Assessing the Effects of Endocrine Disruptors in the National Children's Study

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Children are uniquely vulnerable to toxic chemicals in the environment. Among the environmental toxicants to which children are at risk of exposure are endocrine disruptors (EDs)—chemicals that have the capacity to interfere with hormonal signaling systems. EDs may alter feedback loops in the brain, pituitary, gonads, thyroid, and other components of the endocrine system. They can affect development. Effects of EDs have been described in wildlife populations, in animals exposed experimentally, and to a more limited extent in humans. Mechanisms of action of EDs are increasingly being elucidated, and genetic polymorphisms that convey differential susceptibility to EDs are beginning to be explored. It is hypothesized that *in utero* and early childhood exposures to EDs may be responsible, at least in part, for decreases in semen quality; increasing incidence of congenital malformations of the reproductive organs, such as hypospadias; increasing incidence of testicular cancer; and acceleration of onset of puberty in females. The National Children's Study (NCS) will provide a unique opportunity to test the validity of these hypotheses in the context of a large prospective multiyear epidemiologic investigation. It will be essential in the NCS to assess exposures to a range of putative natural and synthetic EDs, to assess outcomes possibly due to ED exposure, to examine the potential interplay between EDs and genetic polymorphisms, and to seek links between ED exposures in early life and endocrine, reproductive, neurobehavioral, and other outcomes throughout the life span. *Key words:* endocrine disruptors, environmental epidemiology, exposure assessment, National Children's Study. *Environ Health Perspect* 111:1678–1682 (2003). doi:10.1289/ehp.5799 available via *http://dx.doi.org/* [Online 18 March 2003]

The National Children's Study (NCS) is a very large prospective epidemiologic study being developed by the National Institute of Child Health and Human Development, in collaboration with the National Institute of Environmental Health Sciences, the U.S. Environmental Protection Agency (EPA), and the Centers for Disease Control and Prevention. The goal of the NCS is to examine the influences of early exposures—environmental, behavioral, lifestyle, and socioeconomic—on human development and on child and adult health. The NCS will follow as many as 100,000 children in all regions of the United States, from early pregnancy to 21 years of age (Berkowitz et al. 2001). The NCS offers a unique opportunity to examine critically the possible etiologic contribution of early exposures to the genesis of developmental disabilities, asthma, reproductive problems, and possibly cancer. Critically important to the success of this complex study will be the careful choice of which hypotheses to test, which exposures to measure, which outcomes to assess, what data infrastructure to build, what specimens to store, and what sorts of ethical safeguards to impose.

To provide guidance to the NCS in assessing exposures to endocrine disruptors (EDs) and their effects on children's health and development, the Center for Children's Health and the Environment of the Mount Sinai School of Medicine convened a workshop titled "Endocrine Disruptors and Children's Health: A Workshop to Examine the Effects of Endocrine Disruptors on Child Development for a National Longitudinal Study" on 16–17 March 2000 (New York, NY). The goals were to review evidence of the impact of EDs on health and to provide evidence-based guidance on how to measure exposures to EDs and on how to assess the possible impacts of EDs on child health and development in the NCS.

The workshop was divided into three sessions: "Exposure Assessment," which identified chemical exposures suspected of causing endocrine disruption and discussed routes of exposure, timing of exposure, and approaches to quantification of these exposures; "Cellular and Molecular Mechanisms of Endocrine Disruption"; and "Epidemiology and Assessment of Outcomes," which offered recommendations on how to incorporate recent research on EDs into the NCS. In this article we introduce the series of reports that derived from this workshop and present an overall rationale for incorporating assessment of EDs into the NCS.

Why Study Children?

Children are uniquely vulnerable to toxic chemicals in the environment. They are at risk of exposure to more than 85,000 synthetic chemical compounds, most of which have been developed since World War II (U.S. EPA 1998a). They are at especially high risk of exposure to the approximately 3,000 high-production-volume (HPV) chemicals that are produced or imported in the United States in quantities ≥ one million lb/year. HPV chemicals have the potential to be widely dispersed in foods, household products, air, water, and waste sites. Many hundreds of HPV chemicals have not been tested for their potential human toxicity, and less than 20% have been studied for their possible developmental or pediatric toxicity (National Academy of Sciences 1984; U.S. EPA 1998b).

Children's heightened susceptibility to chemical toxins stems from several sources (Landrigan et al. 1999; National Research Council 1993): *a*) Children have disproportionately heavy exposures to environmental toxicants. *b*) Children's metabolic pathways, especially in the first months after birth, are immature. Children's ability to metabolize, detoxify, and excrete many toxicants is different from that of adults. In some instances, children are actually better able than adults to deal with environmental toxicants. Often, however, they are less well able to metabolize and excrete toxic chemicals and thus are more vulnerable to them. *c*) Children are undergoing rapid growth and development, and their developmental processes are easily disrupted by exposures to xenobiotics. *d*) Because children have more future years of life than most adults, they have more time to develop chronic diseases that may be triggered by early exposures. Many diseases that are caused by toxicants in the environment require decades to develop. Many of those diseases, including cancer, reproductive impairment, and neurodegenerative diseases, are now hypothesized to arise through a series of stages that require years or even decades to evolve from earliest initiation to actual manifestation of disease.

This article is part of the mini-monograph "Endocrine Disruptors and Children's Health."

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Why Study EDs in the NCS?

EDs are among the environmental toxicants to which children are at risk of exposure. Evidence of the ability of EDs to affect development and reproductive capacity came initially from studies of wildlife, but more recently has been buttressed by *in vitro* studies that have begun to elucidate some of the molecular mechanisms of action of EDs. Additionally, clinical and epidemiologic studies have begun to explore the possibility that human exposures to hormonally active compounds, particularly *in utero* and during early childhood, may be responsible, at least in part, for changes in semen quality, increasing incidence of congenital malformations of the reproductive organs, increasing rates of testicular cancer, and an apparent increase in incidence of precocious puberty.

Endocrine disruptors. EDs are chemicals that have the capacity to interfere with hormonal signaling systems. EDs may mimic, block, or modulate the synthesis, release, transport, metabolism, binding, or elimination of natural hormones. They may temporarily or permanently alter feedback loops in the brain, pituitary, gonads, thyroid, and other components of the endocrine system (Gore 2001, 2002). Compounds with estrogenic activity were the focus of most initial concern about EDs. More recently, chemicals with antiestrogenic, progestogenic, androgenic, antiandrogenic, antithyroid, hypothalamic, and other effects have also come to be recognized (National Research Council 1999). The results of endocrine disruption are often not easily detected. They may be subtle and delayed in onset and may not necessarily manifest in the exposed individual, but rather in succeeding generations.

Suspected endocrine-disrupting chemicals. EDs can occur naturally in the environment, and they can be produced synthetically. Plant-produced estrogens—phytoestrogens—are prominent among the naturally occurring EDs. There is growing concern that exposure to high levels of phytoestrogens, such as genistein, found in soy formulas may influence disease risk. For example, Yellayi et al. (2002) exposed juvenile and adult mice to genistein at a range of doses and found that serum genistein concentrations comparable with those found in soy-fed infants appear capable of producing thymic and immune abnormalities. Newbold et al. (2001) found that genistein is carcinogenic in mice if exposure occurs during critical periods of organ differentiation. But in contrast to those positive studies, a retrospective cohort study among adults 20–34 years old who had participated during 1965–1978 in controlled feeding studies found that exposure to soy formula did not appear to lead to alterations in health or reproductive outcomes (Strom et al. 2001).

Synthetically produced EDs include pesticides [e.g., dichlorodiphenyltrichloroethane (DDT) and endosulfan], certain plastics (e.g., bisphenol A), and other industrial chemicals [e.g., polychlorinated biphenyls (PCBs) and phthalates] (National Research Council 1999). Some of these substances have been banned in the United States, at least partly because of their ability to interfere with endocrine function. These banned substances include DDT, diethylstilbestrol (DES; a synthetic estrogen prescribed in the 1950s and 1960s to prevent miscarriage), and PCBs. Information is not available on how many EDs are currently in commercial use because most industrial chemicals have not yet been tested for their ability to interfere with the endocrine system. Enhanced testing of chemicals for potential to cause endocrine disruption was mandated under the Food Quality Protection Act of 1996 (1996).

Evidence of Endocrine Disruption

Effects of EDs have been observed in wildlife populations in several contaminated ecosystems, in experimental animals exposed in the laboratory, and to a more limited extent in humans (Schantz and Widholm 2001).

Wildlife studies. The ability of pesticides to disrupt endocrine function in wildlife has been understood for nearly four decades. Wide recognition of the phenomenon began in 1962 with publication of Rachel Carson's *Silent Spring* (Carson 1962). Carson's work showed that eagles and ospreys, predatory species at the top of the food chain that were heavily exposed to bioaccumulated DDT, had suffered disruption of estrogen function such that they were producing thin-shelled, nonviable eggs. It was on the basis of Carson's work and to prevent extinction of the bald eagle that the newly formed U.S. EPA banned DDT in the early 1970s.

The Lake Apopka alligator is another example of a wild species in which environmental xenoestrogens appear to have damaged endocrine and reproductive function. Lake Apopka in central Florida is adjacent to the former Tower Chemical Company, now a Superfund site. From 1970 to 1980, a pesticide mixture containing high levels of DDT and its metabolites contaminated the Tower site. The site was then cleaned, and the resulting residual levels of pesticides were thought to be safe. However, subsequent research comparing alligators from Lake Apopka with those in other Florida lakes found that Lake Apopka male juvenile alligators had significantly smaller penis size as well as abnormalities in gonadal morphology and lower concentrations of plasma testosterone (Guillette et al. 1999a). Although the precise cause of these abnormalities has not been determined and could not be linked quantitatively to current pesticide levels in the lake, the authors suggest that these findings could reflect past exposures of young alligators to organochlorine pesticides, the metabolites of those pesticides, and PCBs during embryonic development (Facemire et al. 1995; Kelce et al. 1995). Lending support to this hypothesis is the finding that Lake Apopka alligators have elevated levels of the DDT metabolite dichlorodiphenyldichloroethene (DDE) stored in body fat (Guillette et al. 1994). Guillette et al. (1999b) also found elevated concentrations of dieldrin, endrin, mirex, oxychlordane, and *trans*-nonachlor in juvenile serum samples from Lake Apopka alligators compared with alligators from two nearby, less polluted lakes, Lake Woodruff and Orange Lake. Additionally, animals in Lake Apopka demonstrate altered patterns of hepatic androgen biotransformation (Gunderson et al. 2001).

Wild birds exposed to agricultural chemicals and industrial wastes including DDT, PCBs, and organochlorine mixtures manifest adverse effects in reproduction (Fry 1995). The wide range of chemical pollutants to which birds are potentially exposed can result in physiologic effects at several life stages—during breeding in adults as well as in early development. Effects observed in adult birds include reduced fertility, suppression of egg formation, eggshell thinning, and impaired incubation and altered chick-rearing behaviors, all of which can lead to reproductive failure. Reported embryonic effects include increased mortality and reduced hatchability, failure of chicks to thrive, and teratologic effects involving skeletal abnormalities and impaired differentiation of the reproductive and nervous systems. These effects have been observed in populations of gulls breeding in polluted "hot spots" in southern California, the Great Lakes, and Puget Sound (Fry 1995).

Experimental studies. Laboratory studies have documented that certain chemicals and mixtures observed to produce hormonal disruption in wildlife produce similar effects under controlled, experimental conditions (National Research Council 1999). Additionally, laboratory investigations have elucidated some of the biochemical mechanisms through which EDs exert their actions. The first effects studied were estrogenic in nature, and these remain the most extensively evaluated. More recent work (McLachlan 2001) has shown, however, that certain EDs are capable of mimicking the actions of progesterone, whereas others are antiestrogenic, androgenic, antiandrogenic or capable of acting on the thyroid or the hypothalamus.

Binding of EDs to hormone receptors, with resultant alteration in the transcription of messenger RNA, followed by altered gene expression, appears to be one mechanism by which EDs can alter endocrine function.

Other mechanisms involve alteration in hormone synthesis, metabolism, and transport as well as effects mediated through changes in the hypothalamic–pituitary–gonadal axis.

An extensive review of these varied mechanisms of action and also of the assays being developed to assess them is presented in the National Research Council report *Pesticides in the Diets of Infants and Children* (1993). Other mechanistically oriented reviews include McLachlan (2001), Fang et al. (2000), Brouwer et al. (1999), and Birnbaum (1994). Recent work has also demonstrated the potential for EDs to yield synergistic effects when an experimental system is exposed to numerous xenoestrogens (Rajapakse et al. 2002).

Human studies. Effects of EDs on human health have begun to be studied only relatively recently; thus, this research is still in its very early stages. The ability to investigate the possible impacts of EDs on human health has been limited by the fact that most previous studies have employed case–control designs with retrospective assessments of exposure. Except for studies of pharmacologic agents, such as DES, most of these studies have been limited in their ability to accurately assess either the amount or the timing of exposure to putative EDs.

DES exposure. The first observation of the impact of EDs on humans was the seminal observation by Herbst and Bern (1981) of eight cases of clear cell adenocarcinoma (CCA) of the vaginas in young women who had been exposed *in utero* one to two decades earlier to DES, a synthetic estrogen prescribed to pregnant women in the 1950s and 1960s to prevent miscarriage. Ultimately, more than 300 cases of CCA have been documented in women exposed *in utero* to DES (National Research Council 1999). In males exposed to DES *in utero*, reproductive tract abnormalities were observed (Giusti et al. 1995), including increased rates of cryptochordism and hypospadias (National Research Council 1999). Continuing follow-up of these men and women is proceeding to determine whether effects occur in later generations. No abnormalities were observed in the pregnant women who had received DES, an observation that underscores the extraordinarily enhanced susceptibility of the fetus to this potent ED (McLachlan et al. 2001).

PCB exposure and neurobehavioral alteration. The first observation of the effects of PCBs and related compounds on neurologic and reproductive development occurred in 1978–1979 in central Taiwan, where high concentrations of PCBs and their combustion products, the polychlorinated dibenzofurans, came to contaminate cooking oil as the result of a leak from a heating pipe in a rice oil production factory. More than 2,000 Taiwanese, including several hundred pregnant women, ingested contaminated oil in this incident, and their infants were exposed to PCBs and furans *in utero* as well as through breast milk. For the past two decades, researchers have been following the children born to these exposed mothers. Boys exposed prenatally have sperm with abnormal morphology, reduced motility, and reduced strength. These results are consistent with studies of animals exposed *in utero* to PCBs (Guo et al. 2000). Children exposed prenatally also had intrauterine growth retardation, abnormal skin pigmentation, delayed developmental milestones, lower IQs than unexposed siblings, and long-term adverse effects on cognitive development (Chen et al. 1992; Lai et al. 2001). Men exposed to PCBs before 20 years of age had a lower chance of having a baby boy compared with age- and neighborhood-matched controls. There was no significant difference in the birth ratio of infants born to exposed and unexposed mothers (del Rio Gomez et al. 2002). No abnormalities were observed in the pregnant women who had ingested the contaminated oil (del Rio Gomez et al. 2002).

Subsequent studies have shown that lower-level exposures to PCBs also appear capable of altering children's learning and behavior. Studies of women who had eaten PCB-contaminated fish from the Great Lakes before and during pregnancy documented dose-related delays in development and reductions in intellect in their infants in the absence of any overt symptoms (Jacobson and Jacobson 1997). In addition to impacts on development, behavioral effects have also been observed. A recently published study examined the possible impact of prenatal PCB and dioxin exposure on sex-specific play behaviors in Dutch children (Vreugdenhil et al. 2002). Boys who had a high prenatal exposure to PCBs partook in less masculinized play behavior, whereas girls with a similar high prenatal exposure took part in more masculinized behavior. Both boys and girls, when exposed to high prenatal dioxin levels, engaged in behavior associated with a more feminized play style (Vreugdenhil et al. 2002). In another study, Koopman-Esseboom et al. (1996) examined children who were exposed to PCBs and dioxins *in utero* and through lactational exposure at 3, 7, and 18 months of age. At 3 months of age, prenatal PCB exposure was found to have a slight negative effect on psychomotor ability. At 7 months of age, exposure to PCB and dioxin through breast-feeding was found to have an adverse effect on psychomotor ability. At 18 months of age, development was not affected by either PCB or dioxin exposure (Koopman-Esseboom et al. 1996). In a similar study, Huisman et al. (1995) found that at 18 months, developmental effects were not seen from postnatal exposure to PCBs and dioxins (breast milk and infant formula). However, transplacental PCB exposure had a negative effect upon the neurologic condition of children at 18 months. Perinatal background exposure to PCBs and dioxins have been shown to persist into childhood and may be associated with a greater susceptibility to infectious diseases (Weisglas-Kuperus et al. 2000).

TCDD and altered sex ratios at birth. In 1976 in Seveso, Italy, a community-wide exposure to high concentrations of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) occurred after an explosion at a plant that manufactured the herbicide 2,4,5-trichlorophenol (Mocarelli et al. 1996, 2000). Follow-up studies of the exposed population indicate that an increase in TCDD exposure of adults during pregnancy was associated with substantially lowered male:female ratio (0.38) at birth in the offspring (Mocarelli et al. 2000); worldwide, the usual sex ratio at birth is 106 males for every 100 females, a ratio of 0.514 (51.4%) (James 1996). The Seveso incident has also been linked to an increase in cancer in the most heavily exposed populations; an increase in diabetes, notably among exposed women; and moderate increases in chronic circulatory and respiratory diseases (Bertazzi et al. 2001).

A second example of alteration of the sex ratio was recently reported among the offspring of men exposed occupationally to TCDD in a pesticide manufacturing plant in Ufa, Bashkortostan, Russia. The median level of TCDD in workers was 240 ng/kg, a level 30 times background. The major finding was that the ratio of boys to girls at birth was 0.40; this effect was seen only in relation to paternal exposures (Ryan et al. 2002).

PBBs and accelerated onset of puberty. Accidental contamination of the Michigan food chain in 1973 by FireMaster, a fire retardant containing polybrominated biphenyls (PBBs), led to exposure of more than 4,000 persons who ingested contaminated meat and milk. Heaviest exposures occurred among farm families. To assess possible impacts of this exposure on endocrine function, researchers assessed the timing of onset of pubertal development in females 5–24 years old (Blanck et al. 2000). Exposures to PBBs throughout gestation and by breast milk were considered to be the routes by which these girls had been exposed. The main finding was that breast-fed girls exposed to high levels of PBBs *in utero* had an earlier age of menarche than did either breast-fed girls exposed to lower levels of PBBs *in utero* or girls who were not breast-fed. The authors concluded that perinatal PBB exposure was associated with earlier pubertal stage in breast-fed girls. Possible mechanisms for the action of PBBs in relation to puberty include alteration of endocrine feedback loops and alteration of circulating hormone levels (Blanck et al. 2000).

Developmental effects and the importance of timing of ED exposure. The DES and PCB studies described above underscore the unique vulnerability of the embryo and fetus to EDs. Experimental data also indicate that fetuses and infants are especially vulnerable to the effects of EDs (Soto et al. 1994). This sensitivity reflects the fact that in early development, *in utero* as well as postnatally, hormonal messengers provide critical information to cells and tissues that guides the direction and timing of development. The period between conception and adolescence, when cells and tissues are growing and developing most rapidly, is especially delicate. Experimental data indicate that even low-dose exposure to endocrine-disrupting pesticides in early life can have devastating effects (Soto et al. 1994).

In rodents, exposure to estrogenic compounds *in utero* or immediately after birth produces pathologic changes of the reproductive tract, as well as functional differences at puberty and throughout adulthood (Bern 1992). There are also well-documented instances in which exposure to chemicals such as PCBs and TCDD early in development caused severe defects, whereas exposure later in development had no adverse effects (National Research Council 1999).

These observations indicate that consideration of timing of exposure needs to be added to the classic dose–response paradigm of Paracelsus in considering the consequences of exposures to EDs and other environmental toxins.

Potential Relevance of EDs to Children's Health

Increases in incidence of various cancers and reproductive conditions have occurred in the United States over the past three decades. It will be important in the NCS and other studies to explore the hypothesis that ED exposures may be contributing to these trends. The National Cancer Institute reported, for example, that between 1973 and 1999, a 34.8% cumulative increase in incidence of breast cancer occurred among African-American women of all ages, with a corresponding cumulative increase of 27.9% for Caucasian women (Ries et al. 2002). For prostate cancer, there was a 74.4% cumulative increase in incidence across all ages for the period 1973 through 1999 for Caucasian men, and a corresponding cumulative 82.5% increase for African-American men (Ries et al. 2002). For testicular cancer, for Caucasians across all ages, there was a 51.8% cumulative increase in incidence from 1973 through 1999 and a 49.4% increase for African Americans (Ries et al. 2002). For children 14 years of age and younger, the reported incidence of brain cancer increased by 50.2% from 1973 through 1999 (Ries et al. 2002).

Semen quality has been decreasing in the same time period in certain geographic areas (Carlsen et al. 1992; Irvine 1994; Swan et al. 1997). Swan et al. (2000) recently reanalyzed and confirmed previous studies and found that, from 1934 through 1996, sperm density in the United States had decreased at approximately 1.5% per year and in Europe and Australia had decreased at approximately 3% per year, whereas in non-Western countries, no decline in sperm density has been witnessed. Incidence of hypospadias has increased sharply in at least some geographic areas (Paulozzi et al. 1997).

Studies to examine the possible etiologic contributions of EDs to these trends have been undertaken in the case of hypospadias and cryptorchidism (Toppari et al. 1996), testicular cancer (Carlsen et al. 1995), and timing of onset of puberty in young girls (Blanck et al. 2000; Colon et al. 2000). The data so far have been uninformative, but virtually all of these studies were hampered by retrospective assessments of exposure with all of their associated potential for misidentification of exposure and therefore bias toward the null.

Gaps in Knowledge

Lack of accurate information on the level and timing of past exposures to EDs has been the principal limitation of most previous studies of the potential human impacts of known and suspected EDs. This limitation will be directly addressed by the prospective design of the NCS, in that exposures to chemicals will be measured during pregnancy, in breast milk, and in the perinatal period before the appearance of health effects. Also, the NCS with its large base population of 100,000 children will have significant statistical power to investigate possible links between ED exposures and health outcomes. Additional advantages of the NCS that will further sharpen its ability to discern endocrine, neurodevelopmental, reproductive, and other effects of ED exposures include state-of-the-art laboratory assessment of chemical exposures and genetic fingerprinting. The latter will permit examination of genetic polymorphisms that may influence gene–environment interactions and thus will allow assessment of genetically determined interindividual differences in susceptibility to EDs.

These strengths will enable the NCS to generate new knowledge in the following areas: *a*) Determine which ED chemicals, at what doses and at what time in development, contribute to the genesis of health problems in children and adults; *b*) assess impacts of combinations of ED chemicals; *c*) examine modification of ED effects by genetic polymorphisms; and *d*) study late impacts of early exposures—for example, alterations in onset of puberty, adult cancers, and even neurologic degeneration in the elderly. Additional unanswered questions and unexamined hypotheses relative to ED that may be solved by the NCS include identification of the causes of reported increased rates of hypospadias, the causes of increased incidence of testicular cancer, and the causes of reported acceleration of the onset of puberty.

Conclusion

The finding that certain chemical substances in the environment, some of them naturally occurring and others synthetic, can alter endocrine function has raised concern that early human exposures to these chemicals, even at low doses, could have adverse effects on health and development in childhood and throughout the life span. Findings from laboratory animals, as well as evidence from wildlife, indicate that endocrine-disrupting substances may alter sexual development and reproductive function, reduce intelligence, and possibly increase risk of cancer.

It is important that measurements of exposures to EDs and assessments of the possible effects of EDs on the health of children be incorporated into the NCS as an integral component of a larger effort to understand the relationship between environmental exposures and children's health. At the beginning of the 21st century, knowledge of the potential contributions made by environmental exposures to human disorders is surprisingly basic; consequently, our ability to prevent disease that may be caused by these exposures is limited. To close this gap in knowledge, it will be important that sensitive and well-validated instruments that can assess exposures to potentially endocrine-disrupting chemicals and that can evaluate the possible short- and long-term impacts of those exposures on human health be incorporated into the NCS.

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