Developmental Effects of Endocrine-Disrupting Chemicals in Wildlife and Humans

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Large numbers and large quantities of endocrine-disrupting chemicals have been released into the environment since World War II. Many of these chemicals can disturb development of the endocrine system and of the organs that respond to endocrine signals in organisms indirectly exposed during prenatal and/or early postnatal life; effects of exposure during development are permanent and irreversible. The risk to the developing organism can also stem from direct exposure of the offspring after birth or hatching. In addition, transgenerational exposure can result from the exposure of the mother to a chemical at any time throughout her life before producing offspring due to persistence of endocrine-disrupting chemicals in body fat, which is mobilized during egg laying or pregnancy and lactation. Mechanisms underlying the disruption of the development of vital systems, such as the endocrine, reproductive, and immune systems, are discussed with reference to wildlife, laboratory animals, and humans. *Key words:* developmental effects, diethylstilbestrol, differentiation, endocrine function, estrogen, fertility, hormones, organochlorines, pesticides, phenolics, reproductive function. *Environ Health Perspect* 101: 378–384(1993)

Convincing evidence exists that a variety of pollutants, some of which can disrupt endocrine development in wildlife and laboratory animals, is found in rain water, well water, lakes, and oceans, as well as freshwater, marine, and terrestrial food products. This paper identifies the need for a greater awareness about the long-term health consequences associated with exposure to endocrine-disrupting chemicals during early life. Endocrine-disrupting effects are not currently considered in assessing risks to humans, domestic animals, and wildlife. Taking into consideration what is currently known about chemicals that disrupt the endocrine system, the effects 1) may be manifested in an entirely different way, and with permanent consequences, in the early embryo, fetus, and neonate from effects as a result of exposure only in adulthood; 2) can change the course of development and potential of offspring, with the outcome depending on the specific developmental period(s) of exposure; and 3) are often delayed and thus may not be fully or obviously expressed until the offspring reaches maturity or even middle age, even though critical exposure occurred during early embryonic, fetal, or neonatal life.

In mammals as well as all other vertebrates, communication among cells is required for development to progress normally. Substances produced by one group of cells can direct the course of development and thus determine the future functioning of another group of cells (*1*). For example, a group of compounds, the steroid hormones produced by the mother's ovaries and adrenal glands, the placenta, and the fetal gonads and adrenal glands, has been identified as playing a major role in regulating developmental processes in many tissues (*2*). Organogenesis, a particularly vulnerable stage of development, begins in humans at the end of the second month of gestation. At this time the course of development of many tissues is regulated by endogenous steroid hormones along with other endocrine and paracrine factors (*3*).

It is now recognized that numerous endocrine-disrupting chemicals have been released into the environment in large quantities since World War II (Table 1). Some of these chemicals bind to intracellular receptor proteins for steroid hormones (*4*) and evoke hormonal effects in animals (*5*), humans (*6*), and cell culture (*7,8*). They thus interfere with the functioning of receptors whose normal role is to mediate the effects of the endogenous steroid hormones (*9*). Laboratory experiments have demonstrated that exposure of fetuses to endocrine-disrupting chemicals can profoundly disturb organ differentiation (*10,11*) because they can act as hormone agonists or antagonists. Organs that appear to be at particular risk for developmental abnormalities in offspring because of maternal exposure are those with receptors for gonadal hormones: in female fetuses this includes the mammary glands, fallopian tubes, uterus, cervix, and vagina, and in male fetuses it includes the prostate, seminal vesicles, epididymides, and testes. In both sexes the external genitalia, brain, skeleton, thyroid, liver, kidney, and immune system are also targets for steroid hormone action and are thus potential targets for endocrine-disrupting chemicals, although these chemicals may have multiple modes of action, in addition to acting as hormone agonists and antagonists, in different target tissues (*11–15*).

A major concern is the profound and permanent effects that exposure to endocrine disruptors during critical periods in development can have on the future well-being of wildlife and humans, although chronic exposure after maturity can also present a health risk. It is generally assumed that after maturity, exposure to endocrine disruptors does not permanently alter the functioning of hormone-responsive tissues. However, experimental studies in animals have shown permanent changes in brain (*16*) and vaginal epithelium (*17*) in females and prostate in males (*18*) after administration of estrogenic chemicals in adulthood. The possibility thus exists that chronic, low-level exposure to estrogenic chemicals in the environment after maturity can have effects in humans similar to those observed in laboratory animals administered estrogen (*19*).

Wildlife

Exposure to endocrine-disrupting chemicals in the environment has been associated with abnormal thyroid function in birds (*20*) and fish (*21*); decreased fertility in birds (*22*), fish (*23*), shellfish (*24*), and mammals (*25*); decreased hatching success in fish (*26*), birds (*27*), and turtles (*28*); demasculinization and feminization of male fish (*29*), birds (*30*), and mammals (*31*); defeminization and masculinization of female fish (*32*), gastropods (*33*), and birds (*30*); and alteration of immune function in birds (*34*) and mammals (*35*). These deleterious health effects have been observed in many areas where the presence of multiple man-made chemicals, such as byproducts of industrial chemical synthesis (chemical waste) and pesticides (*36*), has been established. The effects were not reported before the 1950s and are currently observed in many areas, such as the Great Lakes in North America. Although much of the data presented here is from studies conducted in and around the Great Lakes, it is important to note that the level of contamination in the Great Lakes region is no greater than some of the other major drainage basins in the United States (*37*).

Researchers from Guelph University report a 100% prevalence of thyroid enlargement in 2–4-year-old salmon in the Great Lakes. Moreover, in some Great Lakes salmon stocks, there is an extremely high prevalence of precocious sexual maturation in males (40–80% depending on the year), poor egg survival (<15%), and low egg thyroid hormone content (*23*). Multiple abnormalities, including behavioral

changes, reproductive loss, and early mortality in offspring have been documented in bird species that feed on Great Lakes fish (*38*). Reproductive loss and early mortality have also been observed in offspring of confined mink that were fed Great Lakes fish (*39*).

The devastating effect of DDT on embryonic survival in bald eagles due to eggshell thinning and cracking has been known for some time (*40*). DDT was introduced on a large scale into the environment in the early 1940s. Restrictions on the use of DDT since 1972 have been only partially successful in reducing levels in the Great Lakes (*36*). Monitoring nesting sites along the Great Lakes shoreline indicates that while eggshell thinning has abated, embryonic and chick survival is not adequate to maintain stable populations. Recruitment is from inland populations that responded to the restrictions on DDT and other chemicals and that do not depend on contaminated fish in the Great Lakes as a primary food source. However, adult bald eagles that migrate to the shoreline have difficulty producing viable offspring after consuming fish and other food from the Great Lakes for 2 or more years (*36*). The shoreline has thus become a "black hole" for bald eagles that migrate from successful inland populations. Abandoned eggs hold as much as 10 times the critical concentration of DDT below which stable populations of bald eagles can be maintained (*41*). In addition to DDT, bald eagles carry elevated concentrations of other compounds that are known endocrine disruptors, such as chlordane, dieldrin, and polychlorinated biphenyls (PCBs) (*41*). Similar findings have been reported for bald eagles nesting along the Columbia River in Washington State (*42*).

There are several explanations for the continued elevated concentrations of endocrine-disrupting chemicals in wildlife tissues and the associated instability in wildlife populations, despite the fact that some of the chemicals have been regulated. First, many pesticides, such as DDT, are still manufactured abroad and used extensively in developing countries where there are limited safeguards or monitoring of use. There is now evidence that DDT, PCBs, and other chemicals that readily vaporize are being transported long distances over the globe via the atmosphere (*43,44*). For example, it is estimated that 90% of the PCBs entering Lake Superior, the largest of the Great Lakes, is derived from the atmosphere (*36*). Second, some chemicals are very persistent: DDT has a half-life of 57.5 years in temperate soils (*45*). PCBs were introduced in 1929, and production ceased in the United States in 1972. Many PCB residues which are

Table 1. Chemicals with widespread distribution in the environment reported to have reproductive and endocrine-disrupting effects

Chemical	Reference
Pesticides	
Herbicides	
2,4-D	*(98,99)*
2,4,5-T	*(100)*
Alachlor	*(99,101)*
Amitrole	*(102,103)*
Atrazine	*(104–106)*
Metribuzin	*(107)*
Nitrofen	*(10)*
Trifluralin	*(108,109)*
Fungicides	
Benomyl	*(110)*
Hexachlorobenzene	*(111–114)*
Mancozeb	*(108)*
Maneb	*(115,116)*
Metiram-complex	*(117)*
Tributyl tin	*(118,119)*
Zineb	*(116)*
Ziram	*(99)*
Insecticides	
ß-HCH	*(120)*
Carbaryl	*(100)*
Chlordane	*(121)*
Dicofol	*(30)*
Dieldrin	*(113)*
DDT and metabolites	*(30)*
Endosulfan	*(122; A. Soto, unpublished)*
Heptachlor and H-epoxide	*(113)*
Lindane (γ-HCH)	*(123)*
Methomyl	*(107)*
Methoxychlor	*(5,124)*
Mirex	*(A. Soto, unpublished)*
Oxychlordane	*(121)*
Parathion	*(125)*
Synthetic pyrethroids	*(126)*
Toxaphene	*(A. Soto, unpublished)*
Transnonachlor	*(121)*
Nematocides	
Aldicarb	*(107)*
DBCP	*(10,99)*
Industrial chemicals	
Cadmium	*(127)*
Dioxin (2,3,7,8-TCDD)	*(85–87)*
Lead	*(128,129)*
Mercury	*(130)*
PBBs	*(131)*
PCBs	*(72,132,133)*
Pentachlorophenol (PCP)	*(134)*
Penta- to nonylphenols	*(8)*
Phthalates	*(135–140)*
Styrenes	*(8,141,142)*

endocrine disrupting and/or developmental toxicants have not been properly stored and are already dispersed in the environment. PCBs will be around over geologic time (*46*).

Effects of pollutants on the reproductive system, in addition to the well-documented reduction in eggshell thickness, became apparent in the late 1970s when histopathological examination of herring-

gull embryos and newly hatched chicks collected in Lake Ontario revealed oviducts and gonads resembling ovaries in male birds and abnormal development of the oviductal system in female birds (*38*). Follow-up laboratory studies using DDT and other pesticides which remain in wide use today (dicofol, kelthane, and methoxychlor) produced the same results in kestrels, western gulls, and California gulls (*30,47*). Today, adult female herring gulls have been observed tending double clutches in their nests in unstable populations (*38*). Elevated concentrations of DDT, its metabolite, DDE, PCBs, and other organochlorine residues have been found in eggs from these populations (*48*). It has not been determined whether half of the birds that are pairing are genotypic males that had been feminized during embryonic development by environmental chemicals with estrogenic activity or whether they were all genotypic females showing abnormal behavior. Recent laboratory experiments with small mammals corroborate many of the anomalies cited above, although the effects vary among species and among chemicals (*5*).

The DES Syndrome: A Model for Exposure to Estrogenic Chemicals in the Environment

Diethylstilbestrol (DES) is a synthetic estrogen that was used by physicians to prevent spontaneous abortions in women from 1948 until 1971, when its use for this purpose was banned. DES-exposed humans thus serve as a model for exposure during early life to any estrogenic chemical, including pollutants in the environment that are estrogen agonists. The primary model for determining estrogenic activity of a chemical is the stimulation of mitotic activity in the tissues of the female genital tract in early ontogeny, during puberty, and in the adult (*49*), although estrogen also affects other tissues in females and males (*2,19*). Daughters whose mothers took DES (about 1 million or more between 1960 and 1970) suffer reproductive organ dysfunction, abnormal pregnancies, a reduction in fertility, immune system disorders, and periods of depression (*50,51*). As young adults these women also suffer increased rates of vaginal clear-cell adenocarcinomas (*52*); this is a reproductive tract cancer found in women beginning in their fifties, but it is rare in women in their twenties (*50,51*). A major concern is that when women exposed *in utero* to estrogenic chemicals (DES and/or environmental pollutants that are estrogen agonists) reach the age at which the incidence of reproductive organ cancers normally increases, they will show a much higher incidence of cancer than unexposed individuals.

There is a substantial literature documenting the detrimental effects of exposure to DES during the critical period of organ differentiation in experimental studies using rodents. Animal models corroborate clinical studies in humans. For example, dysplastic changes in the rodent prostate (53) are comparable to those seen in stillborn male offspring of women treated with DES (54). In female mice, DES exposure during early life leads to permanent cornification of the vaginal epithelium, which may be independent of effects on the brain–pituitary–ovarian axis (50,55,56). Significant impairment of immune function (particularly the T-cell system) has also been reported after exposure to DES during early life (57) as well as an increase in autoimmune diseases in women (58). These outcomes were typically not noticeable at birth and often not detected before maturity. For example, treatment of male rats with DES during the first month after birth [accessory reproductive organs are still developing (2)] did not result in observable malignancies at 6–9 months of age, but by 20 months (old age), squamous cell cancer was detected with involvement of the dorsolateral prostate (59). In female mice treated during early life with DES, an increase in sensitivity of mammary glands to carcinogens has been reported (60).

A variety of agricultural and industrial chemicals produced today (either within or outside the United States) are capable of binding to intracellular estrogen receptors either directly, such as o,p'-DDT (61), or after in situ conversion to an active metabolite. For example, the pesticide methoxychlor (62) is demethylated in situ to a more estrogenic bisphenolic compound (63). Pesticides such as o,p'-DDT, chlordecone (6), and components of plastics, such as nonylphenol (7), mimic the action of endogenous estrogens (and exogenous DES) both in laboratory animal models as well as in estrogen-sensitive cells in culture (8). A number of conditions in wildlife (reviewed earlier) parallel those reported in laboratory animals and humans exposed to DES during development.

It is worth noting that the estrogenicity of chlordecone was first detected in people working at a pesticide-producing plant (64), and although many effects of estrogenic chemicals may be primarily due to exposure during in utero development, chronic exposure throughout adulthood is also a concern. For example, in studies with male dogs, which show prostatic hyperplasia during aging, the disease only developed in castrated males treated with both androgen and estrogen, not androgen alone (18). Exposure of adult men to estrogen has been implicated in the etiology of prostate hyperplasia (19,65). Both prostate

cancer and benign prostatic hyperplasia in men and cancers of estrogen-responsive tissues in women (vaginal, cervical, endometrial, and breast) represent major medical problems faced by older people.

It is now suspected that increases in the incidence of numerous pathologies in men and women may be related to exposure to pesticides and other endocrine-disrupting chemicals that can mimic DES and are thus estrogen agonists. The clinical and experimental findings with DES show that consideration must be given to the following facts: 1) an increase in breast and prostatic cancer in the United States occurred between 1969 and 1986 (66), 2) a 400% increase in ectopic pregnancies occurred in the United States between 1970 and 1987 (67), 3) a doubling of the incidence of cryptorchidism occurred in the United Kingdom between 1970 and 1987 (68,69), and 4) an approximate 50% decrease in sperm count worldwide over the last 50 years (70).These trends may be a reflection of the increase from estrogenic pollutants in the environment. It has been suggested that the decrease in sperm count in men is the result of exposure during the fetal period of testicular differentiation to pollutants that have estrogenic activity (71). For example, an association between reduced sperm motility and PCBs in men with fertility problems has been reported (72); some PCBs are directly estrogenic while others become estrogenic after in vivo conversion, although the binding affinity of estrogen receptors for estrogenic PCBs is lower than that for estradiol-17ß (4).

Characterization of Endocrine-Disrupting Chemicals

Literally thousands of synthetic compounds, a number of which are endocrine disruptors, have been released in the environment, generating concern about their additive and synergistic effects. Also, many of the endocrine disruptors are persistent, lipophilic, and have low vapor pressures, which facilitates their widespread dispersal.

It is common to find PCBs, dioxins, DDT, and a number of other organochlorine pesticides together in human breast milk and adipose tissue (73,74). Of concern for humans, domestic animals, and wildlife are the likely additive effects due to exposure to these and other endocrine-disrupting chemicals either together or at different times in life. For example, possible exposure to multiple estrogenic chemicals may be related to the fact that not all offspring of DES-exposed mothers show abnormalities. Although genetic factors may partially account for this outcome, it is also possible that the most affected individuals are those whose mothers were exposed to endocrine-disrupting environ-

mental pollutants with estrogenic activity before or during treatment with DES. Many of the effects of endocrine disruptors that have been reported in wildlife are associated with the presence of a toxic contaminant in the mother due to exposure before egg production in birds and fish or pregnancy and lactation in mammals.

Evidence already exists that a number of organochlorine chemicals (such as dioxin, PCBs, and DDT) has reached concentrations in aquatic food sources that can lead to substantial functional deficits in animals that consume this food. Male rats fed Lake Ontario fish showed hyperreactivity to stress, and offspring of females fed Lake Ontario fish during pregnancy also expressed the same hyperreactive condition, although the offspring were never fed fish (75). In addition, offspring of women who ate two to three Lake Michigan fish a month for at least 6 years preceding their pregnancies were slightly preterm, had lower birth weight, smaller skull circumference, and cognitive, motor (hypotonicity and hyporeflexivity), and behavioral deficits at birth compared with offspring whose mothers did not eat fish (76). The effects were associated with the mothers' lifetime experience of eating fish, not just what they ate during pregnancy. These findings emphasize the importance of exposure of females to contaminants before pregnancy in terms of effects on their offspring.

Subsequent studies of the above cohort beginning at 6–7 months revealed delays in psychomotor development and poorer visual recognition compared with controls (77). When examined at 4 years of age, the children of women who had eaten fish in this study exhibited short-term memory problems, and 17 of the children became intractable and refused to cooperate during testing; they were the children of the mothers with the highest PCB concentrations (measured in their breast milk) in the study (78). The childrens' intractable behavior appears to be analogous to the behavior of the rats fed Lake Ontario fish. In another study using the infants of mothers who ate Lake Michigan fish and infants of mothers exposed to a PCB "farm incident," both cohorts experienced growth retardation and neurological effects which were related in a dose-dependent manner to umbilical cord serum PCB concentrations (reflecting the levels in fetal blood) (79). It remains to be determined whether the neurotoxic effects mentioned above are mediated through the endocrine system. It is recognized that endocrine-disrupting chemicals may act via multiple mechanisms, some of which may only operate during specific developmental periods (11,80,81).

Based on current breast milk concentrations nationwide, it is estimated that at least 5% and possibly more of the babies born in the United States are exposed to quantities of PCBs sufficient to cause neurological effects (82). These findings provide evidence that contemporary PCB exposure is above "any regulatory guideline" (82: 247). The possible immunological and endocrinological consequences remain to be determined in these cohorts. A major concern is that some of these consequences may not become apparent until young adulthood or even middle age.

Accumulation of pollutants increases the probability of repeated or constant exposure but, as the literature on dioxin shows, administration at only one time in development, rather than the more likely chronic exposure, can profoundly affect the embryo, fetus, or perinatal infant. Ample evidence exists from both *in vivo* and *in vitro* studies that dioxin can antagonize the action of estrogen in some estrogen target cells (83,84), although this effect does not appear to be due to dioxin binding to estrogen receptors (11). The fact that dioxin is antiestrogenic is important because the conversion of androgen to estrogen in some target cells plays a critical role in masculinization (2). For example, a series of studies describing the dose-related inhibition (dose range: 0.064–1.0 µg/kg/body weight to the dam) of masculinization and persistence of feminine traits in male rat offspring whose dams were fed one meal of dioxin during pregnancy at a critical period during sexual differentiation illustrates the vulnerability of the male rat fetus *in utero* to administration of only one low dose of dioxin to the dam. In these studies the effects were not fully manifested until the rats reached adulthood (85–87). These effects would be expected from either chronic, low-dose exposure to dioxin before pregnancy or to a single exposure during a critical time in pregnancy.

Dioxin accumulates in human tissue and is generally found in all tissues of people living in developed countries (88). However, only the toxic congeners of the dioxin family complex bioaccumulate in human breast milk (88). Similarly, these chemicals have also been found in follicular fluid obtained during *in vitro* fertilization procedures in women (89). Although direct correlations have not yet been reported between reproductive success and the presence of xenobiotics in the follicle, these substances could disrupt oocyte development (19,90,91).

Many endocrine-disrupting chemicals have been reported in the reproductive tissues of men and women (74). These lipid-soluble compounds appear to sequester in all fatty tissue in the body, so that organs and tissues with higher fat content hold more of the compounds on a wet weight basis (73). Little is known about the concentrations in embryos and fetuses other than they appear to be similar to those in mothers (73,92). Of considerable concern is bioaccumulation of organochlorine chemicals in breast milk due to its high lipid content, which leads to a much higher concentration in breast milk than in maternal blood (73). It is well documented that the infant is exposed to higher concentrations of many of these chemicals during breastfeeding than at any other time in its life (74).

Consideration should also be given to the fact that man-made chemicals, such as DES, which bind to estrogen receptors in cells, do not bind to estrogen-binding plasma proteins (93). One function of estrogen-binding plasma proteins, such as sex-steroid binding globulin in humans, is to restrict entry of endogenous estrogen into cells (94). As a result of this affinity, only a small fraction of the total endogenous estrogen in blood is able to pass into cells. This is particularly important during pregnancy when the concentration of estrogen-binding plasma proteins increases dramatically (2,95). It is possible that estrogenlike chemicals may show low or no binding affinity to estrogen-binding plasma proteins. These chemicals may be able to freely enter cells (similar to DES), which would greatly increase their biological activity relative to similar blood concentrations of endogenous estrogen, most of which is inhibited from entering cells. This would contribute to the *in vivo* effectiveness of these pollutants, many of which show lower binding affinity to estrogen receptors than the most potent endogenous estrogen, estradiol-17ß (4). Environmental pollutants with estrogenic activity are less potent agonists for the induction of proliferation of breast cancer cells *in vitro* (8).

Summary

The deleterious effects of endocrine-disrupting chemicals in the environment on the reproductive success of wildlife populations have been documented; this is not an isolated problem, and today many wildlife populations are at risk. At present, no coherent policy has been articulated to remedy this problem. This is due in part to the lack of knowledge concerning which of the many chemicals present in the environment are responsible for endocrine-disrupting effects. Regulatory agencies should recognize that the current endpoints of most tests to assess the risk of pesticides and other pollutants (carcinogenicity, acute toxicity, and immediate mutagenicity) have led to the misconception that these chemicals do not pose a threat to the health of wildlife, domestic animals, or humans. Although the effects of mutagens can be seen immediately in terms of gross abnormalities, the consequences of fetal exposure to endocrine-disrupting chemicals would likely not be recognized until young adulthood, at which time abnormalities, particularly relating to the function of the reproductive system, become apparent.

Because endocrine-disrupting chemicals are in most cases neither mutagens nor acute toxicants at ambient concentrations, they may be released without proper caution into the environment. This may be partially remedied by screening for hormone agonistic and antagonistic activity using hormone-responsive cells in culture; this procedure identifies compounds that are endocrine disruptors because they are hormonally active (8). Although this procedure cannot rule out chemicals devoid of hormonal activity that may disrupt development through other mechanisms, it can at least rule out compounds like DDT, chlordecone, alkylphenols, and some PCBs, which are estrogen agonists. It is also essential to continue to examine transgenerational effects in animal studies because some pollutants require metabolism *in vivo* to exert hormonal effects and because neurobehavioral and other developmental effects cannot be addressed with *in vitro* models (96,97).

Wildlife species have provided the model for maternal transfer of environmental endocrine-disrupting chemicals with their resulting suite of effects in offspring; experiments with laboratory animals have confirmed the findings. In humans, the DES model is clear and traceable. However, for clinicians and public health authorities, the implications of these findings regarding man-made endocrine disruptors present in air, water, and food for human health is just coming to light. Transgenerational exposure, hormonal activity, functionality, and delayed expression of effects must be addressed when determining the hazards of exposure to persistent chemicals already in the environment and of new chemicals that might be released in the future.

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