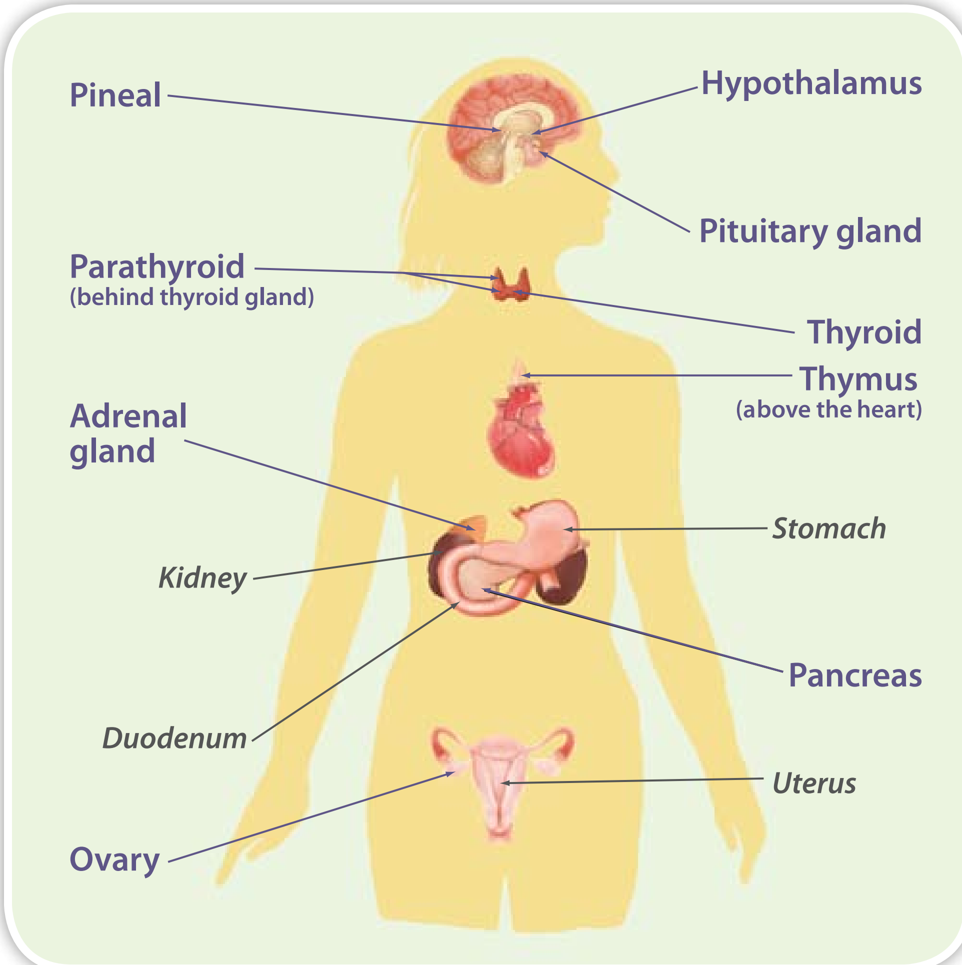


FIGURE 1: Major female endocrine tissues, organs, and glands, in purple (partial listing).

factors play a role in a woman's overall reproductive health, including her genetic makeup, diet, age, exercise habits, racial and economic injustices, sexually transmitted diseases, and access to good healthcare. Emerging science shows that hormone disruptors also play a role.

> **Estrogens are typically considered "female" hormones, and androgens such as testosterone are typically considered "male" hormones, but both estrogens and androgens are present—and needed—to varying degrees in both sexes.**

What Role Do Hormones Play?

In order to understand how hormone disruptors impact female reproductive health, it is important to recognize what hormones do. Hormones are important signaling molecules that help different parts of the body communicate. Examples of hormones include adrenaline, estrogen, insulin, thyroid hormones, and testosterone.

The endocrine system consists of an integrated set of organs that use tiny amounts of these hormones to orchestrate the growth, development, and everyday functioning of several of the body's systems, including the entire reproductive system. Endocrine tissues—including the ovaries (women), testes (men), pituitary, thyroid, adrenal glands, and pancreas—secrete hormones into the blood as chemical messengers that direct communication and coordination among the body's tissues. For example, hormones work with the nervous system, reproductive system, kidneys, gut, liver, and fat to help maintain and control several functions, including:

- Body energy levels
- Reproduction
- Growth and development
- Internal balance of body systems (called homeostasis)
- Responses to surroundings, stress, and injury[8]

It is a complex balancing act. Endocrine tissues are like air traffic control towers at busy airports.

One way that hormones convey messages is by connecting with specific receptors that exist on a cell surface or within a cell. When they connect to their receptor, a cellular response follows. Often this includes a particular gene being turned on or off. In order for a gene to be "read," the DNA uncoils so the "text" of the gene can be ultimately translated into a protein. Proteins comprise much of our body's structures, govern chemical reactions in our cells, keep our metabolic machinery ticking, and regulate our immune response. The uniqueness of each person's genetic code means that people also differ in their protein makeup. This is one reason why two people might respond differently to the same hormone disruptor.

Hormones, Disrupted

Hormone disruptors are substances that interfere with the production, release, transport, metabolism, binding, action, or elimination of the body's natural hormones. Usually, hormones bind to their receptors like a lock and key. When the hormonal key fits the

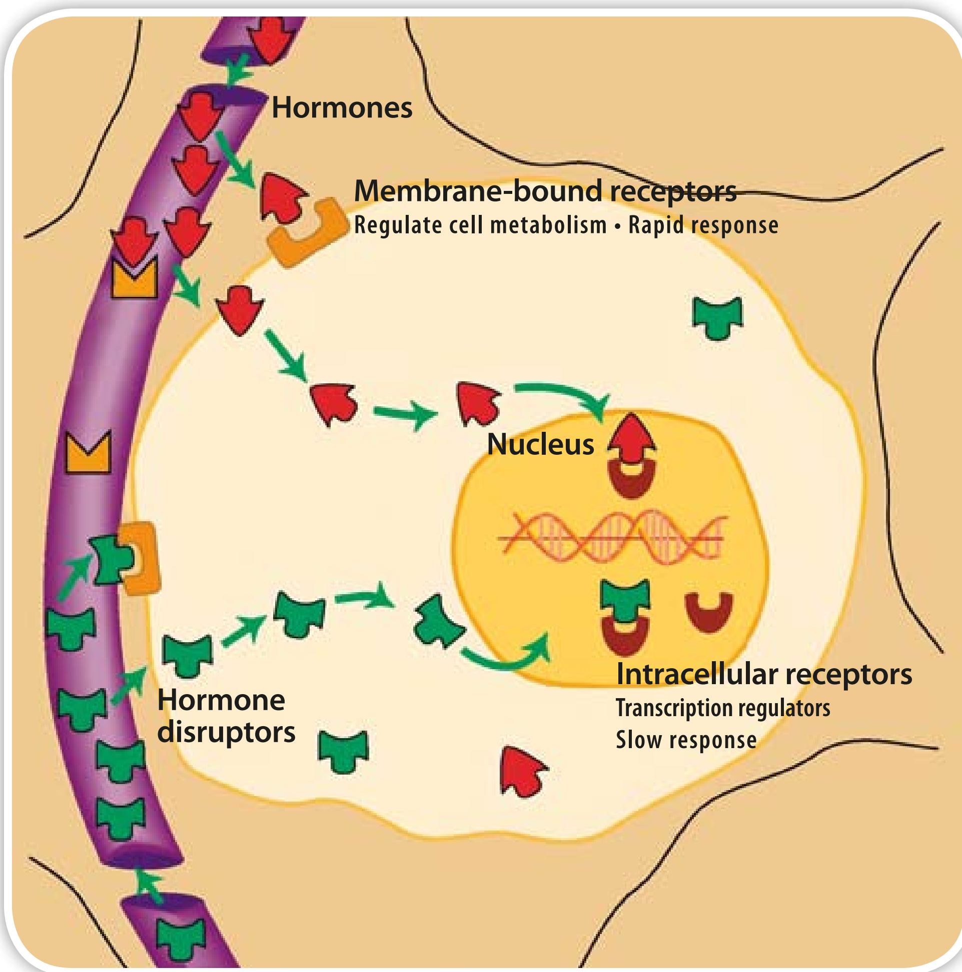


FIGURE 2: A depiction of how hormones connect with specific receptors on a cell surface or within a cell. A cascade of cellular events follows that often results in a particular gene being turned on or off. Hormone disruptors can interfere with this process.

How We Are Exposed

People can be exposed to hormone disruptors indoors and outdoors, at home, in daycare or school, and in the workplace. Hormone disruptors get into our bodies when we breathe, eat, drink, and have skin contact with them. They can be found in household products such as cosmetics, food containers, and toys. They can come from industrial pollution and cigarette smoke. Many pesticides are hormone disruptors and can end up on our food and in our drinking water. The below table provides a few examples of hormone disruptors and their sources, but more research is needed to identify all hormone disruptors and their potential health impacts.

Table 1: Examples of Hormone Disruptors

Atrazine	One of the most heavily used herbicides in the United States and widely applied to lawns, corn, and soy crops. It is banned in the European Union due to concerns of groundwater contamination.[9]
Bisphenol A (BPA)	Invented as a synthetic estrogen in 1936 and was considered for use in pharmaceuticals[10] until the more potent estrogen, diethylstilbestrol (DES), was synthesized in 1938.[11] Thus, BPA was never used as a drug. Instead, since 1957, BPA has been used to make many common products, including some plastic products such as sports bottles and baby bottles, and in the linings of cans for food and infant formula.
Cigarette Smoke *First and Secondhand*	Contains hundreds of chemicals, including some hormone disruptors. More research is needed to fully understand how cigarette smoke affects hormone function. This research is especially important because cigarette smoke is very common and because so many health problems are associated with it.
Dichloro diphenyl trichloroethane (DDT)	This insecticide was widely used in the United States until it was banned in 1972 due to toxicity.[12] DDE, a by-product from the breakdown of DDT is also harmful. DDT is still used in some other countries, often to eliminate mosquitoes associated with malaria risk.
Diethylstilbestrol (DES)	A synthetic estrogen that was first synthesized in 1938[11] and was mistakenly thought to prevent miscarriages. The drug was prescribed until the early 1970s, when its associated health risks became known. We have learned a lot about how hormone disruptors work by studying the daughters of women who took DES during pregnancy.
Dioxins	A family of compounds that are byproducts of some manufacturing and incineration processes. The uncontrolled burning of residential waste is thought to be among the largest sources of dioxins in the United States.[13] The bleaching process used to produce most paper and cotton products also releases dioxins into the environment. Because dioxins accumulate and persist in fat, a major source of exposure for humans is through contaminated foods like high-fat beef and dairy products.
Polybrominated biphenyls (PBBs)	Used as flame retardants in electrical appliances, textiles, plastic foams and other products.[14] In 1976 the manufacturing of PBBs ended in the United States after they contaminated milk supplies.[15-16]
Polychlorinated biphenyls (PCBs)	A class of compounds that were used as coolants and insulation in electrical equipment,[17] in coating of electrical wiring and for many other purposes. They were banned in the 1970s due to their toxicity.
Phthalates	A family of compounds used as a plasticizer in PVC (vinyl), cosmetics, fragrance and medical products, such as slow-release pharmaceuticals, and plastic tubing and blood bags. Some phthalates were banned from children's products in 2008.[18]
Phytoestrogens	Estrogen-like chemicals naturally found in plant foods such as beans, seeds, and grains. Soy, for example, contains the phytoestrogen genistein.[19] Even though some plants contain small amounts of naturally occurring hormone disruptors, there are many co-benefits from eating a plant-based diet.

> *Some hormone disruptors such as DDT,[20] PBBs,[21-22] and PCBs[23] were banned more than 30 years ago but can still be found in the environment and in the bodies of people and animals to this day.*

receptor lock, it triggers a process of sending messages to regulate functions in the body. Hormone disruptors can interfere with this process by scrambling these messages in different ways. For example, some can mimic natural hormones and bind to their receptors, triggering the process but sending the wrong message at the wrong time. Others can block natural hormones from binding to their receptors at the appropriate time, keeping the right message from being sent.

Some hormone disruptors can change which genes are read and understood by the body, or they can change when genes are turned on and off at critical stages of development. Hormone disruptors can alter when a natural hormone is made or how much of a given hormone is destroyed and removed from the body. Interestingly, scientists are finding that some hormone disruptors have the ability to interfere with normal hormone signaling through several of these mechanisms. If exposure occurs at a critical time in development, even a very low dose of a hormone disruptor can throw the endocrine system off-balance, introducing an error in the development of a tissue or system that may not be apparent until much later, like leaving a brick out of a building's foundation.

Getting Perspective: The Historical Context

Wildlife observations and unfortunate human tragedies caused the scientific community to re-evaluate what was known about reproductive health and the environment in the 20th century. The following past discoveries laid the foundation for current scientific directions.

The Myth of the Impermeable Placenta

A mother's exposure to environmental contaminants can affect the future health of her children and possibly grandchildren. We did not always know this. We used to think the placenta, which provides blood, oxygen, and nutrients to a developing fetus, was a virtually impermeable shield protecting the fetus from harmful agents. There were several unfortunate incidences in the mid–twentieth century that disproved this theory. One of the most poignant was a tragedy involving a drug called thalidomide that demonstrated that pharmaceuticals taken during pregnancy could in fact harm a fetus.

Thalidomide was a sedative drug prescribed to pregnant women in the late 1950s and early 1960s to treat morning sickness and sleeplessness. The women who took it did not experience any side effects, but thousands of their babies were born with missing or severely disfigured limbs and other birth defects. The tragedy underscored that if a pregnant woman is exposed to a chemical, her fetus can be harmed, even if she unaffected. It also emphasized the importance of the timing of those exposures. With thalidomide, for example, children's limbs were affected only when the drug was taken within a specific time frame in the first trimester, during the period of fetal limb development.[24] The thalidomide tragedy and other similar occurrences demonstrate that the placenta is not an impermeable shield as was previously thought.

What Can We Learn from Alligators?

Since World War II, numerous chemical products have aided modern society, including pesticides, cosmetics, preservatives, cleaning products, pharmaceuticals, and plastics. PCBs (now banned) prevent fires in electrical transformers, DDT kills disease-carrying or crop-destroying insects, and BPA protects food cans

PHOTOS COURTESY OF LOUIS J. GUILLETTE, PH.D., UNIVERSITY OF FLORIDA

FIGURE 3: (left) A recently hatched alligator; (right) an adult American alligator feeding on its prey, Lake Apopka, Florida.

from corrosion and makes plastics clear and hard. Although man-made chemicals have benefited people's lives in many ways, they have also contaminated the environment.

Scientists began documenting the results of this contamination in the 1950s by observing wildlife populations. For years, researchers recorded declining or even disappearing populations of birds, fish, frogs, and other wildlife. They found that many of these animals were suffering from reproductive problems that could be linked to contamination of their habitats with hormonally active industrial chemicals.[24]

One such finding involved the study of the American alligator in Lake Apopka, Florida. In 1985, University of Florida zoologist Dr. Louis Guillette Jr. and his team began studying alligators in Lake Apopka to better understand their reproductive biology. The team soon realized the alligators were suffering from reproductive failure. The male gators had abnormally small penises, and most of the eggs laid by female alligators did not hatch. Half of the baby alligators that did hatch died within days. The researchers linked the alligators' reproductive problems to a severe chemical spill in 1980 that released pesticides into the lake. Right after the spill, more than 90 percent of the alligator population disappeared. But, subsequent samples of the lake water showed the original pesticide contamination had cleared, suggesting the alligator population should no longer be impacted.[24]

Once the research team considered hormone disruption as a possible underlying cause of the continuing reproductive failure, everything became clear. The pesticides, which had accumulated in the alligators' bodies, were hormonally active. They were disrupting the alligators' reproductive systems, even at very low doses.[25] In addition, mother alligators were passing accumulated pesticides on to their offspring through the yolks of their eggs.[26] Lab studies confirmed these findings and also showed that female alligators exposed to the same pesticides during critical periods of development had ovarian follicles that were producing multiple eggs per follicle when they should only be producing one.[27-28]

Many other wildlife studies have provided "canary in the coal mine" warnings about hormone disruptors and our own reproductive health. Numerous laboratory studies have confirmed what researchers have observed in wildlife populations. Both wildlife and laboratory studies have helped scientists understand and predict how hormone disruptors can increase our risk for various health problems. Although hormone activity varies across species, the underlying genes and cellular mechanisms controlling reproductive

> *"Although hormone activity varies across species, the underlying genes and cellular mechanisms controlling reproductive development are nearly identical in all vertebrates, whether in alligators, mice or humans.[25]"*

Hormone disruptor research has typically focused on estrogens. But endocrine disruption goes beyond estrogens, androgens, and the reproductive system. Hormone disruptors, for example, can also affect thyroid hormones. Thyroid disruption during development can have lifelong consequences because normal thyroid balance is critical for central nervous system development.[31]

development are nearly identical in all vertebrates, whether in alligators, mice, or humans.[25]

Animal studies are vital for studying the impacts that hormone disruptors can have on human reproductive health, particularly in the absence of comprehensive human data. However, an accidental experiment in the mid-twentieth century demonstrated the devastating impact exposure to a hormone disruptor could have on the development of the human female reproductive system.

Tragic Lessons: Fetal Origins of Adult Disease

In the late 1940s, pregnant women with a history of miscarriage or premature birth were offered a new preventative drug: an estrogenic pharmaceutical called diethylstilbestrol (DES). An estimated 5–10 million pregnant women and their children were exposed to DES.[29] Although there was little evidence to show the drug actually worked, doctors continued to prescribe DES until 1971, when an account was published of several young women with a rare vaginal cancer. Their mothers had taken DES during pregnancy.

Until that time, this type of vaginal cancer, called clear cell adenocarcinoma, had virtually never been reported in women under 50.[30] As researchers explored the health of "DES daughters" further, they discovered that prenatal exposures to DES had caused other reproductive tract abnormalities and health problems, including decreased fertility, increased risk of ectopic pregnancy (when a fertilized egg implants outside the uterus), increased breast cancer risk, and early menopause.[1]

DES taught us three important lessons that can guide our investigations of other chemicals:

- Exposure to hormone disruptors during fetal development can induce reproductive tract defects or other health impacts in the fetus, even if exposure does not affect the mother's health.
- The risk of health impacts from exposure to hormone disruptors is especially high during prenatal development.
- A disease induced during development might only be apparent decades later, and exposure to this one chemical could lead to multiple health risks. Girls who were exposed to DES prenatally appeared to develop normally. Only in adulthood did health impacts like uterine malformations, infertility, vaginal cancer, and breast cancer become apparent.

These lessons continue to teach scientists about the risks of modern hormone disruptors and can help our society avoid another chemical tragedy.

Scientific Evolution

Building on past discoveries and research, scientists continue to refine what we know about hormone disruptors and their effects on female reproductive health and development. Our understanding of health risks continues to evolve and reflect the complexity of chemical impacts to health.

We now know that most disease is caused by interactions between a woman's genetic makeup and the chemistry of her environment, rather than genetics alone. We know that high dose toxicology studies may not accurately predict low dose effects. We know that health impacts from hormone disruptors depend on when exposure occurred, and that disease might only become obvious years or decades later. We know that exposures of one generation can affect the next generation. Finally, we know that development of one reproductive disorder can indicate increased risk for other disorders because the entire reproductive system depends on the same hormonal signals and developmental architecture.

BPA, A Modern Day Human Health Threat: Lessons Learned from DES?

The wisdom we gained from the tragic lessons of DES is now being applied to chemicals with like properties such as bisphenol A (BPA). BPA is also a synthetic estrogen, and appears to act in similar ways to DES. In fact, BPA was intended for use as an estrogenic drug in the 1930s, but was abandoned when DES was found to be more potent.[32] Today, BPA is used in a variety of common products, including baby bottles, food containers, sport water bottles, dental sealants, and in the linings of food cans. The chemical can leach into foods and liquids. Annual worldwide BPA production is estimated to be 6.4 billion pounds.[33] The Centers for Disease Control and Prevention (CDC) detected BPA in nearly 93 percent of the people they tested,[34] raising new questions about its widespread use.

BPA has been linked to a variety of health problems, including changes in behavior,[35] prostate cancer,[36] diabetes, obesity, and cardiovascular disease.[37-38] Many studies also confirm a link between BPA and female reproductive health problems. Studies in which mice were exposed to BPA during fetal development or just after birth showed significant female reproductive system effects such as altered mammary gland development that led to significant changes in adult mammary gland composition. Exposed mice also had irregular or longer fertility cycles and accelerated puberty. These changes may serve as harbingers of later health problems such as breast cancer, changes in lactation, or reduced fertility.[1] The few existing human studies also show reasons for concern. BPA can cause human breast cancer cells to grow and replicate in the lab[39] and become resistant to chemotherapeutic agents.[40] A study of normal human breast tissue found that BPA induced changes associated with highly aggressive breast cancer tumors and poor survival rates.[41] In Japan, researchers described a link between BPA levels in the body and recurrent miscarriage.[42]

The effects in animals, the small but important body of knowledge about BPA's effects on human health, and the widespread human exposure has led to the international questioning of BPA's safety. The potential for such harm has been, and continues to be, an area of intense debate among national governments. Currently, the U.S. and European food safety authorities approve BPA as a food additive.[43-44] However, Canada has banned the use of BPA in baby bottles and is evaluating its use in canned food.[45] At the time of this printing, despite the many scientific reasons for concern, the U.S. federal government has not taken any action to limit the use of BPA.

"Safe" Levels of Exposure: Not So Safe After All

For years, it was assumed that low levels of chemical exposure would not harm our health. This assumption rested upon a classic idea in toxicology that is often summed up in the phrase "the dose makes the poison." This idea holds that increasing doses of exposure to a given toxic substance are associated with increasing levels of harm. For example, the more alcohol someone consumes, the more likely that person is to develop liver disease.

Congruently, the idea holds that if a person is exposed to a small enough dose of the substance, he or she will not be at risk of suffering any health effects. Based on this premise, toxicologists have traditionally assessed chemical risk assuming that there must be a "safe" dose at which levels are too low to cause any real harm. But we are finding that this is not true, particularly when we look at large populations with differences in age, disease status and genetics.

Hormone disruptors are one class of chemicals that illustrate why low levels of chemical exposure matter. Very small amounts of the body's natural hormones play a major signaling role in development, such as triggering and controlling the unfolding of puberty. So the endocrine system is responsive to even tiny doses of hormone disruptors. It is not that hormone disruptors have no effect at these low doses—they simply have different effects. In fact, exposure to

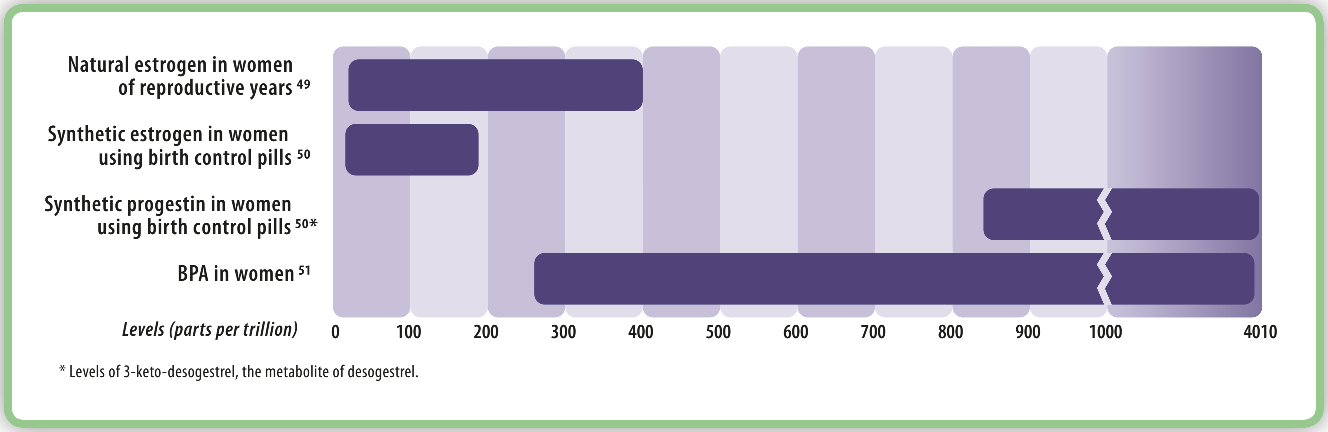


FIGURE 5: *Hormone Activation Levels:* **Natural or synthetic hormones can activate changes at very low levels. This graph shows normal levels of natural estrogen (estradiol) in women and levels of synthetic estrogen (ethinyl estradiol) in women taking birth control pills. These levels are adequate to activate significant functions, such as regulating menstrual cycles and preventing pregnancy, respectively. BPA, which can mimic natural estrogen, can be found in the body under normal conditions at the same or higher levels than natural or synthetic estrogen. BPA is less potent than natural estrogen, but these levels are troubling.**

a small amount of a hormone disruptor can have a graver impact than exposure to a large amount.

Researchers recently reported that mice exposed to extremely low levels of DES in the womb grew to be extremely obese in adulthood, whereas mice exposed to higher levels of DES actually lost weight in adulthood.[46] Likewise, some studies have found that very low levels of BPA can harm reproductive health in female mice[47] and their offspring.[48] More research is needed to fully understand how BPA impacts humans. The ubiquitous chemical has been found in women at levels that are within the range studied in many animal models,[1] and at the same or higher levels than natural estrogen and synthetic estrogen in women taking birth control pills (levels that are sufficient to activate hormonal changes in the body).[49-51] Although BPA is less potent than natural estrogen (meaning it will not bind to the body's natural estrogen receptors as readily), these levels are troubling.

Additionally, people are exposed not merely to one hormone disruptor at a time, but to multiple hormone disruptors throughout their daily lives that can have additive and cumulative impacts.

A Toxic Legacy: Multigenerational Effects

Animal studies and DES daughters continue to teach us about the consequences of developmental hormone disruption. Researchers are now finding that the DES legacy may include the *granddaughters* of the women who took the drug. Preliminary research has found a higher than normal incidence of menstrual irregularities and potential infertility among DES granddaughters.[52] Thus, women who never took DES themselves can be affected by their mothers' or

PHOTO COURTESY OF RETHA NEWBOLD, PH.D., NIEHS

FIGURE 4: **Mice exposed to low levels of DES in the womb grew to be extremely obese in adulthood (right), when compared to mice that were never exposed (left). Further, mice exposed to higher levels of DES actually lost weight in adulthood.**

> *"Women who never took DES themselves can be affected by their mothers' or grandmothers' exposure."*

grandmothers' exposure. Studies with mice have shown that exposure to DES increases susceptibility to uterine tumors and that the trait is passed through the maternal line to subsequent generations.[53]

Timing Matters: Exposure During Critical Stages of Development

The women's environmental reproductive health researchers at the January 2008 meeting identified a recurring theme throughout the scientific literature — that women and girls are particularly sensitive to the effects of hormone disruption during specific windows of vulnerability, or stages of rapid hormone-driven development. Grave impacts on the endocrine, immune, and neurological systems can occur if exposure to hormone disruptors takes place during fetal development and throughout childhood.

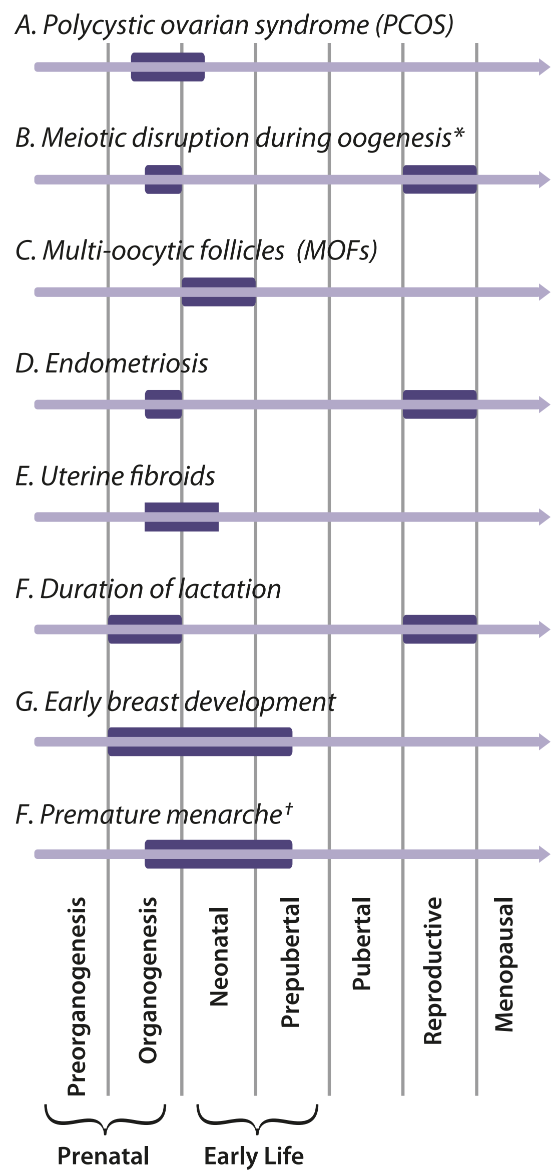
Prenatal and newborn exposures to hormone disruptors can be especially damaging because tissues and organs are just forming, setting the foundation for future reproductive health. Errors made during this critical period of development may not manifest until years later. For example, lab studies have shown that exposing rats and mice to DES in the womb or just after birth can give them a higher risk of developing uterine fibroids (benign tumors of the uterus) when they reach adulthood.[54-56]

Researchers observed that exposing female rats to DES at specific stages of uterine development permanently "programmed" genes in the uterus to be more sensitive to estrogen in adulthood, before tumors were seen. This hypersensitivity made the rats more susceptible to uterine fibroids. When rats with an inherited gene defect that made them more likely to develop tumors were also exposed to DES in the womb or just after birth, they ended up with even more tumors than the DES-exposed rats without the gene defect. Further, their tumors grew larger and faster.[54-55] There is some indication that the same proves true for women exposed to DES in the womb, but more research is needed to confirm this link.[57]

Figure 6 was adopted from the science manuscript that resulted from the Women's Reproductive Health and the Environment Workshop. It shows the known critical stages of development for several female reproductive disorders. Exposure to hormone

Known Critical Stages of Development

Well-defined developmental periods of sensitivity when hormone disruptor exposure greatly increases the risk for reproductive disorders.



*Can lead to abnormal number of chromosomes, or anueuploidy

†First menstrual period

FIGURE 6: The known critical stages of development for several female reproductive disorders. Exposure to hormone disruptors during these windows increases a woman's risk of developing the associated health problem(s). Redrawn from Crain et al. (2008).[1]

disruptors during these windows increases a woman's risk of developing the associated health problem(s).[1] The existing research shows that prenatal development (particularly during organogenesis, or the process of organ formation) and very early life (neonatal development) are critical periods of reproductive system development. It is important to note that scientists are also concerned about other stages of development, such as puberty, but more research is needed to understand the reproductive health risks associated with exposure during puberty and other stages of development.

Development, Disrupted

Research shows that humans and animals are most vulnerable to hormone disruption during prenatal development, when a fetus is undergoing rapid, hormonally orchestrated change. Other crucial points in time when the endocrine system is particularly sensitive to hormone disruption include early life development, puberty, pregnancy, and lactation.

A Brief Look at Female Reproductive Development

Development of the female reproductive system begins in the early weeks of human pregnancy, with genes and hormones precisely orchestrating the occurrence and timing of key events. An enormous amount of growth and differentiation occurs during fetal development. The mammary glands, ovaries, and female reproductive tract (fallopian tubes, uterus, cervix, and vagina) all begin forming during the first trimester. Normal hormonal signaling at this time is critical to future reproductive health. After birth, growth and differentiation of the reproductive system slow dramatically until another series of important hormonal changes begins with puberty. As a result, the impact of hormone disruption during prenatal development may only become evident many years later.

For example, at birth, egg cells in the ovary are individually surrounded by supporting cells, called granulosa cells. These clusters form single follicles that wait for hormonal signals to stimulate further development when a girl reaches puberty. Prenatal follicular development hinges on the balance between estrogen and other hormones within the developing ovary. If balance during this critical time frame is disrupted, ovarian follicle formation can be impaired and the effects undetectable until some point after puberty when the follicle matures. This interference in development can potentially lead to a number of ovarian disorders in women, like polycystic ovarian syndrome (PCOS) and premature ovarian failure (POF), both of which can impair fertility. Follicle health is particularly important because girls are born with all the egg cells they will ever have. The egg cells can be dormant for up to 50 years, during which time they are subject to a lifetime of environmental exposures.

Puberty marks the development of adult reproductive capacity, arising from the hormone-driven maturation of certain parts of the brain, ovary, uterus, and breasts. A hormonal cascade of events, beginning with a signal from the brain, stimulates the ovaries to begin producing estradiol (the principle natural estrogen in women and most other vertebrate females), which in turn initiates breast development and the maturation of the uterus. At this time, pubic hair also begins to grow and ducts in the breasts branch out and differentiate. Breast tissue will again undergo hormone-controlled changes during pregnancy and lactation.

About two years after the start of puberty, menstruation begins, signaling that ovulation has occurred. Ovulation depends upon the pituitary (a gland at the base of the brain) releasing a hormone called follicle-stimulating hormone, which triggers the maturation of several follicles within an ovary that begin to produce estrogen. Eventually, one follicle dominates and the others die off. When the dominant egg has matured, elevated blood concentrations of estrogen produced by the competing follicles, along with other hormonal signals, promote a surge of luteinizing hormone from the pituitary. This

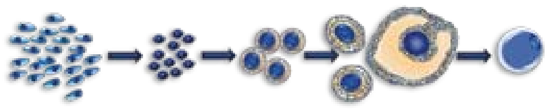


IMAGE COURTESY OF PATRICIA HUNT, PH.D., WASHINGTON STATE UNIVERSITY

FIGURE 7: ***Follicle development:*** **Egg development is a three-stage process, beginning during prenatal development and continuing through birth to puberty. At birth, egg cells in the ovary are individually surrounded by supporting cells, called granulosa cells. These clusters form single follicles that wait for hormonal signals to stimulate further development when a girl reaches puberty, at which time the monthly cycle of ovulation and menstruation ensue.**

surge in turn triggers ovulation, which is the release of the lone egg cell into the fallopian tube. In this way, the pituitary and the ovaries communicate with one another through hormone signaling to regulate the monthly ovulation cycle.

If the egg remains unfertilized, menstruation ensues and another cycle begins. Eventually, egg cells are no longer released and the monthly cycle comes to an end (menopause). Hormones and reproductive organs continue to play an important role in a woman's health as she ages.

Reproductive Health Concerns of Women and Girls

The researchers who gathered at Commonweal in January 2008—in addition to reviewing what is known about effects of hormone disruptors on female reproductive development—explored whether a unifying hypothesis, a counterpart of the testicular dysgenesis syndrome, could be proposed to explain the onset of common female reproductive disorders. Below is a list of some female reproductive health problems and examples of their relationships to hormone disruptors.

Early Puberty

Early puberty is a growing concern. The age of puberty onset has declined over the last half century in several industrialized nations.[58-60] In the United States, girls get their first periods a few months earlier than they did 40 years ago, and they develop breasts one to two years earlier.[61] Many scientists are troubled by this statistic. Girls who go through puberty early are at an increased risk for depression, sexual victimization, obesity, polycystic ovarian syndrome, breast cancer, and a number of social challenges such as experimentation with sex, alcohol, or drugs at a younger age.[58]

The hormonal cues that initiate the onset of puberty are sensitive to a variety of environmental influences. Environmental factors thought to play a role in early puberty include obesity, increased nutrition, psychosocial stress, exposure to environmental pollutants, and exposure to more daylight hours via artificial lighting at night.[1] Prepubertal stages of development, such as in the womb and in early life, are thought to be vulnerable windows for hormone disruption that can lead to the early onset of puberty.[1] In animal and human studies, early puberty has been linked to greater cumulative estrogenic exposure to multiple contaminants, such as phthalates,[62-63] BPA,[64] DES,[65] and some phytoestrogens like those found in soy formula.[65-67] Early puberty is also associated with early life exposure to PCBs,[68] PBBs,[69] cigarette smoke,[70] and organochlorine pesticides like DDT and DDE. [71-74]

There is also evidence that other contaminants, such as lead, can delay puberty.[75] Reduced environmental lead levels over the past 40 years could be contributing to earlier onset of puberty. This observation illustrates the complexity of interactions among the cocktail of contaminants that any one woman is exposed to during her life.

Impaired Fertility/Infertility

Impaired fertility or infertility includes the difficulty or inability to get pregnant and/or carry a pregnancy to term. It is hard to determine exactly how many people experience impaired fertility, but the best estimate is 12 percent of the reproductive-age population in the United States. As was noted previously (on page 7), this number seems to have increased over the last two decades, most sharply in women under the age of 25.[5-7]

There are many causes of impaired fertility. A woman's fertility depends on several body parts working together to produce and transport a healthy egg and nurture the developing fetus. Conception and fetal health also depend on the quality of the father's sperm. Hormone disruptors can affect both parents, and scientists have linked fertility problems to exposure to DDT,[76-78] DES,[79-80] BPA,[42] cigarette smoke,[81-82] and PCBs.[83-85]

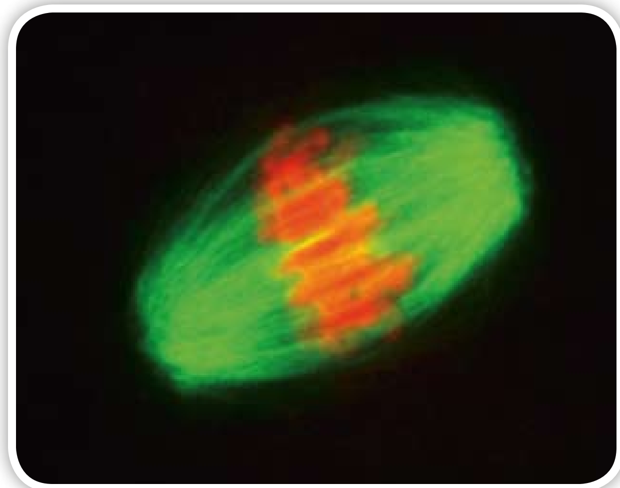
A number of female reproductive disorders can impair fertility, including abnormal numbers of chromosomes in the eggs, menstrual irregularities, polycystic ovarian syndrome, endometriosis, premature ovarian failure, and disorders associated with pregnancy, the three most common of which are miscarriage, preeclampsia, and intrauterine growth restriction. All of these disorders are discussed in greater detail in later sections.

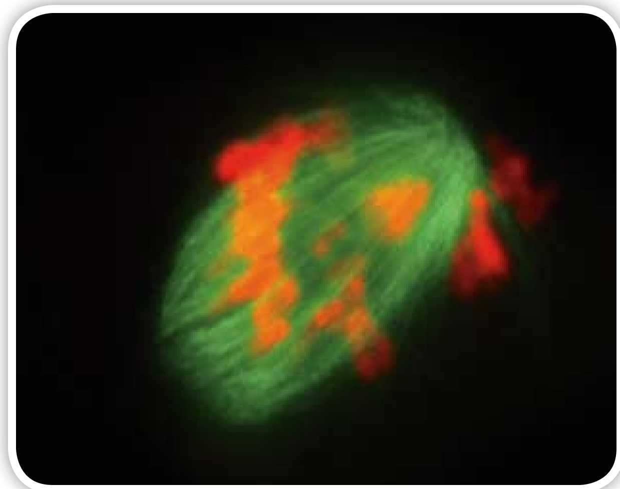
Abnormal Number of Chromosomes (Aneuploidy)

An abnormal number of chromosomes, or aneuploidy, is a condition in which the fertilized egg has extra or missing copies of chromosomes. In humans, aneuploidy is the leading cause of early miscarriage and birth defects. One example is Down syndrome. It is thought to result from errors in chromosome segregation during the cell divisions that give rise to the mature egg.

For still unknown reasons, aneuploidy increases significantly as women age. While studying the phenomenon in adult mice, researchers inadvertently discovered that exposure to BPA caused a dramatic increase in the incidence of aneuploidy. Further investigation revealed that very low levels of BPA, levels to which humans are normally exposed, can cause chromosomal problems that can lead to the production of aneuploid eggs and embryos in mice exposed prenatally and as adults.[47-48] Figure 8 shows two examples of chromosomal alignment during cell division. The top is normal. Chromosomes (stained red) are aligned properly. The bottom photo shows alignment in a cell exposed to BPA. Chromosomes are scattered throughout the cell. In this case, chromosomes are unlikely to be distributed properly, resulting in aneuploidy.

Human studies examining aneuploidy rates in women exposed *in utero* to BPA or other hormone disruptors have not yet been conducted, but animal studies are instructive for humans because cell division in mice is extremely similar to cell division in humans.





PHOTOS COURTESY OF PATRICIA HUNT, PH.D., WASHINGTON STATE UNIVERSITY

FIGURE 8: When a cell is dividing, the DNA condenses into paired structures called chromosomes. As cell division progresses, half of the parent chromosomes are drawn to each side of the dividing cell. The photographs above show two examples of chromosomal alignment during cell division. The top is normal. Chromosomes (stained red) are aligned properly. The bottom shows alignment in a cell exposed to BPA. Chromosomes are scattered throughout the cell. When cell division is completed by the exposed cell, chromosomes are unlikely to be distributed properly, resulting in aneuploidy.

Miscarriage, Preeclampsia, Intrauterine Growth Restriction (IUGR), and Preterm Delivery

Miscarriage, preeclampsia (characterized by hypertension during pregnancy), intrauterine growth restriction (IUGR, poor weight gain during fetal development), and preterm delivery are common disorders of pregnancy. They can be due to poor implantation, when the embryo does not properly attach to the uterus and the placenta does not fully develop.[86-87] Miscarriage affects up to 21 percent of known pregnancies[88-90] and can be caused by a variety of factors, including aneuploidy, environmental and dietary exposures, poor sperm quality, and hormone or immune system disruption.[91] Women with diabetes are also at higher risk for miscarriage.[92]

Both preeclampsia and IUGR carry increased risk of low birth weight,[93] preterm birth,[94] stillbirth, or newborn death.[95-97] These links are important because low birth weight and preterm birth are important factors that can influence future health.[98-99] Preterm delivery is the primary cause of death in the first month of life, and can lead to increased risk of childhood and adult illness.[99] Hormone disruptors have been linked to a variety of adverse pregnancy outcomes,[100] but the Bolinas workshop focused on miscarriage, preeclampsia, and IUGR.

Although few studies have linked hormone disruptors to preeclampsia specifically, several studies have shown an association with poor development of the placenta, IUGR, and/or miscarriage. In humans, first trimester exposure of fetuses to hormonal contraceptives such as Depo-Provera was shown to increase the risk for IUGR.[101] Pesticides such as DDT/DDE[77,102] have been linked to both IUGR and an increased risk of miscarriage. A 2003 review found that DES actually increased the risk of miscarriage for many women (rather than preventing miscarriage as was the drug's intended use).[103] Further, human placenta cells have been shown to grow less and exhibit increased cell death when they are exposed *in vitro* (in the laboratory) to DES, in addition to estrogen and the pesticides glyphosate, Roundup (a glyhosate-based herbicide), and methoxychlor.[104-105]

In mice, first trimester exposure to BPA was shown to decrease growth of the placenta, and increase miscarriage and infant mortality.[106] IUGR associated with poor placental growth was observed in pregnant rats exposed to estrogen.[107] These *in vivo* (within a living organism) and *in vitro* studies suggest that exposure to hormone disruptors during early pregnancy can reduce placental growth, which can reduce nutritional support to the embryo and lead to IUGR, or, in extreme cases embryonic or fetal mortality.

Menstrual Irregularities

The female menstrual cycle is highly regulated by a variety of hormones. Hormone disruptors can interfere with menstruation through multiple pathways, resulting in irregular periods, shorter or longer cycles, and fertility problems.[1] Human studies suggest that adult exposures to hormone disruptors such as PCBs,[108] DDT,[71] and other pesticides[109-110] can impact future menstrual cycles. Scientists are concerned that fetal exposure to hormone disruptors might also impact future menstrual cycles. This concern has been well supported by animal studies. Although rodents do not menstruate, they do have fertility cycles that can serve as a model for human menstruation. Prenatal and newborn exposure to hormone disruptors such as BPA and some phytoestrogens have been shown to alter the mouse fertility cycle,[111-113] and to prematurely end cyclicity altogether.[114] Few human studies exist, but some studies of dioxins[115] and PCBs[116] have shown that fetal exposures can lead to menstrual cycle irregularities later in life. Additionally, women whose mothers were exposed to DES while pregnant have reported cycle irregularities.[52] More research is needed, but there is sufficient scientific evidence to suggest that exposure to hormone disruptors can impact menstruation in women and girls.

Polycystic Ovarian Syndrome (PCOS)

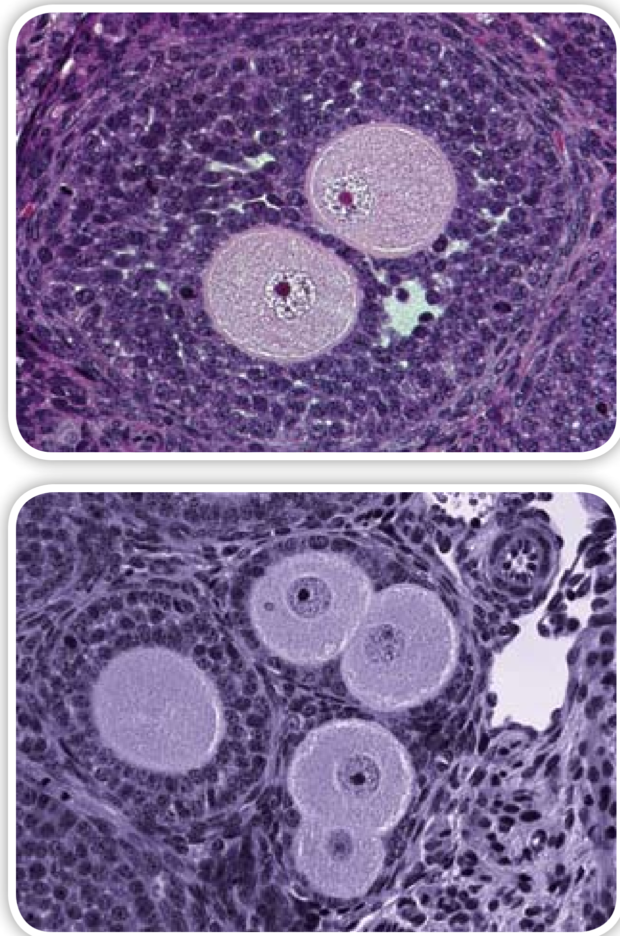
Polycystic ovarian syndrome (PCOS) is a multifaceted disorder affecting metabolism and reproduction, and is rooted in prenatal development.[117] The syndrome includes insulin resistance, diabetes, high cholesterol, high blood pressure, high androgen (for example, testosterone) production, and premature pubic hair growth.[118] Irregular periods, abnormal bleeding, pelvic pain, ovarian cysts,[119] and excess hair on the face and body are common symptoms, and a characteristic feature is an overabundance of maturing follicles in the ovaries. No single follicle is dominant as would be normal. An estimated four to eight percent of women in their childbearing years are affected by PCOS and face a higher risk of developing insulin resistance, diabetes, endometrial cancer, infertility, miscarriage, and hypertension.[120-122] Annual evaluation and healthcare costs associated with PCOS have been estimated to be $4.36 billion.[118]

PCOS has been linked to exposure to high androgen levels during prenatal development of the ovary and follicles.[1] It has been well documented that high testosterone levels during fetal development leads to PCOS in adult monkeys[123] and sheep,[124-125] and high androgen and testosterone levels have also been associated with PCOS in humans.[126-127] Scientists are concerned that exposure to hormone disruptors such as BPA during follicular development in the womb can also cause changes to hormone levels that lead to PCOS in girls and women.[1] BPA has been found in the follicular fluid of women with PCOS and in their fetus' blood,[128] and women with PCOS were found to have five times more BPA in their amniotic fluid compared to other women.[129] It is not yet clear if BPA exposure promotes PCOS, or if the presence of PCOS reduces how quickly a woman's body can clear BPA. More research is needed to know what effect BPA and other hormone disruptors might have on the progression of PCOS, but the fact that hormones play such a vital role during prenatal ovarian development indicates that PCOS could be initiated by environmental exposures.

Multi-oocyte Follicles (MOFs)

Multi-oocyte follicles (MOFs), or polyovular follicles, are defined as ovarian follicles containing several egg cells rather than a single one as should occur normally. In women, MOFs are associated with diminished *in vitro* fertilization success and increased early miscarriage.[130] Additionally, the presence of MOFs (also called biovularity) in women has been associated with ovarian teratomas, a type of tumor present from birth although it may not be detected until adulthood.[131]

As previously discussed (on page 12), multiple eggs per follicle can be induced in alligators by embryonic exposure to hormonally active pesticides.[25] Other estrogenic chemicals such as DES have also been shown to cause MOFs in mice.[132-133] In both alligators and mice, adult reproduction appears to be impaired by this condition. These animal studies give scientists pause because the mechanism of damage appears to involve a signaling route that is also critical in human ovarian development. MOFs have been shown to occur in women,[130,134-135] however more research is needed to understand the role hormone disruptors might play in causing MOF formation in humans.



PHOTOS COURTESY OF SARAH BRISTOL-GOULD, PH.D., NORTHWESTERN UNIVERSITY

FIGURE 9: Photographs of multi-oocyte follicles, or ovarian follicles containing several egg cells (top, two; bottom, multiple) rather than a single one as should occur normally.

Uterine Fibroids

Uterine fibroids are benign tumors of the uterus that occur in 25 to 50 percent of all women, though some estimates are much higher.[136] Fibroids are the number one cause for hysterectomy in reproductive-age women,[137] and can cause pelvic pain, heavy periods and abnormal bleeding, infertility, and complications in pregnancy.[138-143] Annual economic costs due to abnormal bleeding, often a symptom of fibroids, top $1 billion and $12 billion in direct and indirect expenses, respectively.[144] Hormone-associated risk factors include obesity and age of first menstrual period, while use of oral contraceptives, having multiple pregnancies, and menopause actually reduce the risk of developing fibroids.[136,141,145-148]

Uterine fibroids are found in mice, some dogs, and Baltic gray seals with high body burdens of organochlorine pesticides.[149-150] As was discussed previously (on page 16), rodent studies have shown that exposure during prenatal and early life stages to DES can lead to a higher risk of developing uterine fibroids in adulthood.[54-56] DES and several pesticides also cause the cells of uterine fibroids taken from rats to multiply abnormally fast in the laboratory,[151] suggesting that adult exposures to these compounds can promote uterine fibroid growth. Another recent study has shown that environmentally relevant levels of BPA (or levels to which women are currently exposed) can also increase the risk of uterine fibroids in adult mice, when exposure occurs during fetal development and just after birth.[152] Human data is more limited,[57,153] but there is concern that hormone disruptors such as BPA might be harmful to women, particularly at critical stages of uterine development. More research is needed to fill this information gap.

Endometriosis

Endometriosis occurs when the tissue that normally lines the inside of the uterus (called the endometrium) grows outside the uterus on other internal parts of the body, for example the ovaries, abdomen, and pelvis. This chronic disease is a major contributor to female infertility and causes inflammation, pain, and scarring. Estimates vary, but most studies find between 10 and 15 percent of reproductive-age women have endometriosis.[154-155] Some women appear to be more susceptible to developing endometriosis due to immunological or hormonal factors, and endometriosis usually regresses after menopause or surgical removal of the ovaries.[1] Between 35 and 50 percent of women with pelvic pain, infertility, or both have endometriosis, yet it appears to be both under diagnosed and undertreated.[156-157] U.S. healthcare and loss of productivity costs associated with this disorder were estimated to be $22 billion in 2002 alone.[158]

Overwhelming evidence from animal studies involving monkeys and mice show a link between endometriosis and exposure to organochlorine compounds, including DDT, the pesticide methoxychlor, dioxin, and several PCBs that act like dioxin.[159-165] In humans, a few studies have also associated endometriosis with dioxin,[166-167] phthalates,[168-169] and PCBs.[170-176] Most research on an environment-endometriosis link has focused on adult hormone and hormone disruptor levels; however, some research suggests that fetal exposures affect later development of this disorder.[1] First, an on-going study of healthy women reported that DES daughters have an 80 percent higher risk of developing endometriosis.[177] Second, prenatal exposure to dioxin has been shown to promote endometriosis in mice.[178] It also has been suggested that prenatal exposures to organochlorines can program uterine tissue in such a way that it is more likely to develop endometriosis following secondary exposures in adulthood.[1] More research is needed to fully understand how both prenatal and adult exposure to hormone disruptors can impact endometriosis in humans.

Shortened Lactation

Shortened lactation, or reducing how long a woman can breastfeed her baby, can have long-term impacts on the child, including increased risk for infection, heart disease, compromised immunity, diabetes, and obesity.[179] Breastfeeding helps build a child's immune system and later intelligence and is important to the bonding and nurturing process.[179-180] Additionally, breastfeeding is good for the mother. A lack of breastfeeding has been linked to higher disease risks for women such as osteoporosis and ovarian, uterine, endometrial, and breast cancers.[181]

During pregnancy through the first days after childbirth, breast growth and glandular changes set the stage for a woman's ability to breastfeed. Hormones such as estrogen and progesterone are key drivers of this preparation.[182] Duration of lactation is reduced in women with increased blood levels of PCBs and DDT/DDE,[183] as can be the case for women who eat large amounts of Great Lakes fish or live near intensive agriculture.[184-185] In addition, several recent animal studies have shown that fetal exposure to environmentally relevant levels of the herbicide atrazine can reduce breast development and decrease later milk production and duration of lactation.[186-187] Atrazine is one of the most widely used herbicides applied in the United States today. It is broadly used on field crops and is the main herbicide in "weed and feed" type lawn formulations purchased by homeowners.

Breast Cancer

Breast cancer incidence rates in the United States increased by more than 40 percent between 1973 and 1998. In 2008, a woman's lifetime risk of breast cancer is one in eight.[188] Breast cancer arises from genetic, lifestyle and environmental causes, several of which relate to lifetime exposure to hormones (primarily estrogen). It is known that exposure to a high cumulative amount of estrogen across a woman's lifespan increases her risk of breast cancer. This exposure varies by age at first menstrual period, first pregnancy, and menopause, and by breastfeeding and number of pregnancies. Lifetime estrogen exposure may also be increased by exposure to estrogenic hormone disruptors, birth control pills, and hormone replacement therapy.

More than 200 chemicals, including many hormone disruptors such as DES,[189-192] BPA,[193-199] chemicals in first or second-hand smoke,[200-206] and some pesticides, including DDT and atrazine,[207-209] have been associated with an increased incidence of breast tumors in humans and/or lab animals.[210] Exposures during prenatal and pubertal development appear to be especially critical, although the specific details of how each chemical promotes cancer is not yet known. Additionally, breast cancer, like other reproductive disorders, probably results from disruption during more than one stage of breast development. A succession of exposure "hits" is needed, with early ones setting the stage and later ones promoting disease progression.

Studies of DES daughters, who are at an increased risk for breast cancer due to their prenatal exposure to DES,[190] provide a model for breast cancer development that is now being observed with other more widely encountered hormone disruptors such as BPA.[1] Current BPA studies are helping to clarify how hormone disruptors might affect breast development and differentiation. Animal studies, using levels of BPA to which women are exposed, have demonstrated several possibilities. For example, baby mice exposed to BPA were found to have mammary gland tissue comparable to the dense tissue of pregnant mice.[196] This finding is a concern because increased breast density is a risk factor for breast cancer in humans.

Most human studies have focused on adult exposures; however, some retrospective studies provide hints that early hormone disruptor exposure has a role in adult disease. For example, although an earlier study showed no link between DDT and breast cancer, narrowing the suspected exposure to girls younger than 14 revealed a fivefold increase in breast cancer risk after age 50.[207] Puberty is thought to be a critical window of sensitivity for exposure to hormone disruptors that can lead to breast cancer; however, puberty and subsequent development of breast cancer in adulthood needs to be more extensively studied.[1]

Early Menopause (Premature Ovarian Failure, POF)

Early menopause (or premature ovarian failure, POF) is a condition in which a woman ceases to menstruate before age 40.[211] The average age of menopause for women in the United States is in the early 50s.[212] POF appears to be due to genetic or immunological causes that result in too few follicles being created or too many dying early.[213] In addition to a premature loss of fertility, POF carries the burden of postmenopausal health risks such as cardiovascular disease and osteoporosis.[214] Very few studies examine environmental effects on menopause, although the theoretical possibility is recognized.[215]

Like polycystic ovarian syndrome, POF is thought to originate from changes in hormone signaling during critical windows of prenatal follicle formation.[211] Future studies on the impacts of hormone disruptors during this critical period are necessary to understand how the environment influences POF.[1]

Tangled Links

As was stated earlier, many factors other than hormone disruptors can influence the reproductive health of women and girls including age, overall health, diet, obesity, level of physical activity, and socioeconomic status. Emerging research is revealing what seems to be a key link between female reproductive disorders and obesity. New studies are finding links between obesity and the incidence of

Table 2: Summary of Female Reproductive Health Concerns and Links to Hormone Disruptors Discussed in this Report

Female Reproductive Health Concern	*Examples of Associated Hormone Disruptors*
Early puberty	BPA,[64] cigarette smoke,[70] organochlorine pesticides such as DDT/DDE,[71-74] DES,[65] PBBs,[69] PCBs,[68] phthalates,[62-63] and some phytoestrogens[65-67]
Impaired fertility or infertility	BPA,[42] cigarette smoke,[81-82] DDT,[76-78] DES,[79-80] and PCBs[83-85]
Abnormal number of chromosomes (aneuploidy)	BPA[47-48]
Miscarriage, preeclampsia, intrauterine growth restriction (implantation disorders)	BPA,[106] DES,[103-104] and pesticides such as DDT/DDE,[77,102] glyphosate, Roundup, and methoxychlor[104-105]
Menstrual irregularities	BPA and some phytoestrogens,[111-114] DDT[71] and other pesticides,[109-110] DES,[52] dioxins,[115] and PCBs[108,116]
Polycystic ovarian syndrome (PCOS)	BPA[128-129]
Multi-oocyte follicles (MOFs)	DES[132-133] and some pesticides[25]
Uterine fibroids	DES,[54-57,151,153] BPA,[152] and some organochlorine pesticides[149-150]
Endometriosis	Organochlorine compounds such as DDT, the pesticide methoxychlor, dioxin and several PCBs,[159-167,170-176,178] phthalates,[168-169] and DES[177]
Shortened lactation	The pesticide atrazine,[186-187] DDT/DDE, and PCBs[183-185]
Breast cancer	More than 200 chemicals, including some hormone disruptors such as BPA,[193-199] chemicals in cigarette smoke,[200-206] DES,[189-192] and some pesticides such as DDT and atrazine[207-209]

* Although few studies have linked hormone disruptors to preeclampsia specifically, several studies have shown an association with poor development of the placenta, IUGR, and/or miscarriage.

Note: the above reproductive health concerns and their associated hormone disruptors are discussed in this report, but do not constitute an exhaustive list. For a descriptive list of hormone disruptors and sources of exposure see page 10.

hysterectomies and stillbirths. Higher body mass index has also been associated with earlier puberty in girls, while low physical activity in some women has been linked to an increased risk for endometriosis.

Furthermore, interesting relationships among multiple health factors including female reproductive disorders are emerging from current research. For example, children of women diagnosed with polycystic ovarian syndrome (PCOS) are more likely to be exposed to increased prenatal androgen concentrations, in addition to being born with a low birth weight.[216-217] Low birth weight is a complication that has in turn been linked to obesity, insulin insensitivity, and diabetes later in life.[218] This is especially true for those who are not breastfed or who are weaned from the breast early.[219-221] Low birth weight has also been linked to early puberty, fertility problems, and PCOS in later life.[221]

We know that hormones play a key role in the development of obesity and female reproductive disorders such as PCOS. However, in order to better understand how hormone disruptors might contribute to the picture, we need more research that clarifies these relationships. For example, obesity might cause or exacerbate reproductive disorders in women. Or, perhaps obesity and some female reproductive disorders originate from similar prenatal and early life exposure to hormone disruptors. This is a critical area of study, particularly because rates of obesity are rising rapidly in modern Western societies.

Answers, Questions, and the Future

What do we know about hormone disruptors and women's reproductive health and development? What do we still need to explore, and what should we do in the meantime to protect the reproductive health of current and future generations?

What We Have Learned

While we still need significant information, especially at the genetic level, on how the female reproductive health system develops, what causes problems with it, and how hormone disruptors modify reproductive function, we have come a long way in recent years. Here, in a nutshell, is what we know.

- **The placenta is not an impermeable shield** as was previously thought. A woman's exposure to chemicals during pregnancy can cross the placental barrier and harm a fetus, even if the mother's health is not impacted.

- **Animals count.** It was observations of reproductive abnormalities in wildlife that first sparked the idea of environmental hormone disruption. Humans and other animals have very similar genes and cellular mechanisms. Animal studies in the wild and the laboratory serve as warnings about threats to our own reproductive health.

- **Environmental factors such as hormone disruptors contribute** to women's reproductive health problems. Thus, if contaminant pollution is reduced, many female reproductive health problems could be prevented or made less severe.

- **The dose does not make the poison.** Unlike what we have learned from traditional schools of toxicological assessment that focused on high doses, low levels of hormone disruptors can have a negative impact on female reproductive health. Therefore, we cannot assume there are "safe" levels of exposure.

- New science is revealing that hormone disruptors can have **multigenerational effects.** An exposure to a woman during pregnancy can lead to reproductive health problems in her children, grandchildren, and potentially later generations.

- There are clear **windows of vulnerability**. The female reproductive system is particularly vulnerable to hormone disruption during periods of rapid body development or changes that are driven by hormones. This is particularly true during prenatal and early life development, but also during puberty and reproductive maturity.

- There are many **gaps in our understanding** of hormone disruptor and female reproductive health science. We have numerous studies that link hormone disruption to female reproductive disorders in animals, particularly when exposure occurs during critical periods of development (such as in the womb, in early life, and during puberty). But many of the mechanisms are poorly understood and human studies are limited. Further thought is needed for proposing a single common origin for multiple female reproductive health problems (similar to the testicular dysgenesis syndrome in males), but it is clear that prenatal exposures to hormone disruptors are critical. Secondary adult exposures are also important to consider, as they may exacerbate conditions that were set up prenatally. Focused research needs to be done in order to solve the puzzle and answer these key questions. As with any novel approach to understanding a problem, there is an immediate need for additional information.

Where Do We Go from Here?

The investigation of hormone disruptors and female reproductive health is critical. Women's reproductive health problems are common and can have a devastating impact on the lives of the women who suffer from them, as well as their families. Hormone disruptors are ubiquitous in the environment. Below are recommended actions that will help us better understand how hormone disruptors can impact women's health, and what we can do to protect ourselves from exposure.

1. **Support better research on hormone disruptors and female reproductive health.**
   - *Prioritize research funding to study the effects of hormone disruptors on women's health.* Most of the research to date has been limited and focused on health outcomes in males, leaving large gaps in our understanding of how females may be impacted.
   - *Improve health tracking systems.* Currently the systems that track rates of various health problems are inadequate. In order to understand the full impact of hormone disruptors on human health, particularly women's health, we need to track female reproductive health trends.
   - *Assess chemicals for their hormonal and reproductive health effects.* Knowledge about the hormone-disrupting potential of most of the over 80,000 industrial chemicals in production is very limited. These chemicals also have not been systematically assessed for their effects on reproductive health. Since industrial chemicals occur in nearly everything we buy and also are found in food, air, and water, this is a crucial step. Increasing the use of *in vitro* and *in vivo* testing can help identify potentially harmful chemicals.
   - *Investigate the impacts of hormone disruptor exposure during critical windows of vulnerability.* The major impediment to understanding whether hormone disruptors influence female reproductive disorders is the lack of information linking fetal exposures to adult-onset reproductive disorders in humans. We have come to realize over the last decade that the embryonic/fetal origin of adult disease is a very real threat and requires significant research and a change in our approach to linking disease with exposure. We need to carefully examine human exposures—especially during prenatal, newborn, and pubertal development—and consider whether these exposures relate to particular reproductive health disorders later in life. Moreover, the hypothesis that secondary adult exposures may initiate or exacerbate conditions that were set up prenatally requires further investigation.
   - *Support long-term studies.* Because hormone disruptors can have life-long impacts, it is especially important to initiate studies tracking women's health over large spans of their lives and to evaluate longer periods of time in animal studies. This will help us understand long-term and multigenerational effects.
   - *Encourage collaboration.* Currently, most reproductive disorders are studied in isolation. This approach yields detailed information about single disorders, but it neglects commonalities that might exist among multiple disorders. By pooling data such as tissue samples and study results, a broader picture might emerge.
2. **Support policies that require information on whether exposure to hormone disruptors and other chemicals can result in harm, and that prevent exposure to those that do.** Current policies for chemical use do not adequately protect us. New national policies are needed to identify and phase out harmful chemicals and to require that safer substitutes be used. Furthermore, current policies assume chemicals are safe until proven dangerous. A more prudent approach would entail testing before a chemical is put on the market and released into the environment. Chemicals currently on the market should be tested in order to remain on the market.
3. **Use healthier products when possible.** Although we have much to learn about how chemicals impact human health, we know

enough to be cautious in the face of uncertainty. We can act now to protect ourselves from unnecessary exposures. We need to educate women and girls on ways to avoid exposures to chemicals that have been identified as reproductive and developmental toxins. There are many easy, affordable, and simple changes anyone can make at home to reduce their exposure to environmental contaminants. For ideas on how to make these changes, please see www.womens healthandenvironment.org.

4. **Interdisciplinary cooperation.** The researchers that gathered in Bolinas in January 2008 represented a broad range of scientific and medical expertise, with researchers in reproductive medicine, toxicology, and zoology, among others, as well as representatives of non-profit, governmental, and academic organizations. An interdisciplinary consortium to coordinate research, policy, advocacy and education on the impact of hormone disruptors on reproductive health could build upon the accomplishments of the Women's Reproductive Health and the Environment Workshop. The ultimate goal of such an integrated consortium would be to collectively reduce the burden of reproductive disease for the next generation of women and girls.

Key Resources for Further Information on Female Reproductive Health and the Environment

- *Challenged Conceptions: Environmental Chemicals and Fertility,* a report that translates the science from a multidisciplinary workshop on fertility and the environment, held at the Vallombrosa Retreat Center in Menlo Park, California, in 2005. The workshop was titled Understanding Environmental Contaminants and Human Fertility Compromise: Science and Strategy and was convened by the Stanford University School of Medicine's Women's Health@Stanford Program and the Collaborative on Health and the Environment (CHE). www.healthandenvironment.org/infertility/vallombrosa_documents
- *Hormone Disruptors and Women's Health: Reasons for Concern*, a six-page summary brochure on the impacts of hormone disruptors on female reproductive health. The brochure highlights the key scientific takeaways from the Women's Reproductive Health and the Environment Workshop that are also translated in this report. www.healthand environment.org/reprohealthworkshop
- *Our Stolen Future* (www.ourstolenfuture.org). The book *Our Stolen Future*, authored by Theo Colborn, Dianne Dumanoski, and John Peterson Myers, presents the history and development of the hormone disruption hypothesis and explains how hormone disruptors affect animal and human health. The website serves as a sequel to the book and presents news and continuing research related to hormone disruptors.
- *Shaping Our Legacy: Reproductive Health and the Environment*, a nontechnical and comprehensive summary of the latest science on how exposure to chemicals may impair reproductive health. The report translates the science from the January 2007 Summit on Environmental Challenges to Reproductive Health and Fertility, and was produced by the Program on Reproductive Health and the Environment (PRHE) at the University of California, San Francisco (UCSF). The Summit was hosted by UCSF and CHE. www.prhe .ucsf.edu/prhe/pubs/shapingourlegacy.html

- *Silent Spring Institute* (www.silentspring.org). Rachel Carson's work continues through the nonprofit scientific research organization Silent Spring Institute. Institute scientists focus on identifying the links between the environment and women's health, with a particular emphasis on breast cancer.

- *State of the Evidence 2008: The Connection Between Breast Cancer and the Environment*, a comprehensive report on the environmental exposures linked to increased breast cancer risk, including natural and synthetic estrogens; xenoestrogens and other hormone-disrupting compounds; and carcinogenic chemicals and radiation. Published by the Breast Cancer Fund. www.breastcancerfund.org/evidence

- *The Falling Age of Puberty in U.S. Girls: What We Know, What We Need to Know*, the first comprehensive review of the literature on the timing of puberty. The Breast Cancer Fund commissioned ecologist and author Sandra Steingraber to write *The Falling Age of Puberty* to help us better understand this phenomenon so we can protect our daughters' health. www.breastcancerfund.org/puberty

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