Cognitive Effects of Endocrine-Disrupting Chemicals in Animals

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A large number of chemical pollutants including phthalates, alkylphenolic compounds, polychlorinated biphenyls and polychlorinated dibenzodioxins, organochlorine pesticides, bisphenol A, and metals including lead, mercury, and cadmium have the ability to disrupt endocrine function in animals. Some of these same chemicals have been shown to alter cognitive function in animals and humans. Because hormonally mediated events play a central role in central nervous system development and function, a number of researchers have speculated that the changes in cognitive function are mediated by the endocrine-like actions of these chemicals. In this paper we review the evidence that cognitive effects of chemicals classified as environmental endocrine disruptors are mediated by changes in hormonal function. We begin by briefly reviewing the role of gonadal steroids, thyroid hormones, and glucocorticoids in brain development and brain function. We then review the endocrine changes and cognitive effects that have been reported for selected endocrine-disrupting chemicals, discuss the evidence for causal relationships between endocrine disruption and cognitive effects, and suggest directions for future research. *Key words*: cognitive function, endocrine disruptors, learning, memory. *Environ Health Perspect* 109:1197–1206 (2001). [Online 14 November 2001]

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There is increasing concern about chemical pollutants that have the ability to act as hormone mimics. Because of a structural similarity with an endogenous hormone, an ability to interact with hormone transport proteins, or an ability to disrupt hormone metabolism, these chemicals have the potential to mimic, or in some cases block, the effects of the endogenous hormone. In either case, these chemicals serve to disrupt the normal actions of endogenous hormones and thus have become known as "endocrine disruptors." A large number of environmental pollutants including phthalates, alkylphenolic compounds, polychlorinated biphenyls (PCBs), polychlorinated dibenzodioxins, organochlorine pesticides, bisphenol A, and heavy metals including lead, mercury, and cadmium have been shown to disrupt endocrine function in animals. Because hormonally mediated events play a central role in central nervous system (CNS) development and function, there is speculation that some of the cognitive deficits that arise from developmental exposure to environmental chemicals may be the result of endocrine disruption.

For example, thyroid hormone is essential for proper neuronal proliferation, cell migration, and differentiation in the developing mammalian brain (*1*). Disruption of the thyroid system during development has been shown to result in permanent changes in neurochemical (*2*), morphologic (*3,4*), and neurobehavioral end points (*5–7*). There are a number of environmental contaminants that have been shown to affect thyroid system function (*8*). One example is PCBs. PCBs alter thyroid function through multiple mechanisms including direct toxic effects to the thyroid gland, induction of thyroid hormone metabolism via UDP-glucuronyl transferase, and interaction with thyroid hormone carrier proteins (*9*). Further complicating matters is the fact that PCBs have multiple endocrine effects, impacting not only thyroid hormones but the gonadal (*10–12*) and adrenal steroid systems (*13*) as well. PCBs are just one example of the many environmental contaminants capable of disrupting one or more endocrine systems. When one considers that human populations have body burdens of multiple contaminants capable of affecting multiple endocrine systems, the potential human health risk could be significant. Therefore, an understanding of the endocrine-disrupting potential of these chemicals and subsequent neurobehavioral changes that result is an important task facing environmental toxicologists, endocrinologists, and behaviorists.

The goals of the current review are to discuss the evidence for cognitive changes resulting from exposure of laboratory animals to chemicals classified as endocrine disruptors and to examine the extent to which these cognitive changes appear to be mediated by changes in hormonal function. The discussion is focused on the three hormonal systems—the gonadal steroids, the thyroid hormones and the glucocorticoids, for which the richest data set on endocrine disruption exists. Although other hormones, growth hormone in particular, play important roles in brain development and behavior, relatively little is known about the effects of chemical pollutants on other hormonal systems. We begin by reviewing the roles of the gonadal steroids, thyroid hormones, and glucocorticoids in brain development and function. We then review the endocrine changes and cognitive effects that have been reported for several major chemical pollutants including PCBs, dioxins, and lead, discuss the evidence for causal relationships between the endocrine disruption and cognitive effects, and conclude by highlighting important directions for further research.

Role of Hormones in Brain Development and Cognition

Estrogens and androgens. The role of gonadal steroids in the development of brain areas involved in reproduction has been recognized for many years (*14*). The brain is particularly sensitive to the differentiating effects of gonadal hormones during a critical period early in development. The absence of testicular hormones during this period allows the development of a female pattern of behavior and neuroendocrine function. Conversely, the presence of testicular hormones allows the development of a male pattern. In the rat, the critical period for sexual differentiation of the brain starts a few days before birth and ends approximately 10 days after birth. The brain is exquisitely sensitive to estrogens and androgens during this time. Female rats treated with testosterone during the critical period permanently lose the capacity to secrete leutinizing hormone in a cyclical fashion in response to estrogen stimulation and do not show typical female reproductive behaviors, such as lordosis. Conversely, they have the capacity to exhibit masculine sexual behaviors in response to administration of testosterone. Male rats castrated during the critical period are unable to display typical male sexual behaviors after administration of testosterone in adulthood, but will show lordosis in response to estrogen treatment.

In the rat, sexual differentiation primarily occurs through the aromatization of testosterone to estrogen locally within the brain (*14*). Estrogen then acts to organize neural

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components in the hypothalamus and preoptic area in a male-specific pattern. In the absence of testosterone, the hypothalamus develops in a female-specific pattern. The most striking sex difference in brain anatomy is present in an area within the medial preoptic area (MPOA) known as the sexually dimorphic nucleus of the preoptic area (SDN-POA). This nucleus is 5- to 7-fold larger in male rats than in females (*15*). The nucleus is dimorphic not only in terms of its volume, but also in terms of the neurotransmitters in the cell bodies of the neurons comprising the nucleus and in the fibers innervating it (*16*). Another region, the ventral medial nucleus of the hypothalamus (VMN), is also sexually dimorphic (*17*). The roles of these hypothalamic nuclei in reproductive behavior are not completely understood, but the VMN appears to be involved in the lordosis response in female rats (*17*), and the SDN-POA has been implicated in the execution of coital behavior in male rats (*16*). Some aspects of sexual differentiation of the brain, including the development of sexually dimorphic patterns of social play, appear to be regulated by the direct actions of androgens in the brain, rather than by the aromatization of androgens to estrogen (*18*). A similar process of sexual differentiation appears to occur in the brains of all mammalian species including humans. However, in other species, particularly nonhuman primates and humans, the mechanisms are not as well understood.

Recently it has become clear that early exposure to estrogens and androgens has important actions in areas of the brain that are not involved in reproduction. One of these is the hippocampus, which plays an important role in learning and memory, particularly spatial learning and memory (*19*). Sex differences in spatial learning have been reported by many investigators and appear to be present in humans as well as in animals (*20*). In general, men outperform women on tasks that require spatial skills. Male rodents also make fewer errors than females on spatial learning tasks. The work of Williams et al. (*21*) suggests that these differences could be due to differences in the way males and females process spatial information. Male rats appear to attend primarily to geometric cues (the shape of the environment), whereas females use a combination of landmarks and geometry to locate a target.

As reviewed by McEwen et al. (*19*), sex differences in hippocampal morphology also exist. These include differences in the number of spines on the apical dendritic shafts of CA3 pyramidal cells (*22*), as well as differences in the number of mossy fiber synapses to these cells (*23*). Male rats have more spines on the apical dendrites and more mossy fiber synapses. They also have a larger and more asymmetric dentate gyrus (*24*). Neonatal testosterone treatment causes the female dentate gyrus to appear masculine and also improves the spatial learning ability of female rats (*24*). In contrast, neonatal castration of male rats results in a female pattern of spatial learning (*20*).

The rat hippocampus shows a transient increase in estrogen receptors for a short period during perinatal development (*25*). This coincides with transient expression of the aromatase that converts testosterone to estrogen (*26*). Thus, hippocampal estrogen receptors of male rats are exposed to locally generated estrogen during a brief period early in development. Just as in the hypothalamus, this appears to lead to sexual differentiation of hippocampal structure and function. Exposure to chemicals that perturb the delicate balance of gonadal hormones during early development could result in changes in hippocampal morphology and alter the normal pattern of male/female differences in spatial learning.

Estrogen receptors are sparsely distributed in the adult hippocampus, but recent research indicates that estrogen continues to play an important role in the hippocampus during adulthood. Morphologic studies have shown that estrogen induces cyclical changes in dendritic spine density on pyramidal cells in the CA1 region of the hippocampus in female rats (*27*). More recent *in vitro* studies have demonstrated that the estradiol-induced increase in spine density increases the sensitivity of the cells to *N*-methyl-D-aspartate receptor-mediated synaptic input (*28*). There are a number of studies suggesting that learning ability varies over the course of the estrous cycle in female rats (*29–33*), although several other studies have not found any changes (*34,35*). In addition, estrogen replacement therapy appears to preserve memory function in post-menopausal women (*36,37*), as well as in ovariectomized female rats (*38*). Thus, exposure to environmental chemicals that have estrogenic or antiestrogenic actions could also impact cognitive function during adulthood and aging.

There are two estrogen receptor subtypes (ERα and ERβ) that are differentially distributed throughout the CNS. Some regions—including the neurons of the olfactory bulb; supraoptic, paraventricular, suprachiasmatic, and tuberal hypothalamic nuclei; zona incerta; ventral tegmental area; and cerebellar Purkinje cells—contain only ERβ (*39*). In contrast, only ERα is found in the ventromedial hypothalamic nucleus and the subfornical organ. Neurons in many other brain regions contain both ERα and ERβ. However, the relative amounts of the two receptor subtypes vary by region. For example, Shughrue et al. (*39*) found that the cerebral cortex and hippocampus contain both ERα and ERβ, but the relative amount of ERβ is much greater than ERα in these brain regions. Region-specific expression of ERα and ERβ may be important in determining the physiologic responses of neurons to estrogen action. Thus, if different environmental estrogens have different affinities for the two ER subtypes, they could potentially affect brain development and behavior in very different ways.

Thyroid hormones. The actions of thyroid hormones are vital for normal brain development (*1*). Thyroid hormones are involved in regulating many aspects of nervous system development including neuronal proliferation, cell migration, and differentiation. Neonatal hypothyroidism results in delayed myelinogenesis, alterations in cell migration, delayed or impaired neuronal differentiation and synaptogenesis, and alterations in neurotransmitter function (*2–4*). These morphologic and neurochemical changes are associated with permanent impairments in neurobehavioral function, including delayed reflex development, changes in motor activity and emotionality, and deficits in learning and memory (*5,6,40*). Although thyroid hormone imbalances during adulthood can also lead to cognitive and behavioral disturbances, these are usually completely reversible with appropriate hormone therapy.

Many of the biochemical and morphologic changes observed in the brains of neonatally hypothyroid rats appear to recover with time, but several brain regions, including the hippocampus, show persistent morphologic changes in response to early thyroid hormone manipulations (*41*). Early hypothyroidism results in hippocampal CA3 pyramidal cells with markedly stunted dendritic trees (*42*). The CA3 cells originate during the early embryonic period (*43*), but undergo extensive dendritic remodeling during the second and third postnatal weeks (*42*). The timing of these changes coincides with peak levels of thyroid hormones (*44*) and thyroid hormone receptor (*45*), which may explain the unusual sensitivity of the CA3 pyramidal cells to neonatal thyroid hormone imbalances. In contrast, hippocampal CA1 pyramidal cells do not undergo extensive dendritic restructuring during the postnatal thyroid hormone surge and appear to be less affected by neonatal thyroid hormone manipulations (*42*). Neonatal hypothyroidism also reduces the number of dentate gyrus granule cells (*46*) and impairs their dendritic arborization (*42,47*).

The cognitive effects of neonatal hypothyroidism reflect the fact that the hippocampus is one of the most severely damaged brain

regions. Spatial learning and memory is severely impaired on the radial arm maze (*5*) and Morris water maze (*6*), as well as on other complex mazes (*40*). Congenitally hypothyroid children have cognitive deficits not unlike those observed in neonatally hypothyroid rats. These include impaired memory and spatial perception, as well as attentional problems (*1*). Subtle problems with hearing, speech, and word comprehension are also common. A large number of environmental chemicals are known or suspected of altering thyroid hormone function (*8*). Exposure to these chemicals during early development could potentially interfere with brain development and cause permanent deficits in cognitive function.

Glucocorticoids. Glucocorticoids also have a profound affect on brain development. In the rat, the first 2 weeks of life are characterized by low basal levels of corticosterone and hyporesponsiveness of the hypothalamic-pituitary-adrenal (HPA) axis to stressful stimuli (*48*). During this period, the brain is very sensitive to environmental or chemical manipulations. Various environmental stimuli including electric shock, heat stress, exposure to novelty, and handling of the neonate have been shown to produce long-lasting or permanent changes in brain glucocorticoid receptor expression and behavior. The best studied among these is the effect of early handling (*49*). Rats handled during infancy have a permanent increase in glucocorticoid receptors in the hippocampus, which results in greater hippocampal sensitivity to glucocorticoids and better regulatory control of the stress response. Less corticosterone is secreted in response to stress, and levels return to baseline more rapidly. Over the life span, this translates into lower cumulative exposure to glucocorticoids, which results in less hippocampal cell loss and less decline in memory function during aging (*50*). Interestingly, mothers of handled pups spend more time licking and manipulating their pups, and it is these alterations in maternal behavior that seem to mediate the handling effect on glucocorticoid function (*49*).

Unlike the positive effects of neonatal handling, exposure to elevated levels of glucocorticoids during the period when the HPA axis is normally quiescent can have detrimental effects on brain development (*48*). Cell proliferation ceases early, and axonal outgrowth, myelination, formation of dendritic spines, and synaptogenesis are retarded. Some of these effects may be reversible if the exposure to exogenous glucocorticoids ends early enough, but recovery is seldom complete. As with thyroid hormone imbalances, these changes in brain morphology are accompanied by deficits in behavioral function, including deficits in learning and altered motor activity (*48*).

Many studies have shown that hippocampal development and function are exquisitely sensitive to the circulating levels of glucocorticoids. Formation of the granule cells of the dentate gyrus, in particular, is closely linked to adrenal steroids (*51*). Immediately before birth the levels of glucocorticoids are high and the number of dentate gyrus granule cells that incorporate ^{3}H-thymidine is low. As discussed above, after birth, the levels of adrenal steroids drop and remain low for roughly 2 weeks. During this period, the number of dentate gyrus granule cells that incorporate ^{3}H-thymidine increases dramatically. As glucocorticoid levels rise again at the end of the hyporesponsive period, granule cell proliferation diminishes once again. In adulthood, the levels of adrenal steroids are relatively high and the rate of granule cell proliferation remains low. Injecting either developing pups or adult rats with corticosterone reduces the rate of granule cell proliferation, whereas removal of the adrenal gland increases proliferation. Paradoxically, adrenal steroids also suppress granule cell death. Throughout the life of the rat, the level of adrenal steroids correlates negatively with the number of degenerating dentate gyrus granule cells. In the adult animal, adrenalectomy results in massive granule cell death.

Normal levels of circulating adrenal steroids appear to be necessary for accurate performance on spatial tasks, which is not surprising given the role of the hippocampus in spatial learning and memory. Either increases or decreases in corticosterone impair spatial learning in the rat. Adrenalectomy has been shown to impair performance on the radial arm maze (*52*) and the Morris water maze (*53*). Conversely, restraint stress, which elevates corticosterone levels, also impairs radial arm maze performance (*54*). Chemicals that alter the levels of adrenal steroids or mimic or block their actions, would have the potential to alter dentate gyrus morphology and disturb spatial learning and memory. Although exposure during development is more likely to lead to permanent functional changes, cognitive deficits are possible regardless of whether exposure occurs during development or in adulthood.

Interactions between hormone systems. It is important to note that individual hormonal systems interact with each other in complex ways. Thus, the possibility exists for alterations in one specific hormonal pathway to cascade through multiple systems, producing nervous system effects that are complex and difficult to interpret (*55*). For example, thyroid hormones appear to be involved in mediating the effects of handling on glucocorticoid receptor expression (*49*). Handling activates the hypothalamic-pituitary-thyroid axis, increasing the levels of thyroid hormones. This results in increased 5-hydroxytryptamine turnover in the hippocampus, which in turn acts to permanently increase hippocampal glucocorticoid receptor expression. Direct neonatal treatment with thyroid hormone has the same effect, whereas treatment with the goitrogen propylthiouracil blocks the increase in hippocampal glucocorticoid receptor binding usually observed after handling (*49*).

Alterations in thyroid hormones during the critical period can also affect androgen-dependent sexual differentiation of the brain. Hyperthyroidism shortens the critical period for androgen exposure, whereas hypothyroidism prolongs it. In addition to these indirect effects, there is recent evidence that thyroid hormone may also inhibit estrogen's actions directly at the genomic level (*56*). Thus, agents that increase thyroid hormone bioavailability or mimic the actions of thyroid hormone might be expected to attenuate estrogen-mediated responses such as sexual differentiation of the brain, whereas agents that reduce or block thyroid hormone action would be expected to have the opposite effect.

Effects of Endocrine-Disrupting Chemicals on Cognition

A large number of synthetic chemicals have been identified as known or suspected endocrine disruptors (*57*). For the most part, these are compounds that have estrogenic or antiestrogenic actions (*58*) and/or disrupt thyroid function (*8*). A much smaller number of chemicals have been evaluated for effects on other endocrine systems such as androgens and adrenal steroids. Keith (*59*) has compiled a comparative list of environmental endocrine disruptors based on lists obtained from scientists at the U.S. Environmental Protection Agency (U.S. EPA), the Centers for Disease Control and Prevention (CDC), and the World Wildlife Fund (WWF). Although many chemicals appear on all three lists, there are also significant differences among the three lists. A total of 103 different chemicals are represented with 60, 48, and 68 chemicals appearing on the U.S. EPA, CDC, and WWF lists, respectively. The discrepancies between the three lists highlight the fact that we do not have adequate scientific data on many potential endocrine disruptors. Because of the limited scope of this review, we will limit our discussion primarily to those chemicals that all three sources identified as environmental endocrine disruptors. These fall into several broad chemical classes including phthalates, alkylphenolic compounds, organochlorine pesticides, PCBs, dioxins and furans, bisphenol A, and heavy metals (Table 1).

The lack of good scientific data on endocrine disruptors becomes even more

obvious when one attempts to investigate the effects of these chemicals on cognitive function. Despite the fact that hormones play a central role in CNS development and function, few endocrine disruptors have been evaluated for cognitive effects in animal models, and few, if any, mechanistic studies directly relating changes in cognitive function to altered endocrine status have been conducted. Table 1 lists individual endocrine disruptors by chemical class, identifies some of the hormonal systems they act on, and indicates whether cognitive function has been assessed. Because few or no data exist for most of the chemicals on the list, it will be necessary to focus this discussion on a few examples for which cognitive effects have been documented.

PCBs and dioxins. PCBs and dioxins are widely dispersed, environmentally persistent organic compounds. PCBs were manufactured commercially in the United States from the 1930s through the 1970s and were widely used as dielectric fluids in capacitors and transformers (*60*). Dioxins are structurally similar compounds that are formed as unwanted by-products during the manufacture of certain herbicides and wood products. Dioxins are also formed during combustion of chlorinated compounds and are found in fly ash from municipal and hospital incinerators (*61*).

The endocrine-disrupting properties and cognitive effects of PCBs and dioxins have been extensively studied in animal models. Both have complex effects on multiple endocrine systems (*10,62*). PCBs and dioxins have been shown to alter thyroid function in rodents by multiple mechanisms, including direct toxic effects on the thyroid gland, induction of thyroid hormone metabolism via the UDP-glucuronyl transferases, and interactions with thyroid hormone plasma transport proteins, particularly transthyretin (*9*). A number of investigators have evaluated the effects of maternal PCB exposure on thyroid function of rat pups (*63–65*). Pup serum thyroxine (T_4) levels are markedly reduced by PCB or dioxin exposure, but the levels of the active form of the hormone, triiodothyronine (T_3), are generally unchanged, or only slightly reduced. A relationship between exposure to dioxins and PCBs and alterations in thyroid hormones has also been reported in human infants (*66*). Infants exposed to higher levels of PCBs and dioxins had lower free T_4 levels and higher thyroid-stimulating hormone levels. Thyroid hormone is transported to the brain as T_4 and then converted locally to T_3 (*67*). Based on this knowledge, it has been argued that the dramatic reductions in serum T_4 reported in rats after perinatal PCB exposure could place the brain at special risk for hypothyroid-related effects (*68*). However, recently Morse et al. (*64*) found that, although both serum and brain T_4 levels were reduced after fetal PCB exposure, brain T_3 levels remained normal or near normal. To complicate the situation even further, a recent report suggests that PCBs may actually act as thyroid hormone mimics in the brain (*69*). Exposure to the PCB mixture Aroclor 1254 caused marked reductions in circulating T_4 concentrations, yet elevations in the expression of two key thyroid-hormone responsive genes, RC3/neurogranin and myelin basic protein, were observed in the developing brain. Chemical goitrogens such as propylthiouracil and methimazole reduce the expression of these same genes (*70,71*).

Commercial PCB mixtures have long been known to be estrogenic (*11,12*), but more recent studies focusing on individual PCB congeners have revealed a complex array of estrogenic and antiestrogenic effects (*10*). Certain congeners appear to act as estrogens in some assays and antiestrogens in others. Until recently, coplanar PCBs and dioxins were considered to be strictly antiestrogenic, but it now appears that coplanar PCBs can act as estrogens in some assays (*72,73*). PCBs and dioxins can also disrupt androgen production (*74*). The ability of dioxins to act as antiestrogens and antiandrogens has spawned a number of studies assessing the effects of *in utero* exposure on

Table 1. Effects of synthetic chemicals on endocrine and cognitive function.

Compound	Estrogen/ androgen	Thyroid	Glucocorticoids	Alters cognitive function?	References
Industrial chemicals					
Bisphenol A	A–; E+	?	?	?	
PCBs, dioxins, and furans					
Dioxins	A–; E–	Mixed (↓T_4; unchanged or ↓T_3; unchanged or ↑TSH)	Mixed (↑C; ↓C; unchanged or ↑ACTH)	Yes	(*85,86,94,95*)
PCBs	E+/–; A–	Mixed (↓T_4; unchanged or ↓T_3; unchanged or ↑TSH)	↓C	Yes	(*82–84,87,88*)
PCDFs	E–	↓T_4; ↑TSH	?	?	
Pentachlorophenol	E+; A–	G; ↓T_4	?	?	
Phthalates					
Butylbenzylphthalate	A–; E+	?	?	?	
Diethylhexylphthalate	?	↓T_4	?	?	
Di-*n*-Butylphthalate	E+	?	?	?	
Alkylphenols					
p-Nonylphenol	A+; E+	?	?	?	
Organochlorine pesticides					
Alachlor	E+	↓T_4; ↑T_3; ↑TSH; G	?	?	
Chlordane	A–	G	↓C (females) ↑C (males)	Yes	(*142*)
Chlordecone (Kepone)	E+	?	Mixed (↓C or no change)	Yes	(*128,132–134*)
DDT	A–;E+	↑T_3; ↓PBI; G	↓C; ↓response to ACTH	Yes	(*128,135–137*)
DDE	A–;E+	G; ↓I uptake	↓C; ↓response to ACTH	?	
Dieldrin	A–;E+	G; ↓PBI	?	Yes	(*123–126*)
Endosulfan	E+	↑T_4; ↓T_3; G	?	Yes	(*129–131*)
Heptachlor	A–	?	↓C	?	
Lindane	E+/–	↓T_4; ↓T_3; ↑TSH; ↓PBI; G	?	Yes	(*127,128,143*)
Oxychlordane	?	G	?	?	
Other pesticides/herbicides					
2,4-D	A–	↓PBI; I uptake	?	Yes	(*144*)
Atrazine	A–;E–	Mixed (↑T_3; ↑T_4; ↓T_3)	?	Yes	(*145*)
Heavy metals					
Cadmium	E–	↓T_4; ↓T_3; G	Mixed (↑C; ↓C; or no change)	Yes	(*146,147*)
Mercury	A–; E–	↓T_3; ↓I uptake	Mixed (↓ response to ACTH; or no change)	Yes	(*148,149*)
Lead	A–;E–	Mixed	↑C	Yes	(*110–121*)

Abbreviations: A+, androgenic; A–, antiandrogenic; ACTH, adrenocorticotropic hormone; C, corticosterone; 2,4-D, 2,4-dichlorophenoxyacetic acid; E+, estrogenic; E–, antiestrogenic; G, goiter; I, iodine; PBI, protein-bound iodine; PCDF, polychlorinated dibenzofurans; TSH, thyroid-stimulating hormone; ?, unknown.

neuroendocrine function, reproductive behavior, and CNS morphology of male rats (*75–77*). Demasculinization and feminization of reproductive behavior, as well as feminization of neuroendocrine function, have been reported, but the only study that assessed CNS morphology did not find any evidence of altered sexual differentiation in the brain (*76*), so the mechanism for these effects remains uncertain. In contrast to the wealth of data available for dioxin, there are few studies that assess reproductive behavior and neuroendocrine function after *in utero* PCB exposure.

Early PCB exposure can alter function of the HPA axis (*13*), suppressing basal and stimulated corticosterone levels, but effects on this system have been less extensively studied than the estrogenic and thyrotoxic effects. High doses of dioxin alter adrenal steroid function in adult animals (*78,79*), but the effects of *in utero* exposure on functioning of the HPA axis have not been assessed. Glucocorticoid receptor binding was downregulated in both the palate and thymus after early dioxin exposure (*80,81*). This suggests that there may be alterations in glucocorticoid receptor expression in other tissues, including the brain, after early dioxin exposure.

In summary, PCBs and dioxins have a number of documented endocrine-disrupting effects, which could act individually or in concert to alter CNS development and cognitive function. Neonatal hypothyroidism has profound effects on brain development and cognitive function. Many investigators have hypothesized that PCBs and dioxins alter behavioral function through their actions on thyroid hormones (*1,9*). Others have suggested that it is more likely that the actions of PCBs and dioxins on multiple hormone systems interact in complex ways to produce CNS effects (*55*).

Is there evidence to support the contention that PCBs and dioxins impair cognitive function through their endocrine-disrupting actions? It is clear from laboratory animal studies that developmental exposure to PCB mixtures or *ortho*-substituted PCB congeners results in long-lasting deficits in learning and memory. The evidence for learning deficits after exposure to dioxin or coplanar PCB congeners is not as clear. In fact, under some circumstances exposure to dioxin may facilitate learning. Early studies in monkeys exposed to complex mixtures of PCBs via maternal transfer during gestation and lactation found long-term deficits in spatial learning and memory (*82*). The monkeys were impaired on two types of spatial learning tasks: spatial discrimination-reversal learning and delayed spatial alternation. The deficit on the spatial alternation task was particularly striking. The PCB-exposed monkeys were never able to achieve control levels of performance, even after an extended period of testing. This pronounced deficit in spatial learning was observed when the monkeys were 4–6 years old, even though they had not been exposed to PCBs since they were weaned at 4 months of age. The monkeys were equally impaired at short and long delays, suggesting a deficit in learning or attentional processes rather than memory.

More recently, Rice and Hayward (*83*) exposed monkey infants to a mixture of PCB congeners formulated to represent the PCBs typically found in human breast milk, from birth to 20 weeks of age. Beginning at 3 years of age, the monkeys were tested on a series of learning tasks. As in the earlier study, the PCB-exposed monkeys showed a clear impairment in their ability to learn a delayed spatial alternation task. Again, the impairment in spatial alternation was interpreted as a learning decrement rather than a deficit in memory. Later, the monkeys in the Rice study were tested in several operant schedules, including a multiple fixed interval-fixed ratio schedule (*84*). The PCB-exposed monkeys showed retarded acquisition of the fixed interval schedule. The results of this study are particularly noteworthy because the tissue levels of PCBs after exposure were similar to the tissue levels typically observed in the human population.

In contrast to PCB-exposed monkeys, monkeys exposed to dioxin during development did not show any impairments in spatial learning (*85*). In fact, they did slightly better than control monkeys on both spatial discrimination-reversal learning and delayed spatial alternation (*86*). The dioxin-exposed monkeys were, however, impaired in their ability to learn nonspatial discrimination-reversal problems using color or shape as the relevant cues (*85,86*). Based on these discrepant findings in PCB- and dioxin-exposed monkeys, it has been suggested that the impaired spatial learning in the PCB-exposed monkeys could be related to the non–dioxin-like, *ortho*-substituted PCBs present in the mixtures (*86*).

Later rodent studies using individual *ortho*-substituted and coplanar PCB congeners support this hypothesis. Rats exposed to any of three different *ortho*-substituted PCB congeners (2,4,4′-trichlorobiphenyl; 2,3′,4,4′,5-pentachlorobiphenyl, or 2,2′,4,4′,5,5′-hexachlorobiphenyl) showed impaired learning on a delayed spatial alternation task (*87*). However, a fourth *ortho*-substituted congener (2,2′,3,5′,6-pentachlorobiphenyl) did not cause spatial learning deficits, demonstrating that not all *ortho*-substituted PCB congeners have the same effects (*88*). As in both monkey studies, the rats with spatial alternation deficits were equally impaired at short and long delays, suggesting a decrement in learning or attentional processes. The same rats showed no impairments in learning a working memory task on the eight-arm radial maze. The spatial alternation deficit was present only in female rats. Small group sizes had precluded analyzing for sex differences in the monkey studies, so this finding came as a surprise.

More recently, rats exposed to the PCB mixture Aroclor 1254 were tested on a working-reference memory task on a 12-arm radial maze and a spatial reversal learning task using operant procedures (*89,90*). Sex-specific deficits in spatial learning were again observed. However, in these studies using a complex PCB mixture rather than individual congeners, deficits were observed primarily in male rats. The PCB-exposed male rats showed impairments in both working and reference memory on the radial arm maze, whereas the females were not impaired on either (*89*). The PCB-exposed males also showed a deficit on the first reversal of the spatial reversal learning task (*90*). PCB-exposed female rats were not impaired on the radial arm maze task but showed a learning deficit that emerged on the later reversals of the spatial reversal learning task—a pattern very different from that seen in the males. Analyses of response patterns on the reversal learning task revealed underlying functional differences that explained the different effects in male and female rats. The first reversal deficit in the male rats was attributable to a tendency to perseverate to the previously correct response site. The female rats did not show an increased tendency to perseverate to the previously correct lever. Instead, they spent a longer period responding randomly to the two levers before finally beginning to associate the reward with the new response site. Whereas the males show a deficit early in the task and were able to overcome the deficit on later reversals, the female deficit only emerged on later reversals when the control animals were becoming proficient at performing the task.

The reason for the heightened sensitivity of female rats on some tasks and males on others is unknown. However, the discrepancies between studies could be partially explained by the fact that the animals in the earlier study were exposed to individual *ortho*-substituted PCB congeners, whereas those in the later studies were exposed to a complex PCB mixture. Certain effects of PCB mixtures could be either masked or unmasked when specific congeners from the mixture are given individually. Nevertheless, the sex differences in responses suggest that hormonal influences may be involved. A spatial learning deficit such as that seen in the female rats exposed to *ortho*-substituted

PCB congeners would be consistent with a reduction in thyroid hormone. However, circulating thyroid hormones levels were assessed in litter mates of the tested animals (*65*), and it seems unlikely that alterations in thyroid hormones were directly mediating the learning deficit. The three PCB congeners had roughly equal effects on spatial learning but markedly different effects on thyroid hormone levels. One congener had no effect on serum T_4, one moderately reduced T_4 levels, and one dramatically reduced serum T_4 levels. Furthermore, males and females showed equal reductions in serum T_4, but only females were impaired on the learning task. The learning deficits in the latter studies would also be consistent with a reduction in thyroid hormone, but again only one sex was affected (this time males), whereas Aroclor 1254 is known to dramatically reduce circulating T_4 levels in both males and females (*63*). This evidence is indirect, but it argues against direct mediation of the learning deficit by reduced thyroid hormone. Koopman-Esseboom and colleagues (*91–93*) also failed to find a relationship between alterations in nervous system function and thyroid hormone levels in PCB-exposed human infants. As discussed above, Morse et al. (*64*) found that pups exposed to PCBs during fetal development had reduced serum and brain T_4 levels, but induction of type II 5′-deiodinase within the brain resulted in the maintenance of normal or near normal brain T_3 levels. Because T_3 is the active form of the hormone, these results also argue against a reduction in thyroid hormone as the mediating factor in PCB-induced learning deficits.

The extent to which changes in other hormonal systems, or interactions of altered thyroid function with other hormonal systems, may play a role in mediating PCB-induced learning deficits has not been addressed. As discussed above, thyroid hormones are involved in mediating glucocorticoid receptor expression in the brain and can also influence the actions of estrogen in the brain (*49,56*), both directly and indirectly. As both the glucocorticoid-mediated stress response and estrogen's role in the brain are markedly sexually dimorphic, an interaction of altered thyroid hormone levels (or altered thyroid hormone action) with one or both of these systems could potentially explain the sex-specific effects that have been observed. In fact, given the complex and sexually dimorphic pattern of PCB effects on cognitive function, this seems like a reasonable scenario. If this were the case, a clear relationship between thyroid hormone concentrations and cognitive deficits would not necessarily be present. Thus, a reasonable first step to pursuing this line of research would be to determine if cotreatment of PCB-exposed animals with thyroid hormone ameliorates any of the PCB-induced cognitive deficits. If so, follow-up studies could be designed to determine if interactions of reduced thyroid hormone with the estrogen or glucocorticoid systems are involved in mediating those specific cognitive deficits. If not, follow-up studies could focus instead on determining whether particular cognitive deficits are mediated directly by changes in one of these other hormone systems. The various cognitive effects that have been reported in males and females after PCB exposure could be mediated by several different hormonal mechanisms, and sorting out the mechanisms for each behavioral effect will require a focused, stepwise approach.

In contrast to the findings for *ortho*-substituted PCBs, coplanar PCBs and dioxin did not impair spatial learning in rats (*94*). Dioxin-exposed rats did not differ from controls on delayed spatial alternation and actually made fewer errors than control rats on the radial arm maze. Although both sexes showed a trend toward better performance, the effect was more pronounced in dioxin-exposed male rats. Rats exposed to coplanar PCBs showed a similar but less striking improvement in learning. In a later study dioxin-exposed rats were tested on additional spatial and nonspatial learning tasks to determine whether the apparent facilitation in spatial learning was specific to the radial arm maze or would generalize to other tasks (*95*). The improved learning on the radial arm maze was replicated, but was found to be specific to the radial arm maze. It did not generalize to other spatial learning tasks, including the Morris water maze, which like the radial arm maze is primarily hippocampally-mediated. In addition, the dioxin-exposed rats showed a deficit in nonspatial, cue-based discrimination-reversal learning. This is similar to what was observed previously in dioxin-exposed monkeys (*86*). Another study compared the performance of dioxin-exposed litter mates on two different radial arm maze tasks. The first was the original 8-arm radial maze task in which all 8 arms were baited, and the second was a 12-arm radial maze task in which only 8 of the 12 arms were baited (*96*). Dioxin exposure improved performance on the 8-arm maze task in which all arms were baited, but not on the 12-arm maze task in which only a subset of the arms were baited, further highlighting the specificity of this effect.

Recently Rice and Hayward (*97,98*) tested rats developmentally exposed to a coplanar PCB congener on a series of learning tasks. The coplanar PCB-exposed rats did not differ from controls on delayed spatial alternation (*97*), visual-spatial or sustained attention (*98*) or fixed interval, fixed ratio, progressive ratio, and differential reinforcement of low rate operant tasks (*99,100*). These findings reinforce the fact that the cognitive effects of dioxin and coplanar PCBs are limited in scope, with the primary effect being an improvement in working memory, which is seen only in specific radial arm maze tasks.

It is not clear whether the cognitive changes observed after perinatal dioxin exposure are hormone mediated. However, dioxin has been shown to alter functioning of the HPA axis in adult animals (*78,79*) and to down-regulate glucocorticoid receptor expression in several tissues during development (*80,81*). Previous studies have shown that manipulations of circulating corticosteroid levels (*101*) or hippocampal glucocorticoid receptor expression (*102*) can result in improved spatial learning. Thus, it is conceivable that early dioxin exposure facilitates spatial learning on the radial arm maze by permanently altering hippocampal glucocorticoid receptor expression. This hypothesis could be tested by measuring glucocorticoid receptor expression in the hippocampus after developmental exposure to dioxin, and correlating receptor expression with spatial learning on the radial arm maze.

In summary, despite speculation by many investigators (*1,9,56*), there is currently no direct evidence mechanistically linking either PCB- or dioxin-induced changes in cognitive function to altered endocrine function. It is important that future studies directly assess whether there are mechanistic relationships between altered endocrine function and altered cognitive function after early exposure to these ubiquitous and persistent chemicals.

Lead. Lead exposure early in development has been shown to disrupt multiple endocrine systems, including the gonadal steroids (*103*), adrenal steroids (*104,105*), and thyroid hormones (*105*). The effects of developmental lead exposure on gonadal function are complex and appear to involve multiple sites of action. *In utero* exposure has been reported to reduce circulating estradiol and luteinizing hormone levels, delay the onset of puberty and produce irregular estrous cycling in female rats, and reduce testosterone levels, sperm counts, and masculine sexual behavior in male rats (*103,106*). The volume of the SDN-POA was also reduced in male rats (*106*). The effects of developmental lead exposure on the sexually dimorphic pattern of testosterone metabolism are variable. A partially demasculinizing (20–40%) decrease in adult CYP2C11-dependent 2-α and 16-α hydroxylation and CYP2C11 apoprotein expression have been observed, along with a delay in the development of the sexually dimorphic pattern of hepatic P450 and

sulfotransferase enzymes at puberty (*107*). The findings in both male and female rats are consistent with dual sites of action at the level of the hypothalamus-pituitary and directly on gonadal steroidogenesis (*103*).

The effects of lead exposure on adrenal steroids and thyroid hormones have been less extensively studied, but both adult (*105*) and developmental (*104*) exposure has been shown to elevate plasma corticosterone levels. The evidence for altered thyroid function is mixed. Some investigators report changes in circulating thyroid hormones after lead exposure, whereas others do not (*8*). Although growth hormone is not a focus of this report, it is important to note that early lead exposure also disrupts growth hormone (*107*), and it is possible that some of the cognitive effects of early lead exposure could be related to disruption of the growth hormone system (*108*).

Few, if any, developmental neurotoxicants have been more extensively evaluated for cognitive effects than lead. A large number of independent investigators have reported cognitive impairments in developmentally lead-exposed rodents and primates, and a wealth of epidemiologic data points to cognitive deficits in lead-exposed children as well (*109*). The effects in primates and rodents include deficits in reversal learning (*110–112*), delayed spatial alternation (*113–115*), and schedule controlled behavior, particularly fixed interval and delayed reinforcement of low rates (*116–119*). A leading hypothesis to explain the deficits exhibited by lead-exposed animals on many of these tasks is that the animals continue to respond to a previously correct response site when the reward contingencies change (perseveration), and/or to respond excessively and inappropriately.

Developmentally lead-exposed monkeys were impaired on both spatial and nonspatial discrimination-reversal learning (*110,120,121*). In general, they could learn the initial discrimination problem but made more errors when the reward contingencies changed on the reversals. Deficits were especially pronounced on the first reversal (*110*). Lead-exposed rats showed a similar pattern. They could learn an initial olfactory discrimination but were impaired on the subsequent reversals (*112*). The discrimination-reversal deficit in the rats was not due to perseveration. Analyses of the animals' response patterns indicated that the lead-exposed animals spent longer responding randomly to the two levers before finally beginning to associate the reward with the new cue. They did not perseverate to the previously correct cue. On spatial alternation tasks, both lead-exposed monkeys and rats showed deficits in percent correct responses that were constant across a series of delays (*113,115*). As discussed above, this pattern suggests a deficit in learning or attentional processes rather than in memory. On fixed interval operant schedules, which require the animal to wait a fixed period of time for reinforcement, lead-exposed monkeys and rats showed higher response rates and shorter inter-response times (*116,118*). Similarly, on a delayed reinforcement of low rate schedule, lead-exposed monkeys were slower to learn to withhold their responding to the low rate necessary for reinforcement (*119*). In summary, the nature of the cognitive deficits on a number of different tasks suggests that cognitive processes controlled by the prefrontal cortex including selective attention and the ability to inhibit inappropriate responding appear to be particularly sensitive to lead exposure. However, the deficit on discrimination-reversal learning appears to be the result of a decreased ability to learn new contingencies (i.e., an associative deficit), rather than a deficit in inhibitory control (*112*).

Although lead has been shown to disrupt multiple endocrine systems, little attention has been paid to the role changes in endocrine function might play in mediating the cognitive effects of developmental lead exposure. Interestingly, lead has recently been found to impair choroid plexus transthyretin production (*122*). Because transthyretin is responsible for transport of thyroid hormones into the brain, it has been suggested that lead could impair brain development by depriving the CNS of thyroid hormones. However, there do not appear to be any studies measuring thyroid hormone levels in brain after lead exposure or relating such changes to cognitive deficits. This could prove to be an important area for future research. Developmental lead exposure also increases circulating corticosterone levels, which could potentially alter glucocorticoid receptor expression in the brain. Finally, as discussed earlier, developmental lead exposure decreases circulating testosterone levels and demasculinizes the preoptic area in male rats. Thus, lead could potentially alter hippocampal morphology and spatial learning in male rats. However, the later mechanism is perhaps not as likely since the cognitive effects of early lead exposure do not appear to be sexually dimorphic.

Organochlorine pesticides. As indicated in Table 1, many of the persistent organochlorine pesticides including DDT (and its breakdown product DDE), Alachlor, chlordane, chlordecone, dieldrin, endosulfan, heptachlor, and lindane have been identified as endocrine disruptors (*8,59*). Most are weakly estrogenic and some also alter thyroid or adrenal function. Some organochlorine pesticides have been evaluated for cognitive effects, but the majority of the studies involve adult exposures. The question as to whether there are cognitive effects in developing organisms is largely unanswered.

Dieldrin is a persistent chlorinated hydrocarbon pesticide that was used as a broad range insecticide until the U.S. EPA restricted its use in 1974. Although no longer in use, dieldrin can remain undegraded in soil for many years. It is lipophilic and readily bioaccumulates in animals and humans. Dieldrin exposure during adulthood resulted in deficits in visual discrimination-reversal learning in both sheep (*123*) and squirrel monkeys (*124*) and caused rats to make more errors on a zig-zag maze (*125*). In contrast, one study of perinatal exposure to dieldrin reported facilitated retention of learning on a symmetrical maze (*126*).

Studies of other organochlorine insecticides have been limited almost exclusively to acute exposures followed by testing in simple active or passive avoidance paradigms and have yielded mixed results. Lindane is a chlorinated hydrocarbon insecticide as well as a human and veterinary ectoparasiticide, which continues to be prescribed for the treatment of body lice in humans. It is a powerful neurostimulant capable of causing convulsions and electroencephalogram disturbances. Acute exposure to lindane in the early postnatal period resulted in an apparent facilitation of acquisition on a passive avoidance task (*127*). However, the lindane-exposed animals also showed significant reductions in spontaneous motor activity, so these data must be interpreted with caution. Changes in locomotor activity can influence avoidance behavior, with hypoactivity favoring correct responding in passive avoidance paradigms and hyperactivity favoring correct responding in active avoidance paradigms. Acute exposure to lindane during adulthood did not alter acquisition of a passive avoidance task, but did cause significant deficits in retention when animals were retested 7 days after the original training (*128*). In contrast to the passive avoidance task, lindane-exposed rats did show deficits in acquisition of an active avoidance task. Responding between trials was not significantly different between groups, suggesting that the effect of lindane on active avoidance learning was not due to a reduction in locomotor activity.

Endosulfan is an insecticide in current use. Chronic exposure of either immature or adult rats to endosulfan resulted in learning and memory deficits in an active avoidance task where the rats were required to jump to a pole suspended from the ceiling of the chamber in order to avoid shock (*129–131*). Chlordecone, or kepone, is a polycyclic chlorinated hydrocarbon that was used primarily as an insecticide. Studies assessing the cognitive effects of chlordecone have yielded mixed results. Tilson et al. (*132*) reported

that acute exposure to chlordecone in the early postnatal period did not result in any deficits in learning of a two-choice visual discrimination-reversal task. Larger doses of chlordecone given to adult rats also did not result in any deficits in acquisition or retention of a step-through passive avoidance task (*128*). Acute exposure of preweanling rats to chlordecone did not lead to deficits in acquisition of passive avoidance, but when the rats were retested 6 days after the original training, a memory deficit was observed (*133*). In contrast, pups were impaired on both learning and retention of active avoidance tasks (*134*). DDT, once widely used in the United States as an insecticide, has been banned from use since 1973. However, it continues to be used in other parts of the world and continues to present a health hazard. Tilson et al. (*128*) found few effects of DDT on the ability of rats to learn active and passive avoidance tasks. However, other researchers have reported impaired acquisition on active avoidance tasks (*135,136*), as well as impaired retention on passive avoidance tasks (*135–137*).

In summary, the data on cognitive effects of organochlorine pesticides are sparse, and in most cases, the tests that have been used to measure cognition are simplistic. The results do suggest that many of the organochlorine pesticides have the ability to interfere with the acquisition and use of new information. However, the literature on both the endocrine and cognitive effects of organochlorine pesticides remains too sketchy to form useful hypotheses about the possible endocrine mediation of cognitive deficits.

Other chemicals. A number of other chemicals including compounds such as phthalates and bisphenol A, which are used in the manufacture of plastics, and alkylphenols, which are breakdown products of chemicals used in detergents, have been identified as endocrine disruptors. Most of these were first identified as having estrogenic activity (*59*), but some were later found to disrupt thyroid function as well (*8*). At this time, the data on cognitive effects from any of these compounds is sparse (*138*).

Concluding Remarks

Although it is reasonable to hypothesize that central nervous system effects of endocrine-disrupting chemicals are mediated by interference with hormone action, mechanistic studies establishing causal relationships between the hormonal actions of environmental chemicals and their cognitive effects have not been conducted. At present, the only study we are aware of that establishes a direct link between hormone disruption by an environmental chemical and nervous system dysfunction is a study by Goldey and Crofton (*139*), which showed that PCB-induced hearing loss closely resembles the hearing loss seen after propylthiouracil treatment and can be prevented by cotreatment of PCB-exposed pups with thyroid hormone. Our own research has demonstrated that if a relationship between alterations in thyroid hormones and PCB-induced cognitive dysfunction exists, it is likely to be considerably more complex. The complexity of this issue and the science needed to address it should not keep us from moving forward.

Mechanistic studies directly addressing the relationship between endocrine disruption and the documented cognitive deficits caused by chemical pollutants such as PCBs and lead are desperately needed. For example, thyroid hormone replacement studies similar to those used to investigate the relationship between PCB-induced reductions in circulating thyroid hormone concentrations and hearing loss would be a first step toward determining the role, if any, of reductions in thyroid hormones in mediating specific PCB-related cognitive deficits. However, as we embark on such studies it is important to keep in mind that it is unlikely that all of the cognitive effects of a particular compound such as PCBs will be mediated by a single mechanism. It is more likely that the multiple endocrine effects caused by PCBs interact in complex ways to produce the various cognitive effects that have been reported. Sorting out these interactions will require a focused, stepwise approach. It is also important to keep in mind that typical animal models in which high concentrations of the chemical are given during a narrow window of development may not be relevant to the human condition in which exposures are much lower and occur over an extended period of time. In future studies it will be important to use animal models that are more relevant to the human situation.

An important caveat is that endocrine disruptors such as PCBs and lead can also have direct effects on the nervous system, and these direct actions undoubtedly contribute to the cognitive deficits induced by these compounds. For example, PCBs have been shown to interact directly with ryanodine-sensitive calcium release channels, altering calcium signaling in neurons (*140*), and lead has been shown to act as an antagonist at the *N*-methyl-D-aspartate receptor (*141*). The relative importance of direct mechanisms versus indirect endocrine-related mechanisms in mediating the cognitive deficits induced by these compounds remains to be determined.

Finally, more extensive studies of the cognitive effects of other endocrine-disrupting chemicals such as organochlorine pesticides that are still in active use, components of plastics and cosmetics such as phthalates and bisphenol A, and alkylphenol breakdown products from detergents are desperately needed. These studies should be designed with the goal of determining mechanisms, not just screening for cognitive effects. It is only through the active and continued pursuit of this challenging research area that we will gain the knowledge we need to protect the health of future generations.

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