Endocrine Effects of Prenatal Exposure to PCBs, Dioxins, and Other Xenobiotics: Implications for Policy and Future Research

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Recent reports have suggested that environmental chemicals may be associated with endocrine alterations in people, wildlife, and experimental animals. Pharmacological investigations as well as natural poisoning episodes have led to the association between exogenous chemicals and alterations in multiple hormonal systems. Persistent environmental contaminants such as dioxins and PCBs have been shown to modulate the activities of several different hormones. The unborn child or the neonate may be at special risk from these chemicals because of rapid growth and development, in addition to enhanced exposure. Because most exposure to these persistent chemicals is via food, changes in dietary habits and/or reduced contamination of the food supply may be required. *Key words:* developmental toxicity, dioxins, hormones, PCBs, persistent chemicals, prenatal exposures, reproductive toxicity. *Environ Health Perspect* 102:676–679 (1994)

Recent findings have raised the level of concern that chemicals in the environment can interfere with the endocrine systems of both people and wildlife. It has been reported that in men, sperm counts have decreased over the last 50 years (*1*). There appears to be an increase in cryptorchidism (undescended testicles), testicular cancer, and hypospadias (abnormal urethral opening) (*2*). Young girls are reaching puberty earlier, the incidence of endometriosis is increasing (*3*), and the age of onset of endometriosis may be decreasing. Breast cancer incidence has increased approximately 1% per year over the past 50 years (*4*). Many of these conditions could be associated with elevated exposure to estrogens, either prenatally or during early postnatal life (*5,6*).

However, disruption of other hormonal systems could lead to similar effects. For example, alteration of the immune system is often associated with endometriosis (*7*). Glucocorticoids, adrenal stress hormones, are potent immunosuppressors. In fact, the adrenal cortex may be the most vulnerable endocrine organ to chemically induced injury (*8*). Decreases in sperm count can occur after exposure to anti-androgens (*9*) or to alterations in thyroid status (*10*). Inadequate nutrition can greatly delay menarche (*11*). Multiple examples of impaired reproduction have been reported in fish and wildlife (*12*). Population declines of alligators in certain Florida lakes (*13*), fish in the Great Lakes (*14*), and birds off the coast of California (*15*) have been attributed to exposure to environmental chemicals that interfere with hormonal functions. Sterility of trout in Great Britain has been associated with high levels of plastic constituents in sewage outflows which contaminate the rivers (*16*).

How has the association been made between environmental hormone disruptors and adverse effects in both people and wildlife? Much of the association is based on accidental poisoning episodes. Shepherds have known for many years to keep their sheep out of certain kinds of clover or the sheep become infertile. Scientific studies revealed the reason: high levels of potent estrogens naturally produced by plants and associated fungi (*17*). Young children have developed secondary sex characteristics at inappropriately young ages because they took their mothers' birth control pills. Prenatal exposure of girls to diethylstilbestrol (DES) resulted in vaginal cancer in their teens or twenties (*18*). These kinds of episodes gave clear evidence that chemicals can interfere with endocrine systems. Many other experimental studies have led to the suggestion that hormonal disruption may lead to adverse effects. For example, the effects of DES on male offspring were suggested by studies in mice (*19*). Likewise, some of the noncancer effects of DES on female offspring were first observed in animal experiments. The studies with DES gave us insight into what to expect from prenatal exposure to estrogenic chemicals (*20*).

But, although DES has been a model compound to study the effects of potent synthetic estrogens, it is not an environmental contaminant. DES is a drug that was used medically. What about other chemicals that are present in the environment? Methoxychlor was developed for use as a insecticide and has estrogenic effects (*21*). Other pesticides that may be considered environmental estrogens include Kepone, dicofol, and *o,p*-DDT. Recent studies have suggested that the insecticide endosulfan may be a weak estrogen (*12*). Vinclozolin, a fungicide used on many types of fruits and vegetables, is a potent anti-androgen, blocking the effects of the male sex hormones and resulting in demasculinization of male offspring (*9*). Many thiocarbamide and sulfonamide-based pesticides such as ethylenethiourea (*22*) and linuron (*23*) have anti-thyroid effects, while mirex, toxaphene, and parathion produce alterations in the adrenal (*8*).

Dioxin, the most toxic man-made chemical, is not an estrogen (*24,25*). However, it can block the action of estrogens under certain conditions (*26*). Dioxin can also lower the levels of androgens and affect the amount of thyroid hormones in the body. Dioxin can decrease insulin levels and change the amount of glucocorticoids. It has also been reported to have effects on digestive hormones and on melatonin, the hormone that controls the daily rhythms of the body. Clearly, dioxin affects many endocrine systems as well as the immune system, making the recent report of an association between dioxin and endometriosis most interesting (*27*). Exposure of pregnant animals to extremely low levels of dioxin (doses that do not adversely affect the mother) leads to alterations in the reproductive system of the pups. Many of the effects are not detectable until the offspring reach puberty. Sperm count is decreased in male offspring, and their mating behavior is subtly altered (*28,29*). There are structural abnormalities in the external genitalia of the female offspring, (*30*), and delayed puberty in the male. In the more severely affected pups, fertility is reduced. These effects have been observed in both rats and hamsters (*29*). A recent report from the Netherlands suggests that babies born to women with higher levels of dioxin in their breast milk have elevated levels of thyroxine in their blood (*31*). Whether or not this will be associated with subtle and delayed effects remains to be seen.

What about PCBs? PCBs represent a complex mixture of 209 unique compounds (*32*). Unlike dioxin, which is an unwanted by-product of certain industrial processes and combustion, PCBs were commercially synthesized and used in transformers and capacitors. The very properties that made PCBs desirable in electrical equipment, such as their resistance to thermal degradation and stability, has led to their persistence and bioaccumulation in the environ-

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ment. A small number of the PCBs are dioxinlike in their biological activity and can cause all of the effects mentioned above for dioxin (*33*). Others, or their metabolites, are estrogenic (*34,35*). Still others can alter the levels of thyroid hormones in the blood (*36*). Certain PCB mixtures have been reported to delay puberty after prenatal exposure (*37*). Some PCBs appear to be neurotoxic, with prenatal exposure to certain PCB mixtures resulting in altered behavior in the offspring (*38*).

Two major PCB poisoning incidents have occurred in which adverse effects have been clearly observed in children born to women exposed to high levels of PCBs which were also contaminated with the dioxin analogues, polychlorinated dibenzofurans (PCDFs). In the Yu-Cheng incident, which occurred in Taiwan in 1979, the children have been carefully followed (*39*). At birth, many of the babies had pigmentation abnormalities and problems with teeth and nails. They were small in size and were developmentally delayed, both physically and mentally. Decrease in size and a 5-point IQ deficit have continued to be observed, even as the children mature (*40*). A recent study has observed effects on the external genitalia of boys at puberty who were born to exposed mothers (*41*). Children born to women who ate more PCB-contaminated fish have also been reported to have a lower IQ and exhibit behavioral problems (*42*). A recent report examining Inuit children from Northern Quebec suggests that the elevated levels of PCBs in mothers may be associated with enhanced sensitivity to infectious disease in the offspring (*43*).

Many of the studies, both experimental and epidemiological, suggest that the unborn may represent a population at special risk. This is no surprise when looking at chemicals which disrupt the endocrine system, which is so critical for growth and development. Young children may also be a special risk because of the rapid development which they undergo. However, there are additional concerns which may lead to young children representing a susceptible subpopulation. During lactation, many of the persistent hormonal contaminants, such as dioxins, PCBs, and DDT, concentrate in the milk, leading to lactational transfer to the nursing infant. Exposure to these lipophilic chemicals can be 10–40 times greater than the daily exposure of an adult (*44*). Although this may only occur for a short time, if this period corresponds with a sensitive developmental window, permanent alterations may result. Young children often eat a limited diet. If their dietary source is contaminated, greater relative exposure may occur for them than it would for an adult who eats a more varied diet.

Recent observations suggest that environmental chemicals may be adversely affecting the unborn and children in a subtle manner. Although there are chemical disruptors in the ecological arena, and there are reports of deleterious effects in people, the magnitude and significance of the risk to human health is not clear. Experimental studies indicate that there is clearly a potential for a problem, which is likely to be multifactorial. It has been suggested that the decreases in male reproductive function and effects on puberty in both sexes are related to environmental chemicals. But many of the environmental hormones are very weak. For example, some of the estrogenic pesticides are more than 1000 times less potent than natural estrogens (*21*). The questions that must be asked are how much of these chemicals are present? How persistent are they? Do they interact with each other and with the natural hormones in an additive, synergistic, or antagonistic way? And when are they present? If environmental chemicals alter the hormonal milieu during development, effects could likely result. Recent studies have demonstrated that subtle differences in the hormonal environment, such as that experienced by a female fetus that develops *in utero* between two males, can lead to effects (*45*).

The recognition for the potential of a problem has been quite recent; the effects being noted are much more subtle than those discussed by Rachel Carson over 30 years ago (*46*). The Wingspread conference in the summer of 1991 (*47*) concluded that a problem does exist and suggested that environmental chemicals are to blame. Last year, the National Academy of Sciences released a report, "Pesticides in the Diets of Infants and Children" (*48*), which suggests that the young are a population of special concern in regard to exposure to pesticides, some of which are hormonally active. Congressional hearings (*49*) focused on the issue, as did a BBC documentary entitled "Assault on the Male." A recent meeting was convened on "Estrogens in the Environment," (Washington, DC, 9–11 January 1994), and a special workshop was held at the Washington meeting of the Children's Environmental Health Network (18–19 March 1994).

What needs to be done? We must identify research needs in order to understand the degree of risk which exists. Risk assessment is a scientific process involving hazard identification, understanding of exposure, and analysis of the dose–response relationships. Any chemical may cause a problem at a high enough dose. But are the doses to which we are exposed dangerous? There is a need for additional controlled animal studies and further development of testing requirements, both for new chemicals proposed to enter the market and for those already on the market. Many of the test paradigms focus on the adult animals or on gross abnormalities in offspring. Less attention has been paid to subtle effects. The issue is really one of functional and delayed developmental toxicity. Some of the effects may not be detected until puberty, or even later in life (premature aging). Protocols are available to examine these possibilities, but they are time, labor, animal, and cost intensive. Simple screens, both *in vivo* and *in vitro*, have also been developed that may identify specific hormonal activity of chemicals. These may involve either binding to a specific hormone receptor *in vitro* or in a tissue culture model or altered expression of a function in cultured cells. Such screens will pick up some endocrine disruptors, but not all. What is needed is an integrated functional test, or at the very least, a battery of tests that can indicate potential problems.

Most epidemiological studies have also focused on adults. In fact, the majority of epidemiological investigations have concentrated on adult men. This is often because occupational cohorts were investigated. Studies of women and children are needed. The recognition of this need has led to a series of major ongoing studies. The Yu-Cheng cohort of exposed women and their offspring, some born many years after the actual poisoning incident, is continuing to be followed (*40*). The older children are now reaching puberty, and subtle effects on the reproductive system may become apparent. The exposed women can be studied for endometriosis before they reach menopause. Whether or not menopause is accelerated or delayed can also be examined. A similar study of exposed women is being proposed for the Seveso cohort. This represents a group exposed to high levels of dioxin after an explosion at a herbicide plant in Italy in 1976 (*50*). Children of these exposed women have not yet been examined for subtle developmental deficits, either structural or functional.

Environmental exposures that did not involve clear poisoning episodes are being researched by a number of groups. Two series of studies concerning health effects associated with living around the Great Lakes are in progress. In Canada, the Great Lakes Health Effects Program represents a 5-year multidisciplinary initiative. A variety of studies are concerned with public consultation, policy making, and cleanup assessment activities, surveillance, epidemiology, and toxicology. Many of the health studies focus on the results of exposure to

the developing embryo/fetus or the child. In the United States, the Agency for Toxic Substances and Disease Registry is sponsoring a series of epidemiological and exposure studies and outreach and education programs dealing with potential health effects associated with living around the Great Lakes. Some of the studies involve behavioral effects on offspring of women who may be highly exposed. Another Canadian study is focusing on Inuit children in northern Quebec. The mothers of these children have elevated levels of PCBs in their blood and breast milk because of their diet of marine mammals such as seal and polar bear, which have high concentrations of these persistent chemicals in their fat (*43*). The children are being examined for immune system dysfunction and behavioral changes.

Similar questions are being addressed in a large study in the Netherlands examining women who have relatively high levels of dioxins and PCDFs in their milk (*31*). Their offspring are being examined for hormonal, biochemical, and behavioral effects. In Germany, a study is examining immune alterations in children of women with high PCB levels in their milk (Helge H, personal communication). One of the most carefully conducted and constructed studies is one ongoing in the Faroe Islands in the North Sea in which children are being examined for developmental and behavioral effects related to their mothers' dietary exposure to mercury and/or PCBs (Grandjean P, personal communication).

There may be other populations that offer opportunities to examine an association between maternal exposure to environmental hormone disruptors and effects on offspring. During the Vietnam War, heavy herbicide spraying was conducted in the south. In addition to dioxin, other hormonally active chemicals were present. There was essentially no spraying in the north. A carefully conducted retrospective study might be possible to look for some of the subtle effects which are being suggested by animal and epidemiological studies. In Eastern Europe, high levels of environmental contamination have been reported in certain regions. It is clear that elevated rates of respiratory disease and cancer are present in certain areas (*51*). However, the question of second-generation effects has not been explored. Another potential area of investigation would be in the former Soviet Union. Production of PCBs was only stopped in those countries in 1990. There have also been documented high exposures to both male and female workers in herbicide factories in Russia (*52*). Although DDT production has been banned in the United States since the early 1970s, new factories are still being built to produce DDT in India. There are many populations for future study, only constrained by the time, expense, and cultural considerations.

But what about the policy implications if chemicals in the environment are affecting our hormonal systems, and especially, altering the development and function of our children? First, we need to know more about the problem. Second, what can we do about it? Part of the concern about environmental hormones is that many of these chemicals do not readily go away. Some persist in the environment for tens or even hundreds of years. If these chemicals are causing a problem, we need to reduce additional input into the environment. That part of the equation is relatively easy, depending on new regulations. However, what do we do about the chemicals already in the environment? We need a better understanding of environmental fate and transport of these chemicals. This is not just our problem. Many of these chemicals are no longer being produced in the United States. Some of them are leaching out from waste sites. Others are coming out of incinerators. But many are being made in other places in the world. These chemicals reach us through the atmosphere, where many of them bind to dust particles and are transported through the air, depositing on plants to enter the food chain, or landing on the water, where they eventually enter aquatic species and bioaccumulate.

It is important to note that most exposure of the general population to these environmental chemicals is via food. The levels of these contaminants in food are often low. However, these are persistent chemicals, and once they enter our bodies, they tend to stay there for many years. The question is thus raised, once we have these chemicals, how do we get rid of them? Since many of the environmental hormones are lipophilic chemicals, they tend to be stored in the fat. Weight loss may lead to minor reduction in the body levels. Treatment with agents that disrupt enterohepatic recirculation or prevent uptake of fats into the body have been reported to have some minor success in reducing body burdens (*53*). However, neither of these approaches has been shown to be very effective. The only process that does lead to significant depletion of stored amounts of these chemicals is lactation. However, lactation results in transfer of chemicals from the mother to the infant, who may be more sensitive to any adverse effects than the adult.

How can this cycle be interrupted? Obviously, we need to reduce contamination in the food supply. To do this, we need a better understanding of how chemicals get into the food in the first place. Another possible way to alter our dietary intake of these compounds is to change our diet. Because many of these chemicals are fat soluble, less consumption of animal fat will mean less exposure.

There are no quick and easy solutions. We must do a better job of identifying potential problems. From a scientific point of view, if a chemical has hormonal activity, it has the potential to be a problem. The margin of safety between a therapeutic and a toxic dose has been an issue for a long time in medicine. But in the case of drugs, one may be willing to take risks for the potential benefits of the treatment. Environmental exposure is different. People often do not have a choice or, even worse, do not even know that they are being exposed. Chemicals that are biologically active are two-edged swords. They may help or harm, depending on the situation. Increased knowledge can only help us deal more effectively with these environmental, hormonally active chemicals. Better understanding of the relationship between exposure and adverse effects will lead to a healthier environment for all of us and for our children.

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