

CHEMICALS IN THE ENVIRONMENT

AND THE

ENDOCRINE SYSTEM



300 WILSON BOULEVARD
ARLINGTON, VA 22209

703 - 741 - 5000 6/00



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1. Introduction

Do low levels of chemicals in the environment have hormone-like activity? Do low levels of these chemicals threaten the health of humans or wildlife? This document provides an overview of the science on these important questions. Because of the extensive information available, no attempt was made to cite all of the key studies that have been conducted. This document is not intended to be and should not be relied on as a comprehensive review of the subject. Instead, this document aims to provide a fair and objective summary of the current science. Therefore, it should be regarded only as a summary. It should not be relied upon as a definitive treatise on the subject. It begins with a brief review of the purpose and function of the endocrine system, which controls the levels of natural hormones in the body, and it continues with a discussion of what scientists are finding out about certain chemicals in the environment in relation to health.

The endocrine system is one of the most complex systems in the human body. It controls and coordinates many basic functions as the body grows from a fetus through mature adulthood to old age.

Endocrine glands secrete substances called “hormones” into the blood where they travel to areas of the body where they are most needed. The most commonly recognized

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hormones are insulin and the sex hormones -- estrogen and progesterone made by the ovaries of women, and testosterone produced by the testes of men.

Hormones act like “messengers” that help the endocrine system communicate with and regulate other systems of the body including the reproductive system, immune system, nervous system, respiratory system and digestive system.

Hormonally Active Agents and Endocrine Disruption

Natural or man-made (*i.e.*, synthetic) substances from outside the body that can have the same effect as naturally occurring hormones have sometimes been called “hormone mimics” or “hormonally active agents (HAAs)” as the U.S. National Academy of Sciences termed them in a landmark report issued in August 1999.

HAAs may be beneficial, such as the synthetic hormone drugs, estrogen and progesterone, that are found in birth control pills and in hormone replacement therapy taken by women after menopause.

Many common foods, especially soy and other legumes and some vegetables, fruits and grains, naturally contain large quantities of HAAs with weak estrogen-like activity. These are called “phytoestrogens.” Dietary experts believe that a diet high in such foods may have beneficial effects on health.

In addition, some industrial chemicals and some pesticides may have incidental hormone-like properties.

Some scientists have hypothesized that the presence in the environment of low levels of these HAAs may interfere with naturally occurring hormones or with the normal function of the endocrine system, to cause possible adverse health effects. In this context, HAAs are often referred to as “endocrine disrupters.”

Background on the Endocrine Disruption Hypothesis

In 1991, a science workshop was organized by Dr. Theo Colborn of the World Wildlife Fund to compare a diverse range of developmental and reproductive effects observed in wildlife and laboratory animals over the previous 40 years. Conference participants concluded that a common thread was the ability of some man-made substances in the environment to interfere with the endocrine system, an effect that they hypothesized also could occur in humans.

The theory that some substances in the environment may be harming the health of humans and wildlife by interfering with the endocrine system (*i.e.*, “the endocrine disruption hypothesis”) was presented by Drs. Theo Colborn, Anna Soto and Frederick vom Saal in a 1993 scientific paper in the journal *Environmental Health Perspectives*. Dr. Theo Colborn, Dianne Dumanoski and John Peterson Myers further expanded upon the hypothesis in 1996, in the book “Our Stolen Future,” which suggested that health effects ranging from low sperm counts to cancers of the prostate, testes, breast, endometrium, and brain, as well as various learning and developmental disabilities, could be attributed to endocrine disruption.

Also in 1996, the United States Congress mandated the U.S. Environmental Protection Agency (EPA) to develop a screening and testing program to determine if various substances may have endocrine disrupting properties in humans.

What is Known and Unknown about Endocrine Disruption?

The question of whether low levels of HAAs in the environment are harmful to people or wildlife is undergoing intense scientific investigation.

In April 1996, following the publication of “Our Stolen Future,” the Director of the U.S. National Institute of Environmental Health Sciences reported to Congress that

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there is very little evidence that hormone mimics are hazardous at the levels at which they are present in the environment, in food or in human tissue. By 1997, a governmental report from the U.S. Environmental Protection Agency (published in 1998 in *Environmental Health Perspectives*) characterized endocrine disruption as a mechanism of action, not as a toxicologic endpoint, and noted that a causal relationship between exposure to specific environmental substances and harmful effects on human health operating *via* endocrine disruption had not been established.

Regarding wildlife, the 1997 EPA report noted there was compelling evidence that the endocrine systems of certain fish and wildlife have been disrupted by chemicals that contaminate their habitats. Further, it was not clear whether the adverse effects seen at various sites were confined to isolated areas or represented more widespread conditions. In many cases, the chemicals identified were ones that had already been identified as problem substances and were heavily regulated or banned from commercial use in the U.S., or were complex mixtures known to be hazardous and to have harmful effects in highly exposed populations. However, for many cases, a clear cause-and-effect relationship had not been established and alternative explanations for the observed effects could not be ruled out.

In August 1999, the National Academy of Sciences (NAS) issued a long-awaited, landmark report on the endocrine disruption hypothesis. The expert NAS “Committee on Hormonally Active Agents in the Environment” said “although it is clear that exposures to HAAs at high concentrations can affect wildlife and human health, the extent of harm caused by exposure to these compounds in concentrations that are common in the environment is debated.” It called for more research.

Scientists from industry, regulatory authorities and academic institutions around the world are pursuing many of the questions raised by the endocrine disruption hypothesis. For example, EPA has embarked on a multimillion dollar program of basic research on this topic and on development and validation of screening and testing methods to evaluate substances for potential endocrine effects on humans and wildlife.

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The U.S. National Institute of Environmental Health Sciences (NIEHS), the Chemical Industry Institute of Toxicology (CIIT) and the American Chemistry Council (ACC, formerly the Chemical Manufacturers Association [CMA]) are studying how HAAs affect the endocrine system and the levels at which they may cause harm. International organizations, including the European Commission (EC), the European Chemical Industry Council (CEFIC), the Environment Agency of the Government of Japan, the Organization for Economic Cooperation and Development (OECD), and the International Program on Chemical Safety (IPCS) also have funded research on HAAs and have sponsored conferences and symposia where scientists can share findings and forge new collaborative ties.

It is through continued research that scientists will broaden our understanding of the relationship, if any, between HAAs in the environment, the endocrine system and the health and wellbeing of humans and wildlife.

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2. The Endocrine System

The endocrine system is one of the body's communication systems; hormones are its messengers.

The endocrine system is one of the most complex systems in the human body. It controls and coordinates many basic functions as the body grows from a fetus through mature adulthood to old age. The endocrine system includes the reproductive organs, other glands such as the thyroid, kidneys and pancreas, the hormones they secrete, as well as the receptors that respond to the hormones.

Endocrine glands secrete substances, called "hormones," into the blood where they travel to areas of the body where they are most needed. The most commonly recognized hormones are insulin and the sex hormones -- estrogen and progesterone made by the ovaries in women, and testosterone produced by the testes in men.

Hormones act as "messengers" that help the endocrine system communicate with, integrate and control other systems of the body including the reproductive system, immune system, nervous system, respiratory system and digestive system.

When hormones reach the specific organs to which their messages are addressed, they attach themselves or bind to special molecules called "receptors" in those organs. A reaction then occurs which activates the cells and organs. It is by way of this reaction, which is specific for each organ, that hormones communicate "the message" from the endocrine gland to the target organ and tell it what to do.

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Scientists often use an analogy of “lock and key” to describe the way hormones and receptors work together. When the hormone (the “key”) meets the receptor (the “lock”), they join together just as a specific key fits into a specific lock. The combination signals the cells or organ (*i.e.*, passes the message) to begin producing a specific protein or to perform some other specific function that the body needs.

The amounts of specific hormones in the blood are regulated by “feedback loops.” For example, the pituitary gland, a small gland that lies at the base of the brain, controls the amount of estrogen that is made by the ovaries. The pituitary gland secretes two hormones, luteinizing hormone (also called “LH”) and follicle-stimulating hormone (also called “FSH”) which tell the ovaries to “stop” or to “make more” estrogen, as needed. It is this feedback loop that provides for the maintenance of estrogen in the blood at an optimum level.

How is the Endocrine System Regulated?

How do endocrine glands make sure that only the right amount of each hormone is made?

SOME EXAMPLES OF THE MAJOR ENDOCRINE GLANDS

Pituitary gland – Situated at the base of the brain. It produces growth hormone, and regulates other endocrine glands by secreting a number of hormones.

Thyroid – One of the largest glands in the body. It regulates the use of food – carbohydrates, fats and proteins – in the body.

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Parathyroid glands – The smallest glands. These are located on the lobes of the thyroid gland. The parathyroid gland produces a hormone that regulates the body's use of calcium.

Pancreas – Serves the digestive system as well as the endocrine system. As part of the endocrine system, the pancreas produces the hormones glucagon and insulin to help maintain the sugar level of the blood.

Adrenal glands – Located on each of the body's two kidneys. Part of each adrenal gland secretes several hormones, including aldosterone and cortisone, which regulate metabolism and salt balance. Another part secretes adrenaline, which helps the body respond to injury or stress by increasing heart action and raising blood pressure.

Reproductive system elements – Includes the ovaries of women and testes of men. They secrete estrogen, testosterone and the other hormones that produce sex characteristics.

Because the levels of hormones normally fluctuate, endocrine glands have their own receptors that can sense the amount of a specific hormone in the blood. If the hormone level in the blood drops, the endocrine gland is stimulated to make more. If the hormone level is too high, the endocrine gland stops making the devated hormone. It is this “feedback loop” that allows the body to maintain the right amount of hormones in the blood at all times.

One of the best examples of a feedback loop of an endocrine gland is the way insulin regulates the levels of sugar in the blood to ensure that cells get just the right amount of energy they need. Too much or too little sugar in the blood can be harmful.

To control this, when sugar levels in the blood start to go up soon after a meal, cells in the pancreas (an endocrine gland near the stomach) immediately respond to the elevated levels by stimulating the gland to make more of the hormone insulin. Insulin then is secreted by the pancreas into the blood, where it carries the message to muscle and liver cells instructing them to begin taking up some of the excess sugar from the blood. When the amount of sugar in the blood drops back to normal levels, the pancreas responds by reducing the amount of insulin it makes. It is by this form of feedback loop regulation that the endocrine system maintains a balance between too much and too little sugar in the blood by regulating hormone production.

Among questions currently being researched are whether feedback loops respond to long lived hormonally active agents that may be found at low concentrations in the environment or in the human body. So far, there are no definitive answers to these questions.

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3. Medical Uses of Hormones

Some drugs used in medical treatment are synthetic hormones.

Normal Variation in Estrogen Levels

The two female sex hormones made by the ovaries are estrogen and progesterone. Estrogen is responsible mainly for growth of sexual organs in females and for most secondary sexual characteristics of women. Progesterone is concerned almost entirely with final preparation of the uterus for pregnancy and of the breasts for producing milk after pregnancy.

It is normal for estrogen levels of girls and women to change at the beginning of puberty, during the menstrual cycle, during pregnancy and at menopause. The amount of estrogen produced during each stage of a woman's life is regulated by a feedback loop, and maintained at an appropriate level by hormones of the pituitary gland (a small gland at the base of the brain).

Before puberty, the estrogen level in the blood of girls is low. For 30 years or more after puberty, average estrogen levels are much higher. After menopause, however, estrogen levels drop again to a very low level.

Estrogen levels in women also vary during the monthly menstrual cycle. The normal variation is from 2 or 3 parts of estrogen per trillion parts of blood to about 20 parts of estrogen per trillion parts of blood.

Estrogen levels also change during pregnancy. They can rise by as much as 300 to 1,000 times the highest amount normally found during the menstrual cycle. At the end of pregnancy, estrogen helps prepare the mother for delivery of the baby. Estrogen causes enlargement of the uterus to accommodate the fetus, enlargement of the breasts to prepare them for the mother's milk, and enlargement of the vagina and cervix to prepare for delivery.

These examples help illustrate that hormone levels in the blood vary naturally with age, menstrual cycle and pregnancy. Scientists are still learning about the way everyday activities and stimuli, such as diet, stress, exercise and sunlight cause changes in the amount of various hormones in the blood. Feedback loops in the endocrine system sense these changes and respond by adjusting the amount of hormones that are made to keep them in balance and at the right level needed by the body.

Synthetic Hormones in Medicines

When the endocrine system is unable to make a hormone, the result can be very serious. For example, in young girls, the ovaries sometimes do not develop properly so that they do not produce estrogen and puberty does not occur. Poor development of the pituitary gland also can prevent the production of normal levels of estrogen. Both of these conditions can easily be corrected by treating young girls and women with "synthetic estrogen" (*i.e.*, man-made estrogen). When taken as prescribed, a girl's body can grow normally, with normal development of breasts and patterns of hair growth.

The most common medicines that contain synthetic hormones are oral contraceptives or "birth control pills" and those medicines that are used for hormone replacement therapy after menopause. The potency (*i.e.*, the amount of a substance needed to cause a health effect) of synthetic hormones used in medical treatment for birth control and hormone replacement therapy is approximately the same as that of naturally

occurring estrogen and progesterone. When used in the manner intended, they have the same effect as that caused by naturally occurring hormones in the body.

Modern birth control pills are administered as a combination of two synthetic hormones – estrogen and progesterone - and have been credited with reducing the risk of endometrial cancer, ovarian cysts, pelvic infections and reducing problems associated with acne. Hormone replacement therapy (HRT) is a combination of estrogen and progesterone that is sometimes given to women to lessen the short-term discomforts of menopause and to reduce the long-term risks (e.g., osteoporosis, heart disease) of decreased amounts of estrogen. Many studies have examined the relationship between hormone replacement therapy (and birth control pills) and the incidence of breast cancer. At most the results are suggestive of a weak relationship.

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4. Hormonally Active Agents

Hormonally Active Agents may be man-made or naturally occurring.

Scientists often use an analogy of “lock and key” to describe the way hormones and receptors work together. When the hormone (the “key”) meets the receptor (the “lock”), they join together just as a specific key fits into a specific lock. The combination signals the cell (*i.e.*, passes the message) to begin producing a specific protein or to perform some other specific function that the body needs.

Usually, only one key opens any given lock. However, that is not always the case. Sometimes a second key may be very similar to the first key, with some minor differences, and may actually open the lock. In the same way, sometimes there are man-made hormones (*i.e.*, “synthetic hormones”) that resemble naturally occurring hormones and can bind to the same receptor that binds natural hormones. When synthetic hormones bind to the receptors, they may produce the same effect in the body as naturally occurring hormones. Examples of such hormonally active agents (HAAs) are the synthetic hormone drugs that are found in birth control pills. These synthetic hormones fool the body by binding to the same receptors as the naturally occurring hormones, estrogen and progesterone, and thus prevent pregnancy.

Natural substances that have hormone-like activity are found in many common foods, including soy and other legumes and some vegetables, fruits and grains.

Examples of synthetic substances that are not drugs, but have known effects on the reproductive system in developmental tests in laboratory animals, include some

industrial chemicals and some pesticides. There are many ways a substance can cause effects on reproduction and development. Some of these substances may be assumed to cause these effects through the endocrine system, but in most cases this has not been demonstrated by the scientific weight of evidence.

Environmental Estrogens

A substance that produces the same effect on the body as natural estrogen is sometimes called “estrogen-like,” “estrogenic” or an “estrogen mimic.” If it is man-made, either a drug intended to act as an estrogen or an industrial chemical with incidental estrogen-like properties, it is called a “synthetic estrogen.” If a synthetic estrogen is found in the environment, it is then referred to as an “environmental estrogen.” While some environmental estrogens are synthetic, many are not and are produced naturally by plants or fungi.

Natural estrogen – A hormone that controls the development and function of the reproductive system.

Synthetic estrogen – A man-made substance that may produce similar effects on the body as natural human estrogen; synthetic estrogens include pharmaceuticals and some industrial products with incidental hormone-like properties.

Environmental estrogen – A substance that may produce similar effects on the body as natural estrogen and is found in the environment; environmental estrogens include naturally occurring substances in plants (phytoestrogens) and some industrial products with incidental hormone-like properties.

Plants have been used since ancient times for their ability to prevent pregnancy or induce abortion. Many plants contain substances that have hormone-like activity (*i.e.*, hormonally active agents, HAAs). Some HAAs in plants are very potent (*i.e.*, only a relatively small amount is needed to produce a health effect, such as a spontaneous miscarriage). When animals or birds eat large amounts of these plants, they may experience adverse reproductive effects.

Hormonally active agents that act like estrogen and are found in plants are called “phytoestrogens.” Some plants that make phytoestrogens are common in the human diet and include wheat, oats, rye, rice, soybeans, potatoes, carrots, peas, beans, alfalfa sprouts, apples, cherries, plums, parsley, sage, garlic, coffee and grains that are used in making beer and bourbon whiskey. Many grains, fruits and vegetables that protect against cancer and heart disease also contain phytoestrogens. According to calculations by Prof. Stephen Safe, the average Western diet contains millions of times more potential estrogenic activity from the phytoestrogens naturally present in foods than from the residual levels, if any, of any pesticides that may have incidental estrogen-like properties.

Estrogen Antagonists

In the same manner that a key sometimes may fit a lock but fail to open it, so do some HAAs attach themselves to hormone receptors, blocking access to them by natural hormones, but fail to activate the receptors and produce the desired effect. If such substances interfere with estrogen, they are then referred to as “anti-estrogenic” or as “estrogen blockers.” That is, they prevent or block natural estrogen from binding to the receptor. This same concept also applies to other hormones. For example, “androgenic” substances mimic the male hormone testosterone; “anti-androgenic” substances interfere with the action of testosterone.

Some plants also may contain anti-estrogens. Little is known about the ability of plant anti-estrogens to neutralize the effects of natural or synthetic estrogens, at amounts

typically found in the diet. Toxicologists, botanists and pharmacologists are actively researching this question at major universities and research institutions.

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5. Hazard, Potency, Exposure and Risk

Risk (an estimate of the likelihood that a substance will cause a harmful effect in people or wildlife) is based on three factors: hazard, potency and exposure.

Are Hormonally Active Agents Harmful?

Scientists look at three specific factors – hazard, potency and exposure – when evaluating whether Hormonally Active Agents (HAAs) found in the environment might cause adverse health effects in humans or wildlife.

- **Hazard** is the potential of a substance to cause a harmful effect in humans or wildlife. Hazard is an inherent characteristic of all substances, because all could prove harmful under certain conditions.

- **Potency** is a measurement of how much of the substance is needed to cause a harmful effect. The less of a substance that is needed to cause the effect, the more potent the substance. For example, rattlesnake venom is much more potent than alcohol. Both can be fatal, but it takes only a small amount of rattlesnake venom in comparison to alcohol.

- **Exposure** is the amount of a substance that actually comes in contact with the body. For substances in the environment, exposure is usually gauged by measuring the amount that comes in contact with people through food, water or air. The life stage at the time of exposure may also be important. For instance there may be periods of growth and development when an organism may be more sensitive.

For exposure, there are three important factors to consider: (1) how much of the substance is in the environment; (2) how much of the substance actually reaches the target organ or cells; and (3) how long the substance remains potentially active in the body. For example, it has been estimated that the average Western diet contains millions of times more potential estrogenic activity from the phytoestrogens naturally present in foods than from the residual levels, if any, of pesticides such as DDT and methoxychlor which may have incidental estrogen-like properties.

Some substances are quickly broken up, filtered and cleared out of the blood by the kidneys, lungs or liver. Other substances may take a long time to be removed from the body or may accumulate in the body in specific tissues, such as bone or fat, and remain there for long periods. Buildup of a substance in the body is called “bioaccumulation.”

The life stage at the time of exposure may also be important. For instance, there may be critical periods of development when a fetus is especially vulnerable.

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Hazard and exposure, along with potency, are the factors that constitute “risk.”

- **Risk** is an estimate of the likelihood that a substance will cause a harmful effect in people or wildlife, under certain conditions. A substance that has a specific inherent hazard, such as an ability to cause birth defects, will have very little or no risk if people are not exposed (or have very little exposure) to that substance. However, the substance could have great risk if people are exposed substantially.

If people have substantial exposure to a hazardous substance, they may be able to reduce the likelihood of harm, *i.e.* the risk, by reducing their exposure to that hazard. For example, excessive consumption of alcoholic beverages can cause not only cirrhosis of the liver but also feminization of men, an effect that is likely mediated through the endocrine system. However, moderate consumption of alcohol is not considered a significant risk for cirrhosis or feminization, and some studies have shown that moderate amounts of alcohol may help prevent heart disease.

Understanding a substance’s potency and how it behaves in the body provides additional information to determine potential risk. For example, most plant phytoestrogens and any hormonally active agents in the environment are much less potent than natural estrogen. By knowing how much of a substance reaches sensitive cells and organs, scientists are better able to determine whether a substance can cause harmful effects in people or wildlife.

Overall, as noted by the U.S. National Academy of Sciences in 1999, more research is needed to understand the likelihood of harm (*i.e.*, the risk) from exposure to

the very small amounts of hormonally active agents that may be found in the environment.

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A report by a committee of the National Academy of Sciences of the United States that reviews the state of the science of hormonally active agents in the environment, with conclusions and recommendations for further research.

6. DES: A Lesson Learned

DES, a synthetic estrogenic drug, is far more potent -- and human exposure was to much higher levels -- than any hormonally active agent found in the environment.

From the 1940s until about 1972, an estimated 5 million American women received a drug called diethylstilbestrol (DES), a potent synthetic estrogen, during pregnancy. Doctors prescribed the drug with the hope that it would prevent miscarriages and lead to healthier babies.

In the 1970s, doctors noticed that there was a strong correlation between DES and an unusual form of vaginal cancer (clear cell carcinoma) in women who were exposed to DES before birth (*i.e., in utero*), while their mothers were taking the drug during their pregnancy. The drug's use was discontinued in 1972 and since then, scientists have been studying the health of women who took DES, as well as how DES has affected the health and well-being of DES-daughters and DES-sons.

Among these "DES-daughters," the drug was associated with a significant rise in the number of abnormalities in the female reproductive tract, an increase in adverse pregnancy outcomes and an increased likelihood of infertility, but no apparent increased risk for breast cancer. Among "DES-sons" (*i.e., sons of women who took DES during their pregnancy*), there were more genital tract abnormalities and decreased sperm count and quality. One study reported that fertility (*i.e., the ability to father children*) among DES-sons did not seem to have been impaired. In 1993, the National Cancer Institute concluded there was no link to testicular cancer in DES-sons. This issue will be re-visited

with longer follow up. There is also some evidence that DES mothers may be at greater risk for breast cancer.

Scientists have found that exposure to DES in the early part of a woman's pregnancy was more dangerous than exposure at a later phase of the pregnancy. Also, there is evidence that sons and daughters of women who had taken small amounts of DES may not have experienced any of the ill effects seen in children of mothers who took large amounts of DES.

The experience with DES offers important lessons about the possible effect of substances that act like estrogens. For example,

- **Hazard -- *the potential of a substance to cause a harmful effect.*** Above all, the DES experience showed that, under certain conditions of timing and exposure, a very potent hormonally active agent might have serious, harmful consequences. There may be critical periods of development when a fetus is especially vulnerable.
- **Potency -- *a measurement of how much of a substance is needed to cause a harmful effect.*** DES was intended to act like natural estrogen and is at least as powerful as the most potent natural estrogen in humans. However, hormonally active agents in the environment are much less potent than natural hormones.
- **Exposure -- *the amount of a substance that actually comes in contact with the body.*** People are exposed to much smaller amounts of hormonally active agents in the environment or in their normal diet than the amount of DES that women were exposed to during their pregnancy.

Further Reading

E.E. Hatch and others (1998), "Cancer risk in women exposed to diethylstilbestrol in utero." *Journal of the American Medical Association*, vol. 280, no. 7, pages 630-634.

An examination of the risk of cancers other than of the vagina and cervix in DES-exposed daughters.

R.J. Golden and others (1998), "Environmental endocrine modulators and human health: an assessment of the biological evidence." *Critical Reviews in Toxicology*, vol. 28, pages 109-227.

A review and discussion of the DES story as well as an assessment of the potential of hormonally active agents in the environment to impact human health.

Report of the Committee on Hormonally Active Agents in the Environment, National Research Council (1999), "Hormonally Active Agents in the Environment." National Academy Press, Washington, D.C.

A report by a committee of the National Academy of Sciences of the United States that reviews the state of the science on hormonally active agents in the environment, with conclusions and recommendations for additional research.

7. Human Fertility and the Ratio of Boys to Girls at Birth

There is little current evidence that exposure to hormonally active agents, at levels typically found in the environment, causes a decline in human fertility or a change in the ratio of boys to girls at birth.

Male Fertility

A number of diseases can affect male fertility. For example, an extended, untreated case of the mumps may cause sterility. Another disease that may be localized in the testes and can cause severe damage if untreated is typhus fever. Excessive temperature of the testes is another cause of sterility. Additionally, some male infants are born with damaged reproductive organs as a result of unknown causes.

Sperm from a fertile man are extremely uniform in size and appearance. When uniformity does not exist, even though the sperm may appear to be healthy, either total or “relative” sterility (*i.e.*, inability to father children) usually exists.

Female Fertility

By far the most common cause of female sterility is failure to ovulate (*i.e.*, failure of the ovaries to produce an egg). This can result from a drop in the amounts of certain hormones of the endocrine system that normally stimulate the ovaries to produce an egg. Also, it can result from a structural abnormality of the ovaries themselves.

Endometriosis, the uncontrolled growth of endometrium in the pelvis area (rather than in the uterus) also is a cause of infertility in women.

Occasionally, no abnormality whatsoever is found in the female reproductive tract. In those cases, it is assumed that the infertility is due to abnormal function of the ovaries or to abnormal genetic development of the ovaries.

Is Human Fertility Declining?

There is little current evidence to indicate that fertility is declining. Several national surveys have indicated that rates of infertility in the United States have remained constant during the past 30 years, at 8-11 percent. Male infertility has accounted for approximately one third of all cases.

Hormonally Active Agents and the Ratio of Boys to Girls at Birth

Several studies have reported that the ratio of male to female births has declined since 1970 in Canada, the Netherlands and Denmark. Some scientists have hypothesized that HAAs in the environment might be a cause of the declines in these countries. As noted by the U.S. National Academy of Sciences in 1999, the causes of the declines in sex ratio is yet unknown.

Researchers from the U.S. Centers for Disease Control and Prevention analyzed the birth certificate records in the United States for the years 1969 to 1995. The scientists found that the ratio of male births to female births dropped slightly for white women but went up among African-American women. None of the possible explanations that were considered fully explained these changes. Since there was a definite difference in the birth ratios among white and African-American women, the scientists concluded that

exposure to substances in the environment was a very unlikely explanation for these observations.

A 1999 study in Finland analyzed the ratio of male births to female births over 250 years. The scientists found a rise in the proportion of male births to female births from 1751 to 1920, followed by a drop, with peaks in male births occurring during and after World War I and World War II. None of the parameters that they considered (*i.e.*, paternal or maternal age, age difference of the parents or birth order) could explain these changes. Furthermore, the number of male births began to drop before the period of western industrialization or the introduction of pesticides or synthetic hormone drugs. These results are similar to those from studies in other countries that have more environmental pollution and use much greater amounts of pesticide than Finland. The scientists concluded that it is unlikely that environmental factors are responsible for the drop in the ratio of male births to female births.

Further Reading

R.J. Sherins (1995), "Are semen quality and male fertility changing?" *The New England Journal of Medicine*, vol. 332, pages 327-8.

A review of the hypothesis that sperm quality and human fertility are declining.

M. Marcus and others (1998), "Changing sex ratios in the United States, 1969-1995." *Fertility and Sterility*, vol. 70, pages 270-273.

A review and analysis by scientists from the Centers for Disease Control and Prevention (CDC) of the United States of birth certificate records for the years 1969-1995, with particular attention to sex ratios.

R.M. Sharpe (1998), "Environmental oestrogens and male infertility." *Pure and Applied Chemistry*, vol. 70, no. 9, pages 1685-1701.

A comprehensive review of the causes of male infertility.

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Report of the Committee on Hormonally Active Agents in the Environment, National Research Council (1999), "Hormonally Active Agents in the Environment." National Academy Press, Washington, D.C.

A report by a committee of the National Academy of Sciences of the United States that reviews the state of the science of hormonally active agents in the environment, with conclusions and recommendations for further research. Declines in sex ratio are discussed on page 127.

T. Vartiainen and others (1999), "Environmental chemicals and changes in sex ratio: analysis over 250 years in Finland." *Environmental Health Perspectives*, vol. 107, no. 10, pages 813-815.

A study examining the changes in the ratio of male births to female births in Finland over 250 years with a discussion of whether environmental factors may be responsible for the observed changes.

8. Reproductive Disorders in Males

Current scientific evidence does not support a definitive link between male reproductive disorders and hormonally active agents in the environment.

“Cryptorchidism” and “hypospadias” are two types of male reproductive disorders thought to be caused by improper levels of sex hormones. Cryptorchidism is the failure of one or both testes to descend from the abdomen in the scrotum during the late stages of development of the male fetus. If the condition does not spontaneously resolve during the first year or two of life, surgery is often performed to correct the condition as an undescended testicle is incapable of forming sperm due to the higher temperature in the abdomen compared to the scrotum.

Hypospadias is a malformation in which the urinary exit of boys occurs in the bottom part of the shaft of the penis, rather than the tip. Depending on the severity, surgery is often performed to correct the condition.

Hormonally Active Agents and Reproductive Disorders in Males

It has been suggested that HAAs found in the environment may be responsible for cryptorchidism and hypospadias in young boys. However, to date, no scientific link has been established between these abnormalities and exposure to HAAs.

One study showed no increase in the prevalence of cryptorchidism in the United States between the mid-1950s and 1992. Another indicated that the hypospadias rates had doubled in all four regions of the United States in the 1970s and 1980s.

Reported increases in the incidence of hypospadias in Sweden, Norway, Denmark, England and Wales since the 1970s may have been due to improper reporting and validation of the abnormality. A review by Dr. Robert Golden and others found that any increase in hypospadias was unlikely to be due to exposure to DDT, a chemical with hormone-like properties, and its hormonally active metabolite ρ,ρ' -DDE, since the levels of these substances have declined in these countries since the late 1960s.

A 1999 study showed that the increase in hypospadias leveled off in many countries after 1985 while the rate of cryptorchidism has dropped in most of these same areas. A number of factors may account for the reported changes, including changes in how the abnormalities are defined and diagnosed, and gradual improvement in physician documentation.

The Report of the National Academy of Sciences of the United States

In August 1999, the U.S. National Academy of Sciences (NAS) issued a long-awaited, landmark report on the endocrine disruption hypothesis. The expert NAS “Committee on Hormonally Active Agents in the Environment” said that reported increases in the incidence of male reproductive disorders, such as hypospadias and cryptorchidism, “cannot be linked to exposures to environmental HAAs at this time.”

Further Reading

L.J. Paulozzi and others (1997), “Hypospadias trends in two U.S. surveillance systems.” *Pediatrics*, vol. 100, pages 831-834.

The report reviews two large studies in humans examining the incidences of male reproductive disorders in the United States.

R.J. Golden and others (1998), "Environmental endocrine modulators and human health: an assessment of the biological evidence." *Critical Review in Toxicology*, vol. 28, pages 109-227.

A review of the likelihood that hormonally active agents in the environment play a role in the reported incidences of human diseases, including (pages 148-163) male reproductive disorders.

L.J. Paulozzi and others (1999), "International trends in rates of hypospadias and cryptorchidism." *Environmental Health Perspectives*, vol. 107, no. 4, pages 297-302.

A review of a study of a large number of countries and the incidences of male reproductive disorders.

Report of the Committee on Hormonally Active Agents in the Environment, National Research Council (1999), "Hormonally Active Agents in the Environment." National Academy Press, Washington, D.C.

A report by a committee of the National Academy of Sciences of the United States that reviews the state of the science on HAAs in the environment, with conclusions and recommendations for further research.

S.H. Safe (2000), "Endocrine disrupters and human health – Is there a problem? An update," *Environmental Health Perspectives*, vol. 108, pages 487-493 [Online 12 April 2000].

A review of human health trends which concludes that many of the male reproductive tract problems linked to the endocrine disrupter hypothesis have not increased and are not correlated with HAAs.

9. Sperm Counts and Male Infertility

There is no clear consensus among scientists on whether sperm counts or sperm quality have declined, risen or stayed the same.

The formation of sperm is one of the three major functions of male reproduction. Even though only a single sperm is necessary to fertilize an egg, for reasons not yet completely understood, about 400,000,000 sperm are usually present during fertilization.

It had been thought that a man with only 35,000,000 sperm available for fertilization at any given time would likely be almost completely infertile. However, recent studies have shown that men with as low as 5,000,000 sperm still are able to father children. Nevertheless, for optimum fertility, most fertility experts believe that it is important that the production of sperm not be affected or reduced. To ensure that sperm are of the highest quality and of sufficient quantity when needed, their formation is controlled by hormones of the endocrine system.

Sperm Counts Over the Years?

Some scientists have questioned whether hormonally active agents (HAAs) in the environment affect the number of sperm produced in humans (*i.e.*, the “sperm counts”).

Several conflicting studies on sperm counts have been published in the scientific literature. For example, there have been reports that in many countries, the average number of sperm produced by adult males is declining. On the other hand, other studies showed no drop in sperm counts or quality of semen for specific locations in the United

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States, such as Wisconsin, Seattle and New York, or in Denmark. A different study conducted in Paris, France and another in England showed a reduction in sperm counts while a study in Toulouse, France, showed no changes.

One study published in 1992 suggested that the average number of sperm produced by adult males worldwide has declined by 50 percent over the last 50 years. However, when other scientists analyzed the same information, they noticed that the data varied greatly from one study to another and that the information collected before 1970 could not be compared fairly with information gathered after 1970. When they accounted for this variation, they reached a different conclusion, namely, that sperm counts in humans did not drop and may, in fact, have risen slightly. Furthermore, substantial geographic differences in sperm counts are evident across the world. The observations that suggested declining sperm counts could reflect, to some degree, clustering of these significant geographical variations rather than an actual decline.

An international panel of experts convened in 1995 at Baylor University College of Medicine reviewed the available scientific studies on sperm counts. Their opinion was that, because of weaknesses in methodology, statistical analysis, participant selection and sample collection, it was not possible to conclude that sperm counts have declined over the past 50 years.

According to the U.S. Department of Health Statistics, fertility rates have remained constant for the past 30 years.

There does not appear to be any clear consensus among scientists on whether sperm counts and sperm quality have declined, have risen or have stayed the same. Research continues.

Factors Affecting Sperm Counts

Many lifestyle and environmental factors influence sperm counts in men. Some drugs, such as anabolic steroids and chemotherapeutic agents, and irradiation (X-rays) can greatly reduce the number of sperm that a man produces. Virus infection or high fever, as well as drug abuse, frequent sexual activity, heat and stress can also have an impact on sperm production. Differences in the way sperm are collected and even seasonal changes also can have a profound effect on test results.

Sperm Counts and Male Fertility?

Of all of the recent controversies about the potential effects of HAAs on the human body, the study of sperm counts and the potential effect on male fertility has generated the most attention as well as, perhaps, the most confusion.

Few, if any, studies of sperm counts include information on whether the participants were exposed to HAAs in the environment. Some studies have reported cases where workers exposed to high amounts of certain chemical substances at their workplace experienced a drop in sperm counts. However, the relevance of these observations can be questioned because at least some of the substances are not thought to be HAAs. Moreover, these exposures were to much higher amounts than are typically found in the environment. Consequently, it is difficult to predict from these studies what effect, if any, exposure to low amounts of HAAs would have on sperm production in males.

View of the National Academy of Sciences

In August 1999, the U.S. National Academy of Sciences issued a long-awaited, landmark report on the endocrine disruption hypothesis. The expert NAS “Committee on Hormonally Active Agents in the Environment” said that while regional differences in sperm concentrations have been observed, these “should be studied prospectively to determine whether the differences can be associated with genetic and environmental factors.” The conclusion of the Committee was that more research is needed to determine whether sperm concentrations are declining.

Further Reading

L.I. Lipshultz (1996), “The Debate Continues: The Continuing Debate Over the Possible Decline in Sperm Quality.” *Fertility and Sterility*, vol. 65, no. 5, pages 909-911.

An editorial that discusses a number of the recent studies of sperm counts.

D.J. Lamb (1997), “Hormonal disruptors and male infertility: are men at serious risk?” *Regulatory Toxicology and Pharmacology*, vol. 26, pages 30-33.

A discussion of male infertility, endocrine disruption and environmental factors.

R.M. Sharpe (1998), “Environmental oestrogens and male infertility.” *Pure and Applied Chemistry*, vol. 70, no. 9, pages 1685-1701.

A comprehensive review of the effect of environmental estrogens on sperm counts, male infertility and testicular cancer.

R.F.A. Weber and J.T.M. Vreeburg (1998), “Bias and confounding in studies of sperm counts.” *Pure and Applied Chemistry*, vol. 70, no. 9, pages 1703-1711.

An examination of the various confounding factors and variables that are present in the study of sperm counts in humans.

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J.A. Saidi, D.T. Chang, E.T. Goluboff, E. Bagiella, G. Olsen and H. Fisch (1999), "Declining sperm counts in the United States? A critical review." *The Journal of Urology*, vol. 161, pages 460-462.

A review of the state of the science on sperm counts in the United States and an analysis of regional differences.

Report of the Committee on Hormonally Active Agents in the Environment, National Research Council (1999), "Hormonally Active Agents in the Environment." National Academy Press, Washington, D.C.

A report by a committee of the National Academy of Sciences of the United States that reviews the state of the science on HAAs in the environment, with conclusions and recommendations for additional research.

S.H. Safe (2000), "Endocrine disrupters and human health – Is there a problem? An update," *Environmental Health Perspectives*, vol. 108, pages 487-493 [Online 12 April 2000].

Recent studies show that there are large demographic variations in sperm counts within countries or regions, and that the North American data show that sperm counts have not decreased over the last 60 years. The review concludes that many of the male reproductive tract problems linked to the endocrine disruption hypothesis have not increased and are not correlated with HAAs.

10. Endometriosis and Female Infertility

The relationship, if any, between exposure to hormonally active agents in the environment and endometriosis is unknown.

Endometriosis is the development and growth of endometrial tissue (*i.e.*, tissue that is normally found in the uterus) in areas of the pelvis where it does not belong, in addition to the uterus where it is normally present. Endometriosis is one of the most prevalent causes of female infertility.

Although the specific cause of endometriosis is unknown, some scientists believe that contraction of the uterus during menstruation occasionally allows some of the endometrium from the uterus to move backward into the pelvis area where it remains, grows and causes pain.

Hormonally Active Agents in the Environment and Endometriosis

Scientists have investigated the possibility that HAAs in the environment may be a cause of endometriosis.

Studies of HAAs in laboratory animals have been inconclusive. In one study, laboratory animals were given dioxin by the oral route for four years and then examined for endometriosis 15 years later. The researchers suggested an association between exposure to dioxin and endometriosis. However, another study found no association between endometriosis and long-term ingestion of PCBs (polychlorinated biphenyls) at

amounts that were ten times higher than those used in the dioxin study. The results of both studies are confounded by the high natural incidence of endometriosis, in the absence of any test chemical exposure, in the laboratory animals used.

A report from the U.S. Environmental Protection Agency indicated that while studies in laboratory animals suggest a link between exposure to dioxin and endometriosis, preliminary information from studies of humans suggest that dioxin and related chemicals are not correlated with this disease.

Two comprehensive reviews of the available published information concluded that the existing studies do not support an association between an increase in endometriosis and human exposure to environmental levels of HAAs.

Further Reading

U.G. Ahlborg and others (1995), "Organochlorine compounds in relation to breast cancer, endometrial cancer, and endometriosis: an assessment of the biological and epidemiological evidence." *Critical Review in Toxicology*, vol. 25, pages 463-531.

A review of the available information examining the hypothesis that hormonally active agents in the environment cause endometriosis and endometrial cancer.

T.M. Crisp and others (1998), "Environmental endocrine disruption: an effects assessment and analysis." *Environmental Health Perspectives*, vol. 106, Suppl. 1, pages 11-56.

A comprehensive analysis and summary of the scientific position of the U.S. Environmental Protection Agency on hormonally active agents, including a discussion of the causes of endometriosis and a report of a small clinical study (15 women) which found no correlation between the severity of the disease and 22 of the most common dioxin, furan and PCB congeners .

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R.J. Golden and others (1998), "Environmental endocrine modulators and human health: an assessment of the biological evidence." *Critical Reviews in Toxicology*, vol. 28, pages 109-227.

A review of the likelihood that hormonally active agents in the environment play a role in the reported incidences of human diseases, including (pages 141-148) endometriosis.

11. Breast Cancer

The available studies do not support an association between adult exposure to hormonally active agents in the environment, such as DDT and PCBs, and breast cancer.

Breast cancer is the most common cancer in the U.S., accounting for 16.3% of all cancer cases every year. Some established risk factors for breast cancer include age, gender (while breast cancer predominantly occurs in women, men get breast cancer also, but at a rate 100-fold lower than in women), family history, history of benign breast disease, early onset of menstruation and late age of menopause, age at birth of first child (*i.e.*, a 7-8% rise in cancer risk for each year of delay beyond age 30), never having given birth, radiation (at or near the time of puberty), ethnic background, and socioeconomic status. Other suspected risk factors are consumption of alcohol, diet and lack of exercise.

In the United States, the incidence of breast cancer has increased gradually, about one percent per year, from 1940 to 1982. Between 1982 and 1987, the incidence of breast cancer rose more rapidly, due in part to the widespread use of mammography screening which gave doctors the ability to detect breast cancer at an earlier stage. The NCI recently reported that there has been a 1.2% per year increase in incidence from 1992-1998. Increases were limited to early stage cancers that may again be related to increased screening, according to the NCI. It is also noted that contributions of other risk factors, such as obesity and hormone replacement therapy are unknown.

Breast cancer appears to be more prevalent in some parts of the United States than in others. In 1995, the U.S. National Cancer Institute reported that this geographic variation was due primarily to small differences in known risk factors, such as age at

birth of first child or frequency of never having given birth, at these locations and did not suggest a role for environmental factors.

Hormonally Active Agents and Breast Cancer

Many studies have examined the relationship between birth control pills and hormone replacement therapy – both contain potent HAAs -- and the incidence of breast cancer. The results are indicative of a weak relationship.

The possibility that HAAs in the environment may play a role in causing breast cancer has also been investigated in a number of studies. For example, one early study supported a possible link between exposure to the pesticide DDT [but not to polychlorinated biphenyls (PCBs)] and breast cancer. The study assumed chemicals measured in the blood at the time of diagnosis of breast cancer indicated an earlier exposure. Another study using measurements of chemicals in the blood obtained 20 years prior to diagnosis as indicative of exposure found no association between DDT or PCBs and breast cancer.

In 1995, scientists at the Harvard University School of Public Health reviewed the scientific literature on the relationship between exposure to DDT, PCBs and related compounds and the incidence of breast cancer. Results from tests in animals as well as occupational studies and studies of people in the general population were considered. Their conclusion was that the available information did not show any increases in the likelihood (*i.e.*, the risk) of developing breast cancer from exposure to these chemicals. Since the first early studies suggesting a possible association between DDT or PCBs and breast cancer, more than 10 later studies have found no association between these compounds and breast cancer.

View of the National Academy of Sciences

In August 1999, the U.S. National Academy of Sciences (NAS) issued a long-awaited, landmark report on the endocrine disruption hypothesis. The expert NAS “Committee on Hormonally Active Agents in the Environment” concluded that the available studies did not support an association between adult exposure to hormonally active agents such as DDT and PCBs, and breast cancer.

Further Reading

S.R. Sturgeon and others (1995), “Geographic variation in mortality from breast cancer among white women in the United States,” *Journal of the National Cancer Institute*, vol. 87, pages 1846-1853.

A study by researchers at the National Cancer Institute indicating that when known risk factors are considered, regional differences in breast cancer mortality among younger women disappear and among older women are significantly reduced.

U.G. Ahlborg and others (1995), “Organochlorine compounds in relation to breast cancer, endometrial cancer, and endometriosis: an assessment of the biological and epidemiological evidence.” *Critical Reviews in Toxicology*, vol. 25, no. 6, pages 463-531
The most definitive science review on possible environmental causes of breast cancer, by experts convened by the Harvard University School of Public Health.

Cancer Facts & Figures 2000 New York: American Cancer Society.
An easy-to-read summary of useful information on breast cancer.

L. Rhomberg (1998), “Breast cancer risk factors: What do we know and how well do we know it?” *Risk in Perspectives*, vol. 6, no. 3, pages 1-4.
A review of the risks for breast cancer with specific reference to environmental factors.

J.J. Li and S.A. Li (1998), "Breast cancer: evidence for xeno-oestrogen involvement in altering its incidence and risk." *Pure and Applied Chemistry*, vol. 70, no. 9, pages 1713-1723.

A review of studies in animals and of humans examining the relationship between exposure to estrogens and breast cancer.

Report of the Committee on Hormonally Active Agents in the Environment, National Research Council (1999), "Hormonally Active Agents in the Environment." National Academy Press, Washington, D.C.

A report by a committee of the National Academy of Sciences of the United States that reviews the state of the science of HAAs in the environment, with conclusions and recommendations for further research.

S.H. Safe (2000), "Endocrine disrupters and human health – Is there a problem? An update," *Environmental Health Perspectives*, vol. 108, pages 487-493 [Online 12 April 2000].

Results from studies on HAAs such as DDT and PCBs show that levels were not significantly different in breast cancer patients versus controls. The review concludes that the incidence of breast cancer is not correlated with HAAs.

H.L. Howe et al. (2001), "Annual report to the nation on the status of cancer (1973-1998), featuring cancers with recent increasing trends," *Journal of the National Cancer Institute*, vol. 93 (11), pages 824-842.

A report by the National Cancer Institute (NCI) on recent trends in cancer incidence and mortality, with special focus on 1992 through 1998.

12. Endometrial Cancer

The available studies do not support an association between hormonally active agents in the environment and endometrial cancer.

Endometrial cancer (cancer of the body of the uterus) occurs mainly in mature women, with 56 being the average age for women diagnosed with this disease. Most of the risk factors for endometrial cancer (e.g., nulliparity {no children}, late menopause, obesity, hypertension, gallbladder disease, unopposed estrogen therapy) are characterized by states of continual estrogenic stimulation of the endometrium. Incidence of this disease took a marked increase in the 1970s when women were given unopposed estrogen for treatment of menopausal symptoms. Adding progestins to oral contraceptives and hormone replacement therapy modulates the stimulatory effect of estrogens on the endometrium and reduces the risk of endometrial cancer. Incidence rates after introduction of combined therapy declined and returned to earlier levels.

Hormonally Active Agents and Endometrial Cancer

Scientists have investigated whether HAAs in the environment may be a cause of endometrial cancer.

A comprehensive review of the available information, published in 1995, was conducted by Ahlborg and colleagues at the Institute of Environmental Medicine in Stockholm, Sweden. The purpose of the study was to determine whether people exposed

to environmental levels of DDT, PCBs (polychlorinated biphenyls) or related compounds had an increased incidence of endometrial cancer. The study, which examined the results of experiments conducted in the laboratory animals as well as studies of humans, found no evidence to indicate that this was the case.

No associations between endometrial cancer and blood concentrations of PCBs and 10 chlorinated pesticides were observed in a recent epidemiology study. The authors, Wiederpass et.al. (2000), concluded “the studied environmental contaminants do not cause endometrial cancer at the concentrations found in our population.”

View of the National Academy of Sciences

In August 1999, the U.S. National Academy of Sciences (NAS) issued a long-awaited, landmark report on the endocrine disruption hypothesis. The expert NAS “Committee on Hormonally Active Agents in the Environment” concluded that the available studies did not support an association between hormonally active agents in the environment and endometrial cancer.

Further Reading

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U.G. Ahlborg and others (1995), "Organochlorine compounds in relation to breast cancer, endometrial cancer, and endometriosis: an assessment of the biological and epidemiological evidence." *Critical Review in Toxicology*, vol. 25, pages 463-531.

A comprehensive review of the available information examining the hypothesis that hormonally active agents in the environment cause endometrial cancer.

N. Potischman and others (1996), "Case-control study of endogenous steroid hormones and endometrial cancer." *Journal of the National Cancer Institute*, vol. 88, pages 1127-1135.

A study examining potential other risk factors for endometrial cancer.

Report of the Committee on Hormonally Active Agents in the Environment, National Research Council (1999), "Hormonally Active Agents in the Environment." National Academy Press, Washington, D.C.

A report by a committee of the National Academy of Sciences of the United States that reviews the state of the science on hormonally active agents in the environment, with conclusions and recommendations for further research.

E. Weiderpass and others (2000), "Organochlorines and Endometrial Cancer Risk." *Cancer Epidemiology, Biomarkers and Prevention*, vol. 9, pages 487-493. *A study examining the hypothesis that organochlorines may be related to endometrial cancer.*

13. Prostate Cancer

The available studies do not support an association between hormonally active agents in the environment and prostate cancer.

Cancer of the prostate gland is the most commonly occurring cancer among men in the United States. The U.S. National Cancer Institute (NCI) reported that the incidence of prostate cancer has risen dramatically from 1988-1992, when new screening methods were introduced. Subsequently (1992-95) the rates have begun to significantly decline. They appeared to have leveled off from 1995-98. According to NCI and the American Cancer Society, the rapid apparent increase in the late 1980s is due in part to better detection through increased screening and new laboratory tests, including ultrasound techniques for detecting early-stage prostate cancers that could not be diagnosed before and that may be clinically insignificant.

The biggest risk factor for prostate cancer is age. As a man gets older, the likelihood of having prostate cancer increases. For example, for men below 65 years of age, the rate of prostate cancer is 23 cases per 100,000 whereas for men over 65, the rate is 885 per 100,000.

Other established risk factors for prostate cancer are family history of the disease, ethnic background and country of residence.

Hormonally Active Agents and Prostate Cancer

Some scientists have suggested that hormonally active agents in the environment may be a cause of prostate cancer. To date, however, there is little evidence to support such an association.

For example, scientists who study human populations have known for decades about the higher rate of prostate cancer in African-American men compared to white men. However, no environmental substance has been identified that could account for the higher risk in this population.

A study reported in 1995 indicated that men in Washington county, Maryland, who had prostate cancer did not have higher levels of p,p'-DDE (the main breakdown product of DDT) and PCBs (polychlorinated biphenyls) in their bodies than men who were free of prostate cancer. Certain PCBs have estrogenic (*i.e.*, substances that act like the natural hormone estrogen) activity while others have anti-estrogenic (*i.e.*, substances that interfere with estrogen) activity. DDE is known to have anti-androgenic (*i.e.*, substances that interfere with the male hormone testosterone) activity.

The results with DDE were confirmed in a second study which reported that the incidence of prostate cancer was not associated with human body or environmental levels of DDE. The authors concluded that the study did not provide support to the hypothesis of a link between exposure to DDT derivatives and prostate cancer.

View of the National Academy of Sciences

In August 1999, the U.S. National Academy of Sciences (NAS) issued a long-awaited, landmark report on the endocrine disruption hypothesis. The expert NAS "Committee on Hormonally Active Agents in the Environment" concluded that the

available studies did not support an association between hormonally active agents in the environment and prostate cancer.

Further Reading

P. Boyle and D.G. Zaridze (1993), "Risk factors for prostate and testicular cancer." *European Journal of Cancer*, vol. 29A, no. 7, pages 1048-1055

A recent review of scientific studies.

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K.J. Helzlsouer and others (1995), "Molecular epidemiology of prostate cancer," abstract of presentation at the Organochlorines and Cancer workshop, Ottawa, Canada, September 27-29, 1995.

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P. Cocco and J. Benichou (1998), "Mortality from cancer of the male reproductive tract and environmental exposure to the anti-androgen p,p'-DDE in the United States," *Oncology*, vol. 55, pages 334-339.

A study showing no association between DDE levels and prostate or testicular cancer.

R.K. Ross and others (1998), "Androgen metabolism and prostate cancer: establishing a model of genetic susceptibility." *Cancer Research*, vol. 58, pages 4497-4504

An examination of the role of genetic susceptibility in prostate cancer.

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H.L. Howe et al. (2001), "Annual report to the nation on the status of cancer (1973-1998), featuring cancers with recent increasing trends," *Journal of the National Cancer Institute*, vol. 93 (11), pages 824-842.

A report by the National Cancer Institute (NCI) on recent trends in cancer incidence and mortality, with special focus on 1992 through 1998.

Report of the Committee on Hormonally Active Agents in the Environment, National Research Council (1999), "Hormonally Active Agents in the Environment." National Academy Press, Washington, D.C.

A report by a committee of the National Academy of Sciences of the United States that reviews the state of the science on HAAs in the environment, with conclusions and recommendations for further research.

14. Testicular Cancer

The available studies do not support an association between hormonally active agents in the environment and testicular cancer.

Testicular cancer is uncommon in white men and rare in African American men. It affects fewer than 10 of every 100,000 men in the United States. The incidence of testicular cancer in white Americans has increased by 60% from 1973-1990, but has decreased in African Americans by 16% in the same time period. In a recent NCI report, testicular cancer rates were reported to have increased by 1.7% annually over the 1973-98 time period, mostly in the under 50 year old age group.

Testicular cancer is unlike most major cancers because of its rarity (especially in African Americans) and the fact that young adult males, as opposed to older individuals, are at the highest risk. These observations suggest that the cause of testicular cancer may be related to an event that occurs *in utero* (i.e., in the womb) and/or has some genetic component.

The only established risk factor for testicular cancer is a history of undescended testes (called “cryptorchidism”).

Hormonally Active Agents and Testicular Cancer

Since the testes secrete the hormone testosterone and are regulated by hormones of the pituitary gland, it has been suggested that HAAs might cause testicular cancer.

Some have suggested that *in utero* exposure to synthetic hormones might be a risk factor for testicular cancer. For example, some studies of mothers who took a synthetic estrogenic substance (*i.e.*, a substance that acts like the natural hormone estrogen) called diethylstilbestrol (DES) during their pregnancy have suggested an increase in the likelihood that their male offspring would have testicular cancer or undescended testes at birth. More recent research has not confirmed this early finding.

Results from studies that examined the incidence of testicular cancer in various countries were inconsistent with the “*in utero* hypothesis.” Specifically, the incidence of testicular cancer was found to be high in Denmark but low in nearby Finland despite similarities in economic development, diet and use of chemicals in these two countries. Also, in Bombay, India, a heavily polluted city where DDT (a pesticide with hormone-like properties) is still widely used, the incidence of testicular cancer is substantially lower than in Denmark or New Zealand where DDT is banned. Similarly, the incidence of testicular cancer varies from state to state in the United States, with the highest rates observed in the mountain states (as opposed to the industrial and agricultural states) of Montana, Idaho and Colorado.

View of the National Academy of Sciences

In August 1999, the U.S. National Academy of Sciences (NAS) issued a long-awaited, landmark report on the endocrine disruption hypothesis. The expert NAS “Committee on Hormonally Active Agents in the Environment” concluded that the available studies did not support an association between HAAs in the environment and testicular cancer. Specifically regarding DES, the Committee reviewed the available data and found that “exposure to DES *in utero* does not increase the risk of testicular cancer in male offspring.”

Further Reading

P. Boyle and D.G. Zaridze (1993), "Risk factors for prostate and testicular cancer." *European Journal of Cancer*, vol. 29A, no. 7, pages 1048-1055

A recent review of scientific studies.

R.M. Sharpe (1998), "Environmental oestrogens and male infertility." *Pure and Applied Chemistry*, vol. 70, no. 9, pages 1685-1701.

A comprehensive review of the effect of environmental estrogens on sperm counts, male infertility and testicular cancer.

Report of the Committee on Hormonally Active Agents in the Environment, National Research Council (1999), "Hormonally Active Agents in the Environment." National Academy Press, Washington, D.C.

A report by a committee of the National Academy of Sciences of the United States that reviews the state of the science on HAAs in the environment, with conclusions and recommendations for further research.

S.H. Safe (2000), "Endocrine disrupters and human health – Is there a problem? An update," *Environmental Health Perspectives*, vol. 108, pages 487-493 [Online 12 April 2000].

A review of human health trends, including testicular cancer rates. The incidence of testicular cancer is increasing in most countries. However, in Scandinavia, the difference between high (Denmark) and low (Finland) incidence areas are not well understood and are unlikely to be correlated with differences in exposure to HAAs.

H.L. Howe et al. (2001), "Annual report to the nation on the status of cancer (1973-1998), featuring cancers with recent increasing trends," *Journal of the National Cancer Institute*, vol. 93 (11), pages 824-842.

A report by the National Cancer Institute (NCI) on recent trends in cancer incidence and mortality, with special focus on 1992 through 1998.

CHEMICALS IN THE ENVIRONMENT AND
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R.J. Golden and others (1998), "Environmental endocrine modulators and human health: an assessment of the biological evidence." *Critical Reviews in Toxicology*, vol. 28, pages 109-227.

A review and discussion of the DES story as well as an assessment of the potential of hormonally active agents in the environment to impact human health.

15. Thyroid Disorders and Thyroid Cancer

No chemical substance has been identified as causing thyroid cancer in humans.

The thyroid gland is located on either side of the trachea (also referred to as the “windpipe”). The gland secretes the hormone thyroxine that has a profound effect on normal metabolism of the body.

Thyroid Disorders

Thyroid disorders result mainly from too much (*i.e.*, “hyperthyroidism”) or too little (*i.e.*, “hypothyroidism”) thyroid hormones being made by the thyroid gland. Hyperthyroidism causes people to have high metabolism with symptoms of intolerance to heat, increased sweating, mild to extreme weight loss, and general muscular weakness and nervousness. Hypothyroidism causes people to be very tired, usually sleep 14-16 hours a day, have a slowed heart rate, gain weight and generally feel extremely sluggish.

Visible enlargement of the thyroid gland, called a “goiter,” may be associated with either hyper- or hypothyroidism, or normal thyroxine levels.

Thyroid Cancer

Thyroid cancer accounts for about one percent of the total number of cancers in the general population. The exact cause of thyroid cancer is unknown, but it is considered highly unlikely that it is caused by only one factor based on the current scientific understanding of cancer mechanisms.

Do Hormonally Active Agents (HAAs) Cause Thyroid Disorders or Thyroid Cancer?

Since the thyroid gland is part of the endocrine system, some researchers have hypothesized that hormonally active agents in the environment might cause thyroid disorders or thyroid cancer. To date, however, no chemical substance has been identified as causing thyroid cancer in humans.

A 1998 review of the published scientific information noted that thyroid effects, including changes in the amount of thyroxine made by the thyroid gland, have been observed in humans exposed to dioxin or PCBs (polychlorinated biphenyls) only at exposure levels far greater than those normally found in the environment. Also, high amounts of related organochlorine substances have been shown to cause subtle effects in animals that were studied in the laboratory. However, the effect on people, if any, of exposure to hormonally active agents in the environment remains unclear.

View of the National Academy of Sciences

In August 1999, the U.S. National Academy of Sciences (NAS) issued a long-awaited, landmark report on the endocrine disruption hypothesis. The expert NAS “Committee on Hormonally Active Agents in the Environment” concluded that the

available studies did not support an association between HAAs in the environment and cancer of the thyroid or other endocrine organs.

Further Reading

R.L. Golden and others (1998), "Environmental endocrine modulators and human health: an assessment of the biological evidence." *Critical Reviews in Toxicology*, vol. 28, pages 109-227.

A comprehensive review that examines hormonally active agents in the environment and their possible effects, including (pages 198-204) thyroid disorders and thyroid cancer.

R.N. Hill and others (1998), "Risk assessment of thyroid follicular tumors." *Environmental Health Perspectives*, vol. 106, pages 447-457.

A discussion of the U.S. Environmental Protection Agency's review of thyroid tumors, their cause and relationship to exposure to hormonally active agents.

Report of the Committee on Hormonally Active Agents in the Environment, National Research Council (1999), "Hormonally Active Agents in the Environment." National Academy Press, Washington, D.C.

A report by a committee of the National Academy of Sciences of the United States that reviews the state of the science on HAAs in the environment, with conclusions and recommendations for further research.

16. Immune System Disorders

There is insufficient information to evaluate whether hormonally active agents in the environment have effects on the immune system of humans.

The immune system is responsible for maintaining the body in optimum health by fighting off “germs” (*i.e.*, bacteria, viruses and other microorganisms too small to be visible).

Scientists have shown in the laboratory that hormones can affect the immune system of animals. Some scientists have hypothesized that hormonally active agents (HAAs) in the environment may affect the immune system of humans.

There are very few studies in humans examining the effect of HAAs on the immune system. Many variables, such as age, gender, lifestyle and underlying disease, may better explain the differences in immune function observed in various human populations.

In August 1999, the U.S. National Academy of Sciences (NAS) issued a long-awaited, landmark report on the endocrine disruption hypothesis. The expert NAS “Committee on Hormonally Active Agents in the Environment” reported that in humans, there is inadequate information on the immunologic effects of HAAs to support any definitive conclusions.

Further Reading

R.L. Golden and others (1998), "Environmental endocrine modulators and human health: an assessment of the biological evidence." *Critical Reviews in Toxicology*, vol. 28, pages 109-227.

A comprehensive review that examines HAAs in the environment and their possible effects, including (pages 190-197) immune system effects.

Report of the Committee on Hormonally Active Agents in the Environment, National Research Council (1999), "Hormonally Active Agents in the Environment." National Academy Press, Washington, D.C.

A report by a committee of the National Academy of Sciences of the United States that reviews the state of the science on HAAs in the environment, with conclusions and recommendations for further research.

17. Child Development and Learning

More research is needed to understand possible effects of hormonally active agents in the environment on child development and learning.

During development of the fetus and in early childhood, proper development of the brain is controlled by precisely timed and controlled releases of specific hormones of the endocrine system. Some scientists have hypothesized that hormonally active agents (HAAs) in the environment may affect child development and learning.

In 1968, a number of pregnant women in Japan were exposed accidentally to very high amounts of PCBs (polychlorinated biphenyls) and dioxin-like chemicals called “dibenzofurans.” Offspring born to these women were slightly smaller than average and performed simple tasks less easily than expected for their age.

In a U.S. study begun in 1980, psychologists studied a group of children of women who had eaten large amounts of fish caught in Lake Michigan that presumably had been contaminated with PCBs, mercury and other potential harmful compounds. Children born to these women had greater propensity to startle, poorer reflexes, were less active at birth, and had poorer visual recognition memory at seven months of age compared to children of mothers who had not eaten Lake Michigan fish. Follow-up studies indicated that the children of women who had higher levels of PCBs also had lower performance on verbal and memory tests at four years of age, and lower IQ scores when tested at age eleven.

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A second U.S. study focused on 800 children born in North Carolina from 1978 to 1982 and exposed to levels of PCBs before birth or during the first year of life. The levels of PCBs in the North Carolina study, as in the Michigan study, were slightly above the usual levels found in the United States. The North Carolina study found that children of mothers with higher levels of PCBs had poorer visual recognition memory at seven months, and scored lower in psychomotor tests at six to twenty four months of age than children of mothers with lower PCB levels. However, any differences that were seen prior to two years of age no longer were apparent at ages three to ten.

In the Netherlands, a 1999 study showed that prenatal exposure to higher amounts of PCBs was associated with poorer performance on cognitive tests by children at age three and a half compared to children with lower prenatal exposure to PCBs. Based on these findings, the scientists concluded that efforts should be made to reduce exposure of the fetus to PCBs and related substances by lowering the mother's body burden of these substances.

A review of studies on the effect of PCBs indicated that there is some suggestive evidence of a relationship to child development or learning. These studies, however, have numerous methodological problems, reducing confidence in the results. Other scientists also have noted that because learning and development are influenced by many factors, it is not possible to conclude with any degree of certainty that exposure to PCBs is one of those factors. More research is needed to clarify the role, if any, of PCBs and to determine whether observations can be extrapolated.

Since the 1970s, production of PCBs is banned in the U.S. and PCBs are no longer intentionally produced anywhere in North America. Consequently, the amounts of these substances in the environment, in fish and wildlife, and in human tissues are steadily declining.

In August 1999, the U.S. National Academy of Sciences (NAS) issued a long-awaited, landmark report on the endocrine disruption hypothesis. The expert NAS

“Committee on Hormonally Active Agents in the Environment” reported that in humans, the results of learning and behavioral studies of mother-infant populations accidentally exposed to high concentrations of PCBs and dibenzofurans and of mother-infant populations eating contaminated fish and other food products containing mixtures of PCBs, dioxin, and pesticides such as DDT, dieldrin, and lindane “provide evidence that prenatal exposure to these HAAs can affect the developing nervous system.” The report called for more research on the topic.

Further Reading

B.C. Gladen and W.J. Rogan (1991), “Effects of perinatal polychlorinated biphenyls and dichlorodiphenyl dichloroethane on later development.” *The Journal of Pediatrics*, vol. 119, no. 1, part 1, pages 58-63.

One of a series of articles describing a 10½ year study of children whose mothers experienced “normal” (i.e., non-occupational) exposure to PCBs and DDT.

R.D. Kimbrough and M.L. Doemland (1997), “Review of studies in children: polychlorinated biphenyls, dibenzo-*p*-dioxins and dibenzofurans.” A report prepared for the Chlorine Chemistry Council.

A review of a number of studies on the effect of exposure to PCBs, dioxin and dibenzofurans on children’s health.

R.J. Golden and others (1998), “Environmental endocrine modulators and human health: an assessment of the biological evidence.” *Critical Reviews in Toxicology*, vol. 28, pages 109-227.

A review that includes (pages 175-183) an assessment of the possible effects of HAAs in the environment on child development and learning.

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S. Patandin and others (1999), "Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age." *The Journal of Pediatrics*, vol. 134, no. 1, pages 33-41.

A comprehensive study in Dutch children on the effect of prenatal exposure to PCBs and related chemicals on development.

Report of the Committee on Hormonally Active Agents in the Environment, National Research Council (1999), "Hormonally Active Agents in the Environment." National Academy Press, Washington, D.C.

A report by a committee of the National Academy of Sciences of the United States that reviews the state of the science on HAAs in the environment, with conclusions and recommendations for further research.

18. Childhood Cancers

The National Cancer Institute has reported that childhood cancer incidence rates have been relatively stable since the mid-1980s.

Some researchers have hypothesized that hormonally active agents in the environment might be an explanation for an apparent increase in some childhood cancer rates in the U.S. from 1970s to the 1990s.

A comprehensive study published in 1999 examined all of the available information from the U.S. National Cancer Institute on cancers in children for the period 1975 to 1995. The scientists concluded that the modest increases over the entire time period in leukemia and brain cancer were due to abrupt increases in 1983-84 and 1983-86, respectively, after which rates stabilized. The authors attribute these patterns to diagnostic improvements or reporting changes, rather than effects of environmental exposures.

Very little is known about the causes of childhood cancer. Confirmed causes include genetic factors, therapeutic radiation and *in utero* exposure to DES. Results of studies examining a large number of other hypotheses (e.g., dietary factors, fathers' occupations, pesticides, electromagnetic fields, environmental chemical exposures) remain inconsistent and inconclusive. Many of the studies of these factors were conducted in response to reported clusters of childhood cancer. These studies have been generally unproductive in clarifying causes of childhood cancer due to serious methodological difficulties, such as small sample sizes.

Further Reading

M.S. Linet and others (1999), "Cancer surveillance series: Recent trends in childhood cancer incidence and mortality in the U.S." *Journal of the National cancer institute*, vol. 91, pages 1051-1058.

A comprehensive review and analysis of the incidence and mortality data on childhood cancer in children in the United States for the period 1975-1995.

S.S. Devesa and others (1995), "Recent cancer trends in the United States." *Journal of the National Cancer Institute*, vol. 87, pages 175-182.

An examination of recent cancer trends in the United States with particular attention to the role that changes in diagnostic criteria play in the incidence of reported childhood cancers.

W.C. Black (1998), "Increasing incidence of childhood primary malignant brain tumors – enigma or no-brainer?" *Journal of the National Cancer Institute*, vol. 90, pages 1249-1251.

A further analysis of the study by M.A. Smith and others on brain tumors in children.

19. Precocious Puberty

Whether puberty in girls is occurring sooner than previously, or the information in standard references was based on inadequate information has not been determined.

A recent study has suggested that girls in the United States are developing the body characteristics that normally occur during puberty at a younger age, on average, than had been reported previously. Improved nutrition, the prevalence of taller and heavier girls, and the increased incidence of obesity in children have been suggested as possible causes. Hormonally active agents in the environment have also been hypothesized by some as a possible cause. However, studies have not yet been conducted to determine the causes of the phenomena.

A 1997 study observed that the small numbers of girls examined in previous U.S. studies limited the usefulness of those studies for determining the average age of sexual development for American girls. Consequently, most U.S. pediatricians had relied on results of a 1969 study of British girls to determine the age of puberty. A new study in 1997 evaluated 17,000 American girls between the ages of 3 and 12, using standardized procedures to rate sexual maturity. The findings indicated that the average age of first menses among Caucasian girls was 12.9 (which had not changed over the last 45 years) and 12.2 for African-American girls (a four month decline since the 1960s).

The 1997 study also found that for Caucasian girls, the average age for onset of breast and pubic hair development was about one year earlier than reported in the 1969 British study or in three previous limited U.S. studies. Studies in Brazil, China, Greece,

Israel and Turkey also reported earlier sexual development in girls than did the British and earlier U.S. studies.

It is accurate to say that girls are maturing at an earlier age than predicted in child development textbooks. However, it is difficult to say whether puberty now is occurring sooner than previously, or the information in textbooks was inaccurate because it was based on inadequate studies.

The 1997 study has led to new medical guidelines for precocious puberty in girls: breast or pubic hair development before the age of 7 (Caucasian girls) or 6 (African-American girls). The guideline has not changed for boys: precocious puberty is pubic hair development before 9 years of age.

Further Reading

M.E. Herman-Giddens and others (1997), "Secondary sexual characteristics and menses in young girls seen in office practice: a study from the pediatric research in office settings network." *Pediatrics*, vol. 99, no. 4, pages 505-512.

A comprehensive study examining 17,000 American girls for the onset of puberty.

P.B. Kaplowitz and others (1999), "Reexamination of the age limit for defining when puberty is precocious in girls in the United States: implications for evaluation and treatment." *Pediatrics*, vol. 104, no. 4, pages 936-941.

This study reviews the 1997 study by M.E. Herman-Giddens and makes recommendations on new guidelines for precocious puberty.

20. Autism

Autism spectrum disorders (ASD) is a group of complex, developmental, neurological disabilities, the causes of which remain unknown.

The Centers for Disease Control (CDC) reports that many children in the U.S. have “autism spectrum disorders (ASD),” a group of developmental disabilities caused by a brain abnormality. ASD is a group of permanent developmental disabilities that include autism and related disorders (atypical autism and Asperger’s disorder). These neurological disorders are characterized by problems in the areas of social interaction and communication skills and the need for sameness and repetitive behaviors.

The prevalence rate of ASD in the U.S. is currently unknown. Studies from other countries indicate there may be as many as 2 of every 1,000 children with ASD. Its prevalence rate makes it one of the most common developmental disabilities. The causes, however, are unknown.

In late 1997, a citizens’ group in Brick Township, NJ expressed concern that the prevalence of autism was elevated in that community and that environmental factors, including hormonally active agents (note: there is no mention of HAAs in gov’t reports), may play a role. The U.S. Centers for Disease Control and Prevention (CDC) and the Agency for Toxic Substances and Disease Registry (ATSDR) conducted studies to address these concerns. The CDC report indicated that the prevalence of autism may be elevated in Brick Township, but that there is great uncertainty about the “true”

background rate that would be expected in the U.S. The ATSDR Public Health Assessment found no potential environmental explanation. CDC concluded that autism prevalence data are needed for large, diverse populations and that investigations are needed of genetic, infectious, immunological and environmental factors.

Further Reading

Centers for Disease Control and Prevention, "Prevalence of autism in Brick Township, New Jersey, 1998: Community report, April 2000.

An investigation of the prevalence of autism in Brick Township, N.J. in response to citizen concerns.

Agency for Toxic Substances and Disease Registry, Public Health assessment – Brick Township Investigation, Brick Township Ocean County, NJ (November 2000)

Evaluation of likelihood of link between autism and environmental sources of contamination in municipal drinking water supply, swimming in local river and township landfill.

Online, "Autism Among Children", www.cdc.gov/ncbddd.

P.M. Rodier (2000), "The early origins of autisms," *Scientific American*, vol. 282, Number 2, pages 56-63.

A review on the state of the scientific understanding of autism in children.

21. Wildlife Effects

The National Academy of Sciences concluded there is evidence that some persistent, bioaccumulative hormonally active agents produce adverse effects on wildlife populations, but whether the primary effect is mediated by hormonal activity remains to be determined.

The amounts of known hormonally active agents (HAAs) present in the environment are generally very low. Occasionally, however, wildlife may be exposed to higher amounts due to accidental chemical spills, improper use or disposal of pesticides or hazardous chemicals or inadequate treatment of sewage. The adverse effects observed have been associated with high exposures, indicating that effects on wildlife may be limited to high exposures on a localized scale.

Some studies have provided evidence of HAAs as a probable cause of reproductive or developmental problems observed in certain wildlife. The “masculinization” of female marine snails by tributyltin (an antifouling substance used in some marine paints) is one example.

Studies of alligators at Lake Apopka, Florida, found that some males had underdeveloped sexual organs and were probably unable to reproduce. Scientists were able to establish that the abnormalities probably resulted from exposure to large amounts of pesticides, some with hormone-like properties, present in the lake that resulted from a

large chemical spill in 1980. Alligators that were exposed to much lower amounts of similar pesticides at other lakes in Florida did not suffer from these abnormalities.

In studies of areas of the Great Lakes contaminated from improper use or disposal of hazardous substances with hormone-like properties, such as PCBs (polychlorinated biphenyls), dioxin and dibenzofurans, fish-eating birds were found to give birth to lesser numbers of male offspring. In areas where the amounts of pollutants are low, normal numbers of male offspring were found. Similarly, the decline in trout in the Great Lakes has been associated with high amounts of these same chemicals. In both examples, however, it has not been demonstrated whether the effects were caused by interference with the endocrine system.

A 1994 study conducted in England found that male trout near the pipes of sewage treatment plants that discharged wastes from household and industrial sources developed feminine characteristics. A subsequent study showed that natural estrogen and synthetic estrogen from birth control pills, components of human waste that can remain in treated sewage, were responsible for the observed effect.

Recently, scientific investigations have reported that infection with parasites may be responsible for the rise in the number of deformities reported in frogs in the northern part of the United States. Hormonally active pesticides have also been suggested as a possible cause.

An expert panel of the European Commission's Scientific Committee on Toxicity, Ecotoxicity and the Environment (SCTEE) recently issued a report on hormonally active agents and wildlife effects. The report concluded that impaired reproduction and development causally linked to HAAs are well documented in a number of species and have caused local or regional population changes but "for most reported effects in wildlife, however, the evidence for a causal link with endocrine disruption is weak or non-existing." Further research was recommended.

In August 1999, the U.S. National Academy of Sciences (NAS) issued a long-awaited, landmark report on the endocrine disruption hypothesis. The expert NAS “Committee on Hormonally Active Agents in the Environment” concluded that “there is epidemiologic and experimental evidence that some persistent, bioaccumulative HAAs (also referred to as persistent organic pollutants) produce adverse effects on wildlife populations, but whether the primary effect is mediated by hormonal activity remains to be determined.” The report called for more research on the topic.

Further Reading

L.J. Guillette Jr. and others (1994), “Developmental abnormalities of the gonad and abnormal sex hormone concentrations in juvenile alligators from contaminated and control lakes in Florida.” *Environmental Health Perspectives*, vol. 102, no. 8, pages 680-688.

An important study that shows the biological plausibility of endocrine disruption by certain chemicals in the environment.

J.P. Giesy and others (1994), “Deformities in birds of the Great Lakes region: assigning causality.” *Environmental Science and Technology*, vol. 28, pages 128A-135A.

A study that examines the cause of various deformities found in birds of the Great Lakes region and the possibility that HAAs are involved.

C.E. Purdon and others (1994), “Estrogenic effects of effluents from sewage treatment works,” *Chemistry and Ecology*, vol. 18, pages 275-285.

A study demonstrating that male trout placed near the discharge pipes of sewage treatment plants in the United Kingdom develop feminine characteristics.

G. Van Der Kraak (1998), “Observations of endocrine effects in wildlife with evidence of their causation.” *Pure and Applied Chemistry*, vol. 70, no. 9, pages 1785-1794.

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C.R. Tyler and E.J. Routledge (1998), "Oestrogenic effects in fish in English rivers with evidence of their causation." *Pure and Applied Chemistry*, vol. 70, no. 9, pages 1795-1804.

A review of the causes of the development effects seen in fish in English rivers and the possible effect of HAAs in the environment.

P.T.J. Johnson and others (1999), "The effect of trematode infection on amphibian limb development and survivorship." *Science*, vol. 284, pages 802-804.

An examination of the role of parasite infection in producing severe limb abnormalities in frogs.

Report of the Working Group on Endocrine Disrupters of the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) (1999), "Opinion on Human and Wildlife Health Effects of Endocrine Disrupting Chemicals, with Emphasis on Wildlife and on Ecotoxicology Test Methods." <http://europa.eu.int/com/dg24/>

A comprehensive report discussing the environmental consequences of exposure to HAAs in Europe.

Report of the Committee on Hormonally Active Agents in the Environment, National Research Council (1999), "Hormonally Active Agents in the Environment." National Academy Press, Washington, D.C.

A report by a committee of the National Academy of Sciences of the United States that reviews the state of the science of HAAs in the environment, with conclusions and recommendations for further research.

22. Mixtures and Synergy

Claims of synergy among hormonally active agents have not been substantiated.

Since numerous substances, including hormonally active agents (HAAs), are present in the environment at the same time, it is difficult to predict the magnitude of their combined potential health effects, if any. For example, when several HAAs are present together, as in air or water, their combined effect may be additive (*i.e.*, equal to the sum of the individual effects), synergistic (*i.e.*, greater than the sum of the individual effects) or antagonistic (less than the sum of the individual effects).

In 1996 scientists at Tulane University published in the journal *Science* that, in a laboratory test, a combination of certain weak environmental estrogens was more than 1,000 times as potent than when each of the estrogenic substances was tested individually. That is, the combination of estrogenic substances produced a synergistic effect when tested in the laboratory. This finding received wide attention and was cited by some as the explanation for the observation of hormonal effects from small amounts of HAAs. Other major laboratories were unable to replicate the finding, however, and less than a year later, the authors reported that they could not reproduce their own results and requested that the original report be withdrawn. They concluded “there must have been a fundamental flaw in the design of the original experiment.” The Office of Research Integrity of the U.S. Public Health Service, DHHS, investigated and in 2001 concluded that the leading author of the study, Steven F. Arnold, had “admitted to

scientific misconduct and conceded that there were no original data or other corroborating evidence to support the conclusions reported in the *Science* paper.”

Several other scientists tested mixtures of HAAs for synergistic effects, but could not demonstrate any. Most found an additive effect, but none could find a synergistic effect when they tested amounts that are typically found in the environment.

The suggestion that simultaneous exposure to estrogenic substances results in synergistic effects has not been substantiated by scientific evidence. In general, synergistic-like effects have been observed in laboratory tests only when artificially high doses of each of the substances in the mixture were used (*i.e.*, amounts that caused harmful effects even when each substance in the mixture was tested individually).

Further Reading

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K. Ramamoorthy and others (1997), “Potency of combined estrogenic pesticides,” *Science*, vol. 275, page 405.

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23. The Endocrine Disrupter Screening Program of the U.S. Environmental Protection Agency (EPA)

EPA is implementing a program to screen and test substances for endocrine effects. However, due to the complexity of the scientific issues involved, the suitability of some of the recommended tests for hormonal activity is still under EPA review .

Passed in 1996, the Food Quality Protection Act (FQPA) and the Safe Drinking Water Act (SDWA) amendments mandated EPA to develop a screening and testing program to determine whether certain substances had estrogenic or other endocrine effects. To assist in this undertaking, EPA established the Endocrine Disrupter Screening and Testing Advisory Committee (EDSTAC).

EDSTAC was composed of representatives from EPA and other federal and state agencies; chemical, crop protection and consumer product industries; water providers; worker protection and labor organizations; national environmental, public health and environmental justice groups; and various research scientists. The committee was charged with the task of developing consensus-based recommendations on a screening and testing strategy that is scientifically defensible, and advising EPA on priority setting, implementation and future refinement of the screening and testing program.

EDSTAC submitted a consensus report to EPA in September 1998, recommending a tiered approach as the most effective way to test for potential endocrine effects of chemicals. The tiered approach would begin with initial sorting and priority

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setting phases to identify those chemicals that are a priority for screening and testing. These would go through a testing screen to detect those capable of interacting with the endocrine system. The most responsive then would be further evaluated in a comprehensive testing phase to identify those substances that could cause harmful health effects in humans or wildlife.

The initiation of EPA's Endocrine Disrupter Screening Program (EDSP) has been delayed by the failure of a High Throughput Pre-Screen (HTPS) test that was intended as a key component of the initial sorting and priority setting phases. This automated testing system was developed in the pharmaceutical industry to screen for highly active drug candidates. The initial work, carried out by an EPA contractor, proved unreliable as a preliminary priority setting screen for estrogen, androgen and thyroid hormonally active agents (HAAs). Consequently, EPA now plans to initially use a computer modeling technique called quantitative structure-activity relationship (QSAR) to assist in prioritizing substances that are likely to interact with hormone systems.

Development, standardization and validation of accepted test methods to screen and test substances for endocrine disruption is taking longer than anticipated because of the complexity of the scientific and regulatory issues. This has delayed implementation of the EDSP. Screening results obtained from short-term animal studies or tests conducted in test tubes or other laboratory glassware are not adequate to predict potential effects in humans or wildlife since the endocrine system is so complex. Consequently, screening tests must be evaluated with substances that are known to be HAAs, as well as others that are known not to have hormone-like properties, to determine test sensitivity, specificity and reproducibility. Even well-established tests for detecting the harmful effects of substances may need to be modified somewhat to ensure measurement of endocrine-related effects; therefore these tests will require additional work to standardize and validate such modifications.

Because the process of standardization and validation of endocrine screens and tests has taken much longer than EPA initially anticipated, EPA did not have an

endocrine screening and testing program in place as of August 1999. This prompted environmental activists to file a “deadline” lawsuit to force EPA to move more rapidly. That lawsuit in turn prompted industry groups to file a lawsuit against EPA to ensure that in meeting any schedule for developing and implementing the EDSP, EPA must also meet its obligations under the law to use validated test systems. EPA settled this deadline lawsuit in the fall of 2001. The settlement agreement lays out an implementation schedule which EPA will use “best efforts” to meet.

An additional issue affecting the implementation of the screening and testing program has been concerns expressed by animal rights advocacy groups regarding the numbers of laboratory animals that would be used in EPA’s EDSP. These groups have called for EPA to fund epidemiological studies to confirm the existence of environmental endocrine effects in humans before initiating an extensive screening and testing program. In addition, they have called for development of reliable priority setting methods, exclusive use of non-animal tests for screening, and validation of all tests before implementing the program.

In short, the evaluation of thousands of chemicals for potential endocrine disruption is an enormous scientific and logistical undertaking, the complexity of which was almost certainly underestimated when Congress mandated EPA to develop the program in 1996.

Further Reading

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Endocrine/Estrogen Letter, May 8, 2000: “EPA To Hold ED Screening Priority Setting Workshop.”

24. Identifying Endocrine Disrupters

Standardized and validated toxicology screening and testing methods are needed to evaluate substances for endocrine disruption.

A variety of laws and regulations have been introduced to help protect the environment and human health from the unintended toxic effects of man-made chemicals, such as pharmaceuticals, food additives, pesticides, and industrial chemicals. For example, the U.S. Food and Drug Administration, the U.S. Environmental Protection Agency, and other international regulatory agencies have developed and refined toxicity testing methods and guidelines designed to detect and measure toxic effects produced by man-made chemicals. In addition, there are also national regulations and international guidelines on good laboratory practices to ensure that toxicology studies are performed and reported according to high standards of quality assurance and that data are available for scrutiny by any regulatory agency.

As practical, robust, and high-quality regulatory toxicology studies have been developed, these improvements in methodology have resulted in improvements in our ability to understand the harmful potential of man-made chemicals. Such knowledge permits society to predict potential harmful effects for humans and wildlife, which in turn permits us to use, handle, and dispose of industrial chemicals safely.

The adequacy of current toxicology studies is a contentious subject within the overall debate on endocrine disruption. While there has always been disagreement on the best ways to improve the value of toxicity testing, the topic of endocrine disruption has

attracted considerable attention to this debate. Research in industry, government and academic laboratories has contributed to the development of modern techniques for evaluating substances for potential endocrine activity.

Current toxicology testing protocols provide much information about potential endocrine toxicity. As noted by EDSTAC, for example, the current protocol for the mammalian multiple generation reproduction study contains numerous endocrine-responsive endpoints. However, even these internationally harmonized protocols may be enhanced by adding new endpoints that are more specific to the endocrine system, if such endpoints can be properly standardized, validated, and do not interfere with assessments of endpoints that are currently required.

What is still needed are new and cost-effective short-term screening assays for hormonal activity that are sensitive for detecting substances with the potential to interact with components of the endocrine system. These screens can be applied to large numbers of chemicals to prioritize substances for definitive toxicity testing.

The American Chemistry Council supports development and validation of a hierarchical, tiered “screening” and “testing” approach. The Council is currently cooperating with EPA and OECD on method development, standardization and validation, that is based in large measure on EDSTAC’s consensus recommendations. A combination of screening and testing methods is needed to reduce the large number of substances that must be evaluated.

Screening Assays

Screening assays are relatively quick, cost-effective, and straightforward tests that can be used to detect substances with the potential to interact with components of the endocrine system, i.e., endocrine active compounds.

- Screening assays are useful for identifying substances with little or no potential to elicit endocrine activity and for setting priorities if further, more definitive testing is needed.
- These assays do not identify endocrine disrupters because they do not determine if the substance can cause adverse health impacts (adverse effects) in humans or wildlife.

Definitive Tests

Definitive tests are more comprehensive, expensive, and extensive than screening assays. These tests identify substances that potentially can cause adverse health effects in humans or wildlife, although typically such tests do not yield specific information about mechanisms of toxicity.

- These longer-term tests, using protocols designed to evaluate adverse health effects, provide the scientific data needed for hazard characterization/risk assessment of substances with positive responses in short-term assays.
- The multiple generation reproduction test is generally viewed as the definitive test for endocrine active substances. This test, unlike the shorter-term screens, provides sufficient data to characterize the nature, likelihood, and dose-response relationship of potential adverse effects. This study encompasses all critical life stages and processes, including *in utero* development, a broad range of doses, and administration by a relevant route of exposure. Standardized test guidelines for the multiple generation toxicity study in laboratory animals have been in use for many years, and were recently updated to incorporate additional endocrine-sensitive measurements. A multiple generation reproduction toxicity test in fish is currently being standardized and validated.
- With a definitive test, a comprehensive profile of the potential adverse biological effects resulting from exposure to a substance can be identified and related to the dose that caused them. The outcome of such a definitive test is designed to be

conclusive, and results of definitive tests outweigh and supercede data obtained from screening assays.

EPA, industry, the Endocrine Disrupter Testing and Assessment Task Force of the Organization for Economic Cooperation and Development, and other governmental organizations are currently engaged in development, standardization, and validation of a number of endocrine screening and testing assays.

Integrating the Scientific Information

As defined during the 1996 Weybridge Workshop, “An endocrine disrupter is an exogenous substance that causes adverse health effects in an intact organism, or its progeny, secondary to changes in endocrine function.” When evaluating potential hazards of hormonally active substances, it is important to make appropriate use of all available information by conducting a "weight of evidence" evaluation. This entails an objective and balanced interpretation of the totality of scientific evidence regarding hormonal activity of a particular substance, and adverse effects that might result from an endocrine mechanism. The weight of scientific evidence evaluation includes an assessment of the relevance, repeatability, and significance of each individual study in the data set. The weight of evidence evaluation process also assesses the overall adequacy and concordance of the data set. Substances with inadequate data sets may become a high priority for development of additional screening or testing data. In instances where there is a lack of concordance in the overall data set, decisions should be based on the preponderance of available data. In certain cases, additional new screening or testing data may need to be developed to resolve conflicting information. Substances that have adequate and concordant data sets can proceed to risk assessment and risk management processes as appropriate. The risk assessment process requires consideration of human and ecosystem exposure potential in addition to the hazard data.

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25. Low Dose Effects of Hormonally Active Agents

The National Academy of Sciences noted that little is understood about the effects, if any, of exposure to low amounts of hormonally active agents in the environment.

Typically, with substances that are harmful, the likelihood of observing a harmful effect as well as its severity will increase as the amount of the substance is increased (*i.e.*, a monotonic dose-response curve). This is often stated as: “The dose makes the poison.” It has long been one of the accepted principles of toxicology.

For humans, the highest exposure to hormonally active agents (HAAs) is likely to be the natural hormones produced in the body. According to calculations by Prof. Stephen Safe, the highest exposure to synthetic HAAs is experienced by women taking birth control pills or hormone replacement therapy.

The next highest exposure, and one experienced by the general population, is to the HAAs that act like estrogen and are found in plants. These HAAs, called phytoestrogens, are common in various plants that are important components of the human diet including wheat, oats, rye, rice, soybeans, potatoes, carrots, peas, beans, alfalfa sprouts, apples, cherries, plums, parsley, sage, garlic, coffee and grains used to make beer and bourbon whiskey. According to Prof. Safe, the average Western diet contains millions of times more potent estrogenic activity from the phytoestrogens naturally present in foods than from the residual levels, if any, of pesticides that may have incidental estrogen-like properties.

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In recent years, some researchers have hypothesized that harmful effects may occur when people are exposed to lower amounts of HAAs rather than to higher amounts. While one laboratory has claimed to have demonstrated this phenomenon, others have been unable to replicate the results and the low-dose hypothesis remains controversial.

After studying the relevant data, an expert Committee on Hormonally Active Agents in the Environment of the U.S. National Academy of Sciences reported in 1999 that no conclusions could be drawn about the potential effects of exposure to low doses of HAAs, such as the amounts typically found in the environment, because too little is known or understood about the phenomenon.

Because the issue is pertinent to dose selection in the protocols being developed for EPA's endocrine screening and testing program, the U.S. Environmental Protection Agency (EPA) asked the National Toxicology Program (NTP) of the National Institute of Environmental Health Science (NIEHS) to convene a peer review panel of eminent scientists to critique existing studies on the low-dose hypothesis.

The peer review panel meeting was held October 10-12, 2000. The panel was divided into five subpanels: Bisphenol A, Estradiol and Other Estrogens, Androgens and Antiandrogens, Biological Factors and Study Design, and Statistics and Dose-Response Modeling. The organizing committee of government scientists selected a set of studies it deemed critical for peer review. For this review, principal investigators of the primary research groups active in this field provided their research data on selected parameters for independent statistical re-analysis.

The Statistics and Dose-Response Modeling Subpanel analyzed the data for 38 studies prior to the meeting and provided its analyses to the other subpanels. However, some of the essential data supporting the low dose hypothesis were never provided despite repeated requests by NTP and the Statistics and Dose-Response Modeling Subpanel. This is particularly important in light of the report by the statistical subpanel

that certain study results, particularly for other data supporting the low dose hypothesis, could not be reconfirmed in their independent re-analysis of the data.

The overall conclusions of the NTP Peer Review were mixed. While the overall weight of scientific evidence considered by the NTP peer review subpanels did not demonstrate a non-monotonic dose response in the low dose region that is common across a variety of hormonally active agents, the NTP peer review report recommended additional research and a revisiting of the current testing paradigm used for assessment of reproductive and developmental toxicity.

In March 2002 EPA announced the Agency's interim policy. Citing the NTP report, EPA stated that it would be premature to require routine testing of substances for low dose effects, and that EPA would be considering funding additional research to investigate the hypothesis.

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26. Continuing Research

Extensive research is being conducted worldwide to investigate whether hormonally active agents in the environment cause health effects in humans or wildlife by interfering with the endocrine system.

Continued research is needed to broaden our understanding of the relationship, if any, between hormonally active agents (HAAs) in the environment and the health and well being of humans and wildlife. To that end, scientific studies are being conducted at research institutions and universities worldwide. Almost all are being sponsored by industry or various national and/or international governmental agencies.

Industry

1. The American Chemistry Council

The American Chemistry Council, which represents chemical manufacturers in the United States, has established a five-year \$100 million program to research the health and environmental effects of chemicals. Approximately 85 percent of this budget will be spent in five focus areas, one of which is endocrine disruption.

In this research program, the American Chemistry Council is a major funding sponsor of the Chemical Industry Institute of Toxicology as well as of academic and government research institutes. A science advisory committee, made up of recognized

and respected experts from academia and government, provides advice on the direction of American Chemistry Council research.

2. The Chemical Industry Institute of Toxicology (CIIT)

CIIT is a research institution funded by the American Chemistry Council and nearly 40 chemical companies. CIIT has established a major research program that focuses on understanding the ways by which chemicals interact with various components of the endocrine system and how to best predict potential health effects in humans. CIIT scientists are studying how the amount of HAAs, as well as how they interact with the endocrine system, might affect the likelihood that these chemical substances cause harmful effects.

3. The European Chemical Industry Council (CEFIC)

CEFIC has announced a \$7 million program of research grants to determine whether chemicals have hormone-like properties. The grants will fund studies at universities and independent research institutions in France, the Netherlands, Sweden and the United Kingdom. Studies will be conducted on effects in wildlife and humans.

4. International Council of Chemical Associations (ICCA)

ICCA coordinates activities among the American Chemistry Council, CEFIC and the Japan Chemical Industry Association (JCIA), including a \$20 million global effort to study endocrine disruption that includes the American Chemistry Council, CEFIC, and JCIA programs. ICCA recently formed a research steering group to coordinate basic research, including research on endocrine disruption, to focus research priorities and to avoid duplication of effort.

U.S. Government Agencies

1. Committee on the Environment and Natural Resources (CENR)

CENR, part of the National Science and Technology Council, a White House agency, coordinates overall federal government strategy on endocrine disrupter research. Major activities include research grants on endocrine disrupters (\$6-7 million in funding in fiscal 1999) and preparation of a document (published in 1999) outlining the proposed research strategy.

2. The Environmental Protection Agency (EPA)

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EPA requested \$12.7 million for research on endocrine disruption, including research conducted at EPA facilities, in fiscal year 2000. Of this \$3.9 million is for implementation of an Endocrine Disrupter Screening Program (EPSP). The purpose of the program is to test commercial chemicals for their ability to cause health effects by interfering with the endocrine system. The program is currently focused on the priority setting process for identifying chemicals for screening and testing. The program also plans to develop standardized and validated screens and tests for endocrine disrupters, an effort estimated to require \$42-48 million over four to five years.

3. Other Government Agencies

The National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health, and the Centers for Disease Control and Prevention (CDC) are tracking human exposure to certain chemicals by examining blood and urine samples of approximately 200 people.

The National Toxicology Program (NTP), an inter-agency collaboration among several agencies including EPA and NIEHS convened an expert panel to review studies on the question of whether endocrine disrupters may cause effects at doses lower than are tested using standard toxicological testing procedures. (See Chapter 25 above.)

EPA, the Department of the Interior, CDC, and the U.S. Congress funded the U.S. National Academy of Sciences report, "Hormonally Active Agents in the Environment," published in August 1999, which identified additional research needs.

III. Other National and International Agencies

1. The International Program on Chemical Safety (IPCS)

IPCS is a collaborative program of the World Health Organization (WHO), the International Labor Organization (ILO), and the United Nations Environment Program (UNEP). IPCS is leading an effort to conduct a global inventory of ongoing research activities related to the health and wildlife effects of HAAs, and is working to develop an international assessment of the state of the science on endocrine disrupters.

2. The Organization for Economic Cooperation and Development (OECD)

OECD is leading international efforts on identifying and validating screening tests for HAAs. Current efforts are focused on three test methods using laboratory animals.

3. Others

In December 1996, the European Commission, the European Environment Agency, the World Health Organization, OECD and the environmental agencies of three European governments sponsored a scientific workshop on HAAs to review the state of the science and to set research priorities. Since that meeting, the European Commission and national governments in Europe have sponsored research on endocrine disruption. In 1998, the Japanese government, and in 1999, the Korean government began sponsoring research on endocrine disruption.

IV. Scientific Associations

1. International Union of Pure and Applied Chemistry (IUPAC)

In September 1998 IUPAC, in cooperation with the International Union of Pharmacology and the International Union of Toxicology, published an assessment of the state of the science on HAAs, concluding that more research is needed. The assessment drew upon experts who are members of the three scientific associations.

2. Others

The American Chemical Society, the Society of Environmental Toxicology and Chemistry, the Society of Toxicology, The Toxicology Forum and other scientific organizations continue to sponsor workshops and special sessions of scientific conferences to discuss the latest research on HAAs. Proceedings of the workshops or abstracts of the papers presented are published by the sponsoring organizations.

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1300 WILSON BOULEVARD
ARLINGTON, VA 22209

703 - 741 - 5000 6/00

