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**This is the author's manuscript**

*Original Citation:*

*Availability:*

This version is available <http://hdl.handle.net/2318/88647> since

*Published version:*

DOI:10.1111/j.1365-2826.2011.02229.x

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Published in final edited form as:

*J Neuroendocrinol.* 2012 January ; 24(1): 144–159. doi:10.1111/j.1365-2826.2011.02229.x.

## ENDOCRINE DISRUPTERS: A REVIEW OF SOME SOURCES, EFFECTS, AND MECHANISMS OF ACTIONS ON BEHAVIOR AND NEUROENDOCRINE SYSTEMS

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### Abstract

Some environmental contaminants interact with hormones and may exert adverse consequences due to their actions as endocrine disrupting chemicals (EDCs). Exposure in people is typically due to contamination of the food chain, inhalation of contaminated house dust, or occupational exposure. EDCs include pesticides and herbicides (such as diphenyl-dichloro-trichloroethane, DDT, or its metabolites), methoxychlor, biocides, heat stabilizers and chemical catalysts (such as tributyltin, TBT), plastic contaminants (e.g. bisphenol A, BPA), pharmaceuticals (i.e. diethylstilbestrol, DES; 17 $\alpha$ -ethynylestradiol, EE2), or dietary components (such as phytoestrogens). The goal of this review is to address sources, effects and actions of EDCs, with an emphasis on topics discussed at the International Congress on Steroids and the Nervous System. EDCs may alter reproductively-relevant or non-reproductive, sexually-dimorphic behaviors. In addition, EDCs may have significant effects on neurodevelopmental processes, influencing morphology of sexually-dimorphic cerebral circuits. Exposure to EDCs is more dangerous if it occurs during specific “critical periods” of life, such as intrauterine, perinatal, juvenile or puberty periods, when organisms are more sensitive to hormonal disruption, than in other periods. However, exposure to EDCs in adulthood also can alter physiology. Several EDCs are xenoestrogens, may alter serum lipid concentrations, or metabolism enzymes that are necessary for converting cholesterol to steroid hormones, ultimately altering production of E<sub>2</sub> and/or other steroids. Finally, many EDCs may have actions via, or independent of, classic actions at

cognate steroid receptors. EDCs may have effects through numerous other substrates, such as the aryl hydrocarbon receptor (AhR), the peroxisome proliferator-activated receptor (PPAR) and retinoid X receptor (RXR), signal transduction pathways, calcium influx, and/or neurotransmitter receptors. Thus, EDCs, from varied sources, may have organizational effects during development, and/or activational effects in adulthood, that influence sexually-dimorphic, reproductively-relevant processes or other functions, by mimicking, antagonizing, or altering steroidal actions.

## Keywords

xenoestrogens; diphenyl-dichloro-trichloroethane; methoxychlor; biocides; tributyltin; bisphenol A; diethylstilbestrol; ethynilestradiol; phytoestrogens; aryl hydrocarbon receptor; the peroxisome proliferator-activated receptor; retinoid X receptor

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## Introduction

Endogenous steroid hormones, during critical periods of development, organize sexual dimorphisms in brain and behavior and give rise to sex differences in later responses to steroid hormones (1, 2). These mechanisms have evolved over time to ensure the survival of species and maximize the fitness of each sex. This delicate balance may be at risk, in part because a growing number of contaminants in the environment can accumulate in exposed individuals and may have adverse consequences due to their action as endocrine disrupting chemicals (EDCs). Thousands of chemicals, some banned and some still in use, have been classified as EDCs. They produce their effects by mimicking, antagonizing, or altering endogenous steroid levels (androgens or estradiol, E<sub>2</sub>) via changing rates of their synthesis or metabolism and/or expression or action at receptor targets.

The goal of this review is to address some of the sources, effects and mechanisms of EDCs. The breadth of this topic precludes comprehensive coverage of all EDCs. As such, this review focuses on topics that have been part of the ongoing dialogue at The International Congress of Steroids and The Nervous System. First, the sources of common neuroendocrine disrupting compounds will be described. Second, the effects of EDCs to alter reproductively-relevant, sexually-dimorphic behaviors, and whether there are sex differences in the effects of EDCs, will be examined. Third, the role of EDCs for sexually-dimorphic, non-reproductive behaviors, and in sex-linked developmental disorders (neurodevelopmental, neuropsychiatric, neurodegenerative), is discussed. Fourth, the extent to which these effects of EDCs are differentially programmed (or expressed), based upon critical developmental periods is addressed. Fifth, the species differences in EDCs' effects, and the ecological systems issues (e.g. food chain), is considered. Sixth, the actions of EDCs via altering steroid metabolism, steroid receptor action, and non-traditional receptor targets, as well as altering gonadal steroid dependent neural circuits is discussed. Thus, this review summarizes some of the evidence that EDCs (such as those in Table 1) can profoundly alter reproductive responses following adult exposure and that EDC exposure can result in pervasive effects that extend throughout the life of their progeny (3, 4).

## Sources of Contaminants

There are varied sources of environmental contaminants. Typical human exposure occurs with environmental contamination of the food chain, especially fresh water fish and meat, contact with contaminated household dust, and occupational (5-10). Some were banned or otherwise removed from production years ago, but persist in the environment. For example, a family of industrial PCB compounds, often sold as mixtures (Aroclor), generally act as estrogen mimics and are still found in significant quantities in the environment, although

their manufacture in the U.S. was banned in 1977. In certain uses, PCBs can partially oxidize and themselves become contaminated by extremely toxic compounds, such as polychlorinated dibenzofurans (PCDFs). In some areas, PCB levels in drinking water ranged from 100 to 450 ng/l; in food products, levels were over 200 mg/kg fresh weight. PCB levels in occupationally-exposed workers ranged from 2.2 to 290 ppm in adipose tissue and blood concentrations in capacitor manufacturing workers were up to 3.5 µg/ml (11).

Other EDCs are high production volume chemicals found in a myriad of household products. Bisphenol A (BPA), for example, is present in polycarbonate plastics, including beverage and food storage containers, epoxy resins that line the interior of metal cans, and in the ink used for thermal paper receipts. Many textiles contain contaminants, such as flame-retardants, including tetrabromobisphenol A (TBBPA) and polybrominated diphenyl ethers (PBDE). Some individuals have also been exposed to contaminants with adverse effects due to medical (diethylstilbestrol; DES), dental (diglycidyl methacrylate), or dietary (phytoestrogens) interventions. Synthetic estrogens from anticonceptual pills, such as ethynilestradiol (EE2), are commonly found in surface water, because of their widespread use (12). Thus, exposure to EDCs is ubiquitous and unavoidable and there is growing concern that living in an EDC contaminated world may be contributing to adverse health trends, such as early puberty and infertility, because of growing evidence that a number of EDCs can produce varied effects (13), described below.

## Effects of EDCs to alter reproductively-relevant, sexually-dimorphic neuroendocrine systems and behaviors

Exposure to EDCs has been associated with a myriad of adverse reproductive outcomes including reduced female fecundity, longer time to conception, higher miscarriage rates, and decreased sperm motility (14-15). Studies examining the effects of EDCs on sexual maturation offer further evidence for a possible connection between EDCs and reproduction (16-17). Emerging evidence supports the long held suspicion that age at menarche is advancing in girls, particularly in developed countries (18-19). This observation has led to the hypothesis that exposure to EDCs could be a contributing factor (20-21). Exposure to EDCs has been associated with earlier age at menarche and sexual development in breast-fed girls (22), although some studies have shown the opposite effect, with girls exposed to EDCs showing delayed sexual maturation (23). This type of nonlinear response, where effects differ at low and high dosages may be typical for EDCs (24) and is a phenomenon that has raised concern over low dose exposure (25-26). Mixtures can also influence effects. For example, a report on exposure to EDCs and lead shows that it may advance and delay, respectively, age of menarche, indicating that EDC exposure in combination with lead and other toxicants needs to be considered when attempting to understand how exposure may influence reproductive health (22).

Adverse effects of EDC exposure on reproductive physiology have also been seen in numerous animal models, particularly when exposure occurs early in development (27-28). In mammal and other vertebrates, EDC exposure during development alters both male and female gonad development, reduction in sperm counts, abnormal sperm, and changes in sexual behavior, such as demasculinization and feminization of male offspring (for reviews see 29-31). Lactational exposure of rats to Aroclor 1254 (8, 32, or 64 mg/kg to dams) decreased mating behavior, reproductive success, and ventral prostate and testicular weights of male pups in adulthood (32). Females exposed had delayed puberty, decreased uterine weight, impaired fertility, and irregular estrous cycles (33). As well, acute exposure to Aroclor 1254 (from neonatal day 1 to 7) significantly reduced lordosis quotients of adult female rats in both a paced and non-paced testing paradigm (34). Exposure to 400 ng/kg/day of 17 $\alpha$ -ethinyl estradiol *in utero* and during lactation induces sterility in exposed rat pairs

(35) because it disrupts the estrous cycle with females showing permanent estrus as early as at 60 days of age (36). Lower, environmentally-relevant dosages of 4 ng/kg/day produces significant alterations in fecundity (35). In egg exposure to a variety of EDCs permanently alters male copulatory behavior of the Japanese quail (37-39). These data clearly indicate that developmental exposure to EDCs can adversely affect sexual development in animals, supporting the hypothesis that similar effect may be occurring in people; however, there are different effects depending upon the chemical nature of the EDC, the type of interaction with hormone receptors, and when in development exposure occurs. Because there are many factors that contribute to reproductive functioning, and many ways in which EDCs may alter these factors, it is important to conduct systematic studies in animal models in order to differentiate the specific effects of EDCs on reproductive parameters. Timing of exposure is a crucial factor when considering potential behavioral and endocrine consequences in both animals and people.

### **The role of EDCs for sexually-dimorphic, non-reproductive behaviors and incidence of sex-linked developmental disorders**

Many behaviors, and the neuroendocrine pathways that regulate them, are sexually dimorphic. These sex dimorphisms reflect adaptive differences for behavioral strategies in coping as a result of sexual selection. Disruptions in these behaviors may lead to reduced social adaptation and impaired responsiveness to environmental demands (40). Exposure to EDCs can alter or eliminate these sex differences and produce striking differences between behavioral responses of males and females that were developmentally exposed to EDCs. This potential for altering sexually-dimorphic behaviors may be relevant for concerns regarding increased developmental, cognitive, and/or emotional disabilities reported over the past 30 years (41).

### **EDCs' Effects on Neurodevelopmental Processes**

EDCs may have particularly significant effects on neurodevelopmental processes because many accumulate in fatty tissues of exposed individuals, are readily transferred across the placenta prenatally, and are expressed in breast milk. In the past, much of the human and wildlife health-related research on pesticides and other EDCs has dealt with more or less immediate toxicity at relatively high dosages, or has been concerned only with the primary mode of action. Field and laboratory studies using different animal models indicate that developmental exposure to low doses of these compounds can affect behaviour in a sex-dimorphic fashion. The mechanisms by which pesticides and other compounds exert EDC-like effects at environmentally-relevant dosages might be different from those involved in their acute neurotoxic effects, and a direct interference with steroid/pituitary/thyroid hormones cannot be excluded.

Notably, there are significant increases in the incidence of attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASDs, 42). Development of psychological disorders with sex-biased prevalence rates may be associated with the disruption of developmental trajectory and/or maturation of the sexually-dimorphic brain (43). Autism spectrum disorders (44), attention deficit disorder, and depression (45), are disorders with sex-biased prevalence rates. Disruption of hormonally-controlled, sexual differentiation of the brain, may increase vulnerability for these, or other, sexually-dimorphic functions. Exposure to endocrine disrupters e.g., PCBs, BPA that disrupt hormone function during critical periods of prenatal development may influence susceptibility to sex- and/or hormonally-differentiated aspects of behavior (46-47). Males are more vulnerable to these disorders, which have salient motor and arousal components. Thus, the increase in the

incidence of these disorders may reflect effects of EDCs on male-typical levels of arousal and/or stress responsiveness.

Environmental factors, such as EDCs, in early life can lead to long-term changes in social and/or sensory function, which are features of some developmental disorders. Multiple types of developmental disorders share many characteristics, including a developmental timeline and dysregulation of both social behavior and somatosensory function. Sensory impairment is higher in children with neurodevelopmental disorders than in the general population (48). In individuals with ASD, sensory abnormalities are highly prevalent (30-100%; (49). In addition to atypical sensory function, children with developmental disabilities often manifest social problems, such as aggression (50). Thus, it is important to further understand factors that increase susceptibility to psychological disorders (as indicated by differences in expression of sex-typical behavior).

Organophosphorous insecticides (OPs) make up about 50% of all insecticides used in the world, and are the subject of intensive investigation for their suspected developmental neurotoxicity. These compounds, largely used in agriculture, home and garden for pest control, exert their acute neurotoxic effects through cholinergic hyperstimulation. Since 2004, several epidemiological studies involving children from both agricultural and urban communities have indicated that developmental OP exposure may affect children's neuropsychological maturation (for a review see (51)). Most of experimental research in this field has focused on the OP chlorpyrifos (CPF) the most widely applied compound in the OP class in US and Europe (52). The mechanisms by which CPF interferes with brain and behavioral maturation at environmentally relevant dosages differ from those involved in its acute toxic effects (53). Gestational and neonatal exposure to CPF impairs neuronal differentiation, synaptogenesis and gene expression in rats, and affects neural systems further than the cholinergic one, such as serotonergic and dopaminergic transmission, in a sex-dimorphic fashion (54-55).

The neurobehavioral effects of *per os* gestational and/or neonatal exposure to CPF have been extensively characterized in mouse models. Overall, data show that CPF differentially affects behavioral responses in the two sexes (56-59). *In utero* exposure to CPF modified ultrasound emission in neonates and had pro-aggressive effects in adolescent and adult male mice in a social interaction test. In adult females, prenatal CPF altered the pattern of social interaction, either with same-sex partners or with a male-intruder during a test of the defence of the nest. These behavioral changes are accompanied by permanent alteration in expression of the hypothalamic neuropeptides, oxytocin and vasopressin, which are key effectors of social and reproductive behavior in mammals. Furthermore, decreased behavioural responsiveness to antidepressant drugs acting on serotonin transporter in CPF-exposed males, confirms that serotonergic neurotransmission is implicated in the behavioural effects of CPF (60,61).

In a study still in progress (Calamandrei et al., unpublished), pregnant females have been fed throughout gestation and lactation with a CPF-supplemented diet, to mimic the human exposure scenario. At adulthood, CPF-exposed males display enhanced investigative response towards either familiar or unfamiliar same-sex individuals, whereas CPF females show delayed onset of social investigation and lack of reaction to social novelty. In addition, sexually-dimorphic effects have been revealed so far in the hypothalamus: CPF females show diminished expression of the oxytocin precursor neurophysin I, increase of estrogen receptor (ER)  $\alpha$  and decrease of ER $\beta$ . ER $\alpha$  and ER $\beta$  in the hypothalamus/amygdala circuitry are known to exert a facilitatory role in oxytocinergic control of social recognition in rodents (62). These preliminary data suggest that developmental CPF interferes with maturation of important sexually-dimorphic neuroendocrine pathways.

Together, these experimental findings support the hypothesis that *in utero* or neonatal exposure to extremely low dosages of CPF influences neurobehavioral development, affects multiple signalling systems, including those controlling reproduction, with effects on behavior that are long-term and differ in the two sexes. The case of CPF might be prototypic: it is likely that other environmental neurotoxicants, not yet considered as EDCs, might indeed interfere with neuroendocrine functions, possibly concurring to increase vulnerability to sex-biased neurodevelopmental disorders in children.

### Cognitive Function

There may be sex-specific effects of estrogenic EDCs on spatial learning, which typically favors males. Yu-Cheng boys that were prenatally exposed to high levels of PCBs and PCDFs, when their mothers were accidentally exposed to these contaminants in rice oil, show more disrupted cognitive development, mainly spatial function, than did exposed girls (63). Gestational and lactational exposure to ortho-substituted PCBs produces spatial deficits at adolescence in male mice (64). Prenatal exposure to PCBs 28 or 153 had dose-dependent effects to slow acquisition of the radial arm maze task for female, but not male, rats (65). Notably, gestational exposure to Aroclor 1254 (vs vehicle) produced more working memory errors in the radial arm maze task for male rats, but not female rats (66). Another study showed that of rats exposed *in utero* and postnatally through weaning to Aroclor 1254, males were more likely to perseverate following reversal in the radial arm maze task, whereas females were more likely to have association deficits (67). A small body of literature has shown that EDCs may facilitate cognitive functions in some cases. For example, exposure of male rats to 17 $\alpha$ -ethinyl estradiol during development (from gestation day 5 to weaning) results in enhanced working memory during a Morris water maze hidden platform acquisition test (68). These observations again highlight the potential for non-linear responses and the complexity of interpreting the ethological-relevance of behavioral outcomes. Collectively, the literature supports the conclusion that exposure to EDCs from early development to adulthood alters spatial memory and there may be sex differences in these effects.

### Emotional Reactivity and Stress Responses

Gestational or early life exposure to EDCs may influence arousal. It has long been known that exposure to heavy metals, such as lead or mercury, can lead to behavioral disorders in people (69). Epidemiology studies of populations exposed to high levels of PCBs reveal that EDCs may produce similar outcomes (70). Children exposed to PCBs, lead, or mercury show inattention, hyperactivity, disordered and/or mildly antisocial behavior (41, 45). There is also evidence for increased aggression (69, 72). Prenatal BPA exposure has now been linked with increased externalizing behaviors in 2-year old girls (73). Atypical behaviors in infancy and childhood, including compromised social communication, have also been associated with prenatal exposure to phthalates (74) compounds found in soft plastics that act as androgen antagonists.

In animal models, developmental exposure to EDCs produces similar effects. Exposure to PBDE 209 on post-natal day 3 disrupts spontaneous motor behavior in rats (75). Another study that administered BPA to five-day old rats observed hyperactivity at 4-5 weeks of age, which was associated with changes in dopamine function in midbrain (76). Mice exposed perinatally (from gestation day 11 to postpartum day 8) to BPA or methoxychlor, showed a reversal of sex differences at periadolescence in exploratory activity in a novel open field, elevated plus maze, and social interactions with a conspecific (77,78). Similarly, anxiety, spatial learning and memory, and passive avoidance memory were found to be altered in mice exposed to BPA (40 or 400 g/kg/day) across adolescence and early adulthood, with sex differences eliminated or reversed on many tasks (79). Similar effects of BPA have also

been reported in deer mice (*Peromyscus maniculatus*) (80) and rats (81). To our knowledge, there are few published reports of effects of EDCs on stress reactivity. A recent study revealed that early life stressors, such as cross-fostering, can modulate the effects of BPA on social behavior and anxiety (82). This highlights the need for further investigation of the impact of EDCs on hypothalamic-pituitary-adrenal axis function, albeit there is emerging evidence that EDC can alter oxidative stress (83).

## EDCs Influence Brain Morphology

Several studies have investigated EDCs effects on sexually dimorphic brain circuits. For example, rats exposed to Aroclor 1221 perinatally had fewer ER $\beta$  positive cells in the sexually dimorphic nucleus of the preoptic area (SDN-POA) than did vehicle-administered rats (84). Exposure to BPA during the pre- or postnatal period can alter the differentiation of several neural circuits involved in the control of reproductive functions and behavior. It induces an increase of ER $\alpha$  mRNA and protein expression in the female rat hypothalamus and in the male anterior pituitary (85,86), and alters the sex specific expression of tyrosine hydroxylase (TH) in the rat and mouse anteroventral periventricular nucleus (87-88). Also other systems, such as the rat locus coeruleus (89, 90), the mouse nitric oxide producing system (91), and the rat and mouse kisspeptin system (92, 93), are affected by precocious exposure to BPA, altering in many cases, their sexually-dimorphic expression.

The family of neurohypophyseal nonapeptides (arginine-vasopressin (AVP) in mammals and arginine-vasotocin (AVT) in non-mammalian vertebrates) is present in magnocellular system and in the sexually-dimorphic parvocellular systems of hypothalamus and limbic system. This last system is gonadal hormone-dependent in various vertebrates [for a review of comparative aspects see (94, 95)]. It is involved in the control of male copulatory behavior in birds (96, 97) and in the modulation of aggressive behavior and other social behaviors in mammals and other vertebrates (98). Administration of exogenous estrogens demasculinizes this system in birds (99), whereas in mammals, both estrogens and androgens may contribute to the masculinization of the system (100-103). In adulthood, gonadal hormones modulate the expression of AVP or AVT, both in the parvocellular (104-106), and in the magnocellular system (107). Thus, the AVP system has been considered as a potential target for the action of EDCs (108, 109).

In the Japanese quail, embryonic exposure to different EDCs (DES, genistein, or DDE) induced a significant demasculinization of the sexually dimorphic parvocellular AVT system (37-39). For other EDCs [ethynylestradiol (EE $_2$ ) and methoxychlor (MCX)], the effects on this neural system were absent or not significant, yet they did affect copulatory behavior (110). The dissociation between demasculinization of behavior and the AVT system suggests that estrogens induce these effects via at least partly different pathways. As demonstrated through the administration of an ER $\alpha$  selective agonist, propyl pyrazole triol (PPT), estrogen-induced effects on reproductive organ differentiation are mediated by ER $\alpha$ , whereas demasculinization of male copulatory behavior and of the AVT-immunoreactive (ir) system are probably dependent upon ER $\beta$ , which appears earlier during quail embryonic development than does ER $\alpha$  (111).

In mammals, acute exposure to E $_2$  stimulates the synthesis of the mRNA AVP (112) and induces a significant increase of AVP immunoreactivity in magnocellular nuclei of female rat (107). In rats, dietary exposure to phytoestrogen genistein (from prenatal day 7 up to the age of 2 months and a half) induced an increase of vasopressin content in hypothalamic extract (113). However, exposure to organoalogen compounds, generally believed to act as antiandrogens, inhibited the release of AVP from SON punches and in vivo (114,115).

These studies suggest that also in mammals the AVP system is a target for the action of EDCs (108).

A few studies have investigated the second neurohypophyseal nonapeptide, oxytocin (OT), produced by the magnocellular nuclei in mammals, and released both centrally into the brain, and peripherally into the circulation. OT is involved in social recognition and maternal behavior (116, 117). Oral BPA exposure reduces certain maternal behaviors in female rat, such as licking-grooming and arched back posture, that are related to OT (35). At the same time, BPA may induce an increase in OT-immunoreactive cell number in female rat PVN (118) suggesting that it may inhibit OT release. The behavioral effects of EDCs exposure could also be related to alteration of the expression estrogen-inducible central OT receptors (119), as observed in the cingulate cortex of female pine vole perinatally exposed to MXC (120). Together, these data demonstrate that EDCs can negatively affect sexual dimorphisms in the brain (for recent reviews see (3, 4, 121)).

Other EDCs, as the 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), may have large effects in the brain when prenatally administered. In particular, prenatal exposure to TCDD (700 ng/Kg single dose gavage at gestational day 18) affects the offspring in the number of pups born, myelination, weight gain and sex ratio towards females (122-126). Major alterations observed in offspring of TCDD exposed dams were a higher expression of oligodendrocyte precursor cell (OPC) markers mRNA, *Olig-1* and PDGFaR, in diencephalon and cerebellum and altered content of myelin basic protein being lower in mature cerebellum, diencephalon and medulla oblongata and conversely, higher in the telencephalon (127). Collectively, these results point to a long-lasting gliogenesis defect in mature brain after prenatal TCDD exposure (122).

Different molecular mechanisms could be responsible for the described defects. One effect may be related to a direct TCDD effect on OPC via aromatic hydrocarbon receptor (AhR), during the critical period of OPC proliferation, migration, and maturation (123). As oligodendrocyte generation, maturation and myelin protein expression are under thyroid hormone control, another possibility could be related to indirect effects of TCDD on endocrine function, e.g. thyroid dysfunction. Indeed, perinatal TCDD exposure alters maternal, neonatal, and infant thyroid function, as well as thyroid hormone nuclear receptor (TR)-mediated gene expression and pathways (128). The cerebellar expression of TR $\alpha$  mRNA was down regulated during development, whereas TR $\beta$  mRNA significantly increased, within the second postnatal week, then turning to basal expression levels at adulthood. The expression of deiodinase enzyme D2 mRNA was very low in the first postnatal days, significantly increased during development and reached a peak after 14 days. On the contrary, D3 mRNA was highly expressed at 2 days postnatal but its expression was drastically down regulated during development. These results are in line with what has been already described (129). Interestingly, there are significant difference in the expression of TR $\alpha$ -1 at 14 days postnatal in TCDD-, versus vehicle-exposed, males, but not, female rats. Thus, we can conclude that prenatal exposure to TCDD alters developmental expression profile of several genes, including myelination and thyroid hormone related genes, thereby affecting expression profile of one of the main signalling pathways for brain development.

## Consideration of critical periods

When, in life, exposure occurs may be critical for EDCs' effects. Critical periods of urogenital tract and nervous system development *in utero* or in early post-natal life are especially sensitive to hormonal disruption. Damage during these "critical windows of development" may be more likely to be permanent, yet, in mature individuals, ill effects of exposures can be alleviated when the causative agent is removed (130). This is consistent

with the idea of greater negative consequences with BPA exposure during infancy/childhood vs. adulthood (14). In rats, the effects of EDCs at environmentally-relevant dosages appears to be particularly strong when the exposure is protracted for the entire developmental period, i.e. from gestation to weaning (35-36). Persistent effects have also been observed when exposure is confined to a specific critical window, such as the neonatal period (131-132). In any case, exposure to EDCs is likely to be continuous in natural populations because they are ubiquitous in the natural and human environment (133).

### **Exposure to EDCs during other critical periods- perinatal, juvenile, puberty**

In rats, exposure to environmentally-relevant concentrations of 17 $\alpha$ -ethinyl estradiol (4 ng/kg/day) from gestation day 5 to weaning (postnatal day 32) has serious effects on sexual behavior, cognitive functions, and reproduction (35, 36, 68). In females, sexually proceptive behavior is affected, with a disruption of the timing of appearance of appetitive aspects during the copulatory sequence (36). Reproduction is also affected, with an *increase* in the number of live pups (35). Similarly, there is an improvement in spatial learning in male rats tested in a Morris water maze (68). Inverted U-shaped dose-response curves are quite common for EDCs ('hormesis': see (134), but even if these effects are positive, they are unlikely to be beneficial (135).

In mice, exposure of pregnant dams to low doses of BPA, from prenatal day 10 to postnatal day 8 (5, 10, 20, 40  $\mu$ g/kg/day), induced profound behavioral alterations in adulthood. In our preliminary study (136), males showed an increase in the time spent in the intermediate and central areas of the open field, suggesting that perinatal exposure to BPA may determine anti-anxiety effects. At the same time, we observed a significant increase of the spontaneous activity of mice within the T-maze, suggesting cognitive deficits in animals. BPA-treated mice of both sexes had a strong reduction in the time spent in the arm with opposite-sex bedding; in males, we also observed the reduction of number of sniffing in the same arm. These findings suggest that BPA may alter the olfactory system and, as a consequence, sexual behavior. This is in agreement with the results of our recent study demonstrating alterations in part of nNOS system in mice perinatally exposed to BPA (91). On the contrary, we have neither detected changes in food preference nor searching. Finally, we observed alterations of sexual behavior only in males. In particular, we observed deficits of ano-genital and body sniffing, and allo-grooming behaviors. In females, we observed a significant advancement of puberty. In a second experiment, we exposed perinatally-treated mice to a second exposure to BPA from day 31 to day 60. The behavioral alterations were essentially the same. This suggests that some of the effects of BPA on behavior may be predominantly organizational rather than activational.

Genistein, as other phytoestrogens, is largely present in human and laboratory animal diets. Phytoestrogens have recently gained recognition for their beneficial effects on human health, but little is known about their effects on brain circuitries. Experiments carried out on rats fed with phytoestrogen-rich diet have shown contrasting results on behavior and related brain areas. To understand if exposure to genistein during the postnatal critical period of differentiation of brain circuits and behaviors may alter this process, we orally administered male and female mice from postnatal day 1 to postnatal day 8, genistein (50 mg/kg in sesame oil), or vehicle. Mice were tested at postnatal day 60 for anxiety behavior, using the Elevated Plus Maze and the Open Field. The results indicated a strong sexual difference. In fact, genistein demonstrated an anxiogenic effect in males and an anxiolytic effect in females (137).

## Puberty

Maturation and function of the vertebrate reproductive system is coordinated by the hypothalamic-pituitary-gonadal (HPG) axis. This sexually dimorphic system encompasses a complex network of hypothalamic neuronal signaling pathways, the most notable of which is the newly discovered kisspeptin system (for a recent review see (138) and this issue), that enable the sex-appropriate regulation of gonadotropin secretion by steroid hormones. The neural components of the HPG axis, including kisspeptin pathways, are sexually-differentiated by endogenous gonadal hormones (primarily estradiol in rodents but perhaps both estrogens and androgens in humans) through a series of gestational, pre- and perinatal critical periods (139-142). This sex-specific ontogeny can be manipulated by the exogenous administration of steroid hormones during the neonatal critical period. For example, neonatal estrogen administration masculinizes the female rodent brain, resulting in the loss of the preovulatory GnRH surge, while castration effectively prevents defeminization of the male rodent brain (143).

In females, exposure to EDCs during the neonatal period can also perturb the sex-specific organization of these hypothalamic pathways resulting in advanced vaginal opening, a hallmark of rodent puberty, and abnormal estrous cyclicity (81,-144-148). For example, in female rats, exposure to 10 mg/kg genistein, an isoflavone phytoestrogen common to soy-based foods, across only the first few days of life, results in significantly decreased kisspeptin fiber density in the region surrounding GnRH neurons during peripubertal development (147). This male-like pattern of kisspeptin fiber density persists into adulthood (93, 144) and is accompanied by an impaired capacity to stimulate GnRH neuronal activity (as measured by the immunoreactivity of both of GnRH and Fos) following ovariectomy and hormone priming (144). These results indicate that disrupted organization of the kisspeptin signaling pathways may be a novel yet fundamental mechanism by which a suite of reproductive abnormalities are induced including disrupted timing of pubertal onset, irregular estrous cycles and premature anovulation.

### Exposure to EDCs in Adulthood Also Affects Reproductive Parameters

To date, there has been much less investigation of the activational effects of EDCs compared to their organizational effects. There is some evidence of EDCs altering reproductive responses of adults. Men with infertility had significantly higher tetra- and pentachlorinated biphenyls, DDE, DDT, and lindane than controls (149). Lead exposure increases male and female infertility (150, 151). Administration of Aroclor 1221 or 1254 during adulthood affected the timing of female sexual behavior of rats (152) and women consuming a high soy diet experience disrupted menstrual cycles and difficulty obtaining pregnancy (153). Thus, the extent to which exposure during adulthood may influence previously established sexually dimorphic behaviors is of continued interest.

### Potential Mechanisms by Which EDCs May Produce Their Effects

The putative mechanism by which EDCs may have their effects needs to be more thoroughly explored. An important question is whether EDCs interact with endogenous E<sub>2</sub>. This is relevant not only for women of reproductive age, who have high and fluctuating E<sub>2</sub> levels, but also for children, postmenopausal women, and men, whose E<sub>2</sub> levels are low. Although PCBs have long been known to be estrogenic (154), EDCs vary in their estrogenic effects. Attempts to establish a relationship between PCBs and their estrogenic/antiestrogenic actions have not reached a consensus (155). A review follows of potential species differences and actions of EDCs.

## Effects of endocrine disrupting chemicals mediated by aryl hydrocarbon receptors and CYP1A1

Many effects of EDCs are mediated by the aryl hydrocarbon receptor (AhR), which is present in various tissues including brain (156). This receptor may be responsible for dioxin and dioxin-like PCB intoxications, which create severe clinical problems, such as behavioral and cognitive impairments and an increased number of newborns with improperly formed brains (157). However, it has become evident that AhR may also be involved in neural development, likely through interaction with Wnt signaling (158), in addition to mediating neuronal cell death in response to environmental pollutants.

The molecular mechanism underlying AhR-induced neurotoxicity is largely unknown and related mainly to necrosis. Prenatal exposure to AhR agonist TCDD (tetrachlorodibenzo-p-dioxin) resulted in neurodevelopmental deficits, possibly due to altered activity of Sp1 factor and increased oxidative stress (159). Exposure to TCDD, 8 weeks prior to pregnancy, resulted in 50-75% decrease in serotonergic neurons in the mouse raphe nuclei (160). Furthermore, treating animals or neocortical cell cultures with TCDD altered expression of NMDA receptor subunits, could directly influence necrosis of neuronal cells (161, 162). Little is known; however, about apoptotic effects mediated by AhR. This is particularly important because apoptosis occurs at each stage of neural development and may also be attributed to neurodegenerative diseases.

There are few data, including ours, suggesting that AhR regulates brain apoptosis (163-165). AhR is a ligand-dependent transcription factor that activates transcription of genes, such as: CYP1A1, CYP1A2, and CYP1B1, and oncogenes (166). CYP1A1 is the most commonly and consistently expressed isoform, which is involved in biotransformation, metabolism and detoxification of many environmental contaminants, including polycyclic aromatic hydrocarbons (PAHs). This cytochrome is also involved in the metabolism of endogenous substrates like estradiol (167). EDCs may alter the CYP450 system through binding to the AhR acting as either agonists or antagonists (168). In the absence of ligand, AhR is bound to heat shock protein Hsp90. Upon ligand binding, the AhR translocates into the nucleus whereupon it heterodimerizes with the ARNT protein (hydrocarbon receptor nuclear translocator) and binds to AhR DNA recognition site, known as XRE (xenobiotic response element). The location of XRE close to the ERE (estrogen response element) allows AhR- and estrogen receptor (ER)-mediated transcription processes to be reciprocally affected. At present, both ER subtypes are known to contribute to neuroprotection, but the relative contributions of ER $\alpha$  and ER $\beta$  remain unresolved. It is noteworthy that AhR-dependent activation of proteasomes mediates degradation of ER $\alpha$  (169). We showed for the first time, co-localization of AhR with ER $\beta$  in neocortical tissue, thus suggesting an interactive action between these receptors (165)). One possible interaction is through ARNT, a dimerization partner of AhR that can act as a potent co-activator of ER $\beta$  (170). This supported our biochemical data that, among estrogen receptors, ER $\beta$  is the most crucial for compromising AhR-mediated neuronal cell death.

### Effects of EDCs on E<sub>2</sub> Metabolism

EDCs may have effects on E<sub>2</sub> metabolism in a number of ways. Some EDCs can alter serum lipid concentrations, ultimately enhancing production of E<sub>2</sub> and other steroids. Further, some EDCs can alter metabolism enzymes that are necessary for converting cholesterol to steroid hormones. Numerous EDCs can activate one of the P450 cytochromes (P450 or CYP), which are involved in the metabolism of most steroid hormones and EDCs. Environmental contaminants may contain chemicals that induce P450s, are metabolized by P450s, or both. Induction of CYP occurs when EDCs, such as TCDD, bind AhR. There is a firm link between PCBs, enzyme induction, and AhR effects (171; 172). Coplanar PCBs like TCDD,

activate AhR, cause the induction of CYP, which catalyzes the metabolism of many PCB congeners and other endogenous hormones, including E<sub>2</sub> (169, 173). The binding of EDCs with AhR can result in antiestrogenic activity through increased metabolism and depletion of endogenous E<sub>2</sub> (173). Elevated levels of CYP enzymes, primarily expressed in the liver, but also in brain and other tissues, result in increased E<sub>2</sub> metabolism and excretion. Alternatively, compounds that are metabolized by P450s may produce estrogenic effect if they inhibit endogenous estrogens from being metabolized.

Estrogens can produce anti-androgenic effects by inhibition of testicular androgen secretion via blocking secretion of luteinizing hormone or by direct suppression of T synthesis by Leydig cells. High levels of PCB-inducible androstenedione formation have also been found (174). PCB exposure reduced testicular microsomal P450s and affected androstenedione formation and 16 $\alpha$ -hydroxylation of T. Mitochondrial CYP, the rate-limiting enzyme of steroidogenesis, was inhibited by 50% in testes of animals exposed to EDCs (175). Adult male rats given single doses of TCDD exhibited decreases in plasma T and dihydrotestosterone concentrations by 90 and 75%, respectively, and decreased seminal vesicle and ventral prostate weights (176). PCB 126 can suppress 5 $\alpha$ -reduction of T, or progesterone, in liver microsomes (177). A question for further consideration is the importance of EDCs' effects on steroid metabolism to mediate behavioral processes.

### Species differences and food-chain effects, metabolism

Among vertebrates, teleost fishes exhibit unique features in terms of neurodevelopment and brain sexualization. In contrast to a common thinking, teleosts are not primitive vertebrates, but vertebrates that belong to a lineage that diverged from the tetrapod lineage some 450 million years ago. Among teleosts, there are primitive and highly evolved species. However, all share the property of growing their brains during their entire lifespan, a feature that is supported by the fact that adult fish conserve active radial glia progenitors throughout life. These cells are notably capable of performing asymmetrical divisions that give birth to new neurons not only during embryonic development, but also in adults (178,179). In addition, the radial glial cells of fish are now well documented for expressing steroidogenic enzymes, notably aromatase B, the product of the *cyp19a1b* gene (178-181). This gene is in fact strongly up-regulated by estrogens and any xenoestrogens capable of activating one of the three zebrafish estrogen receptors (178, 181-184). In zebrafish embryos and larvae, exposure to estrogen and estrogen mimics causes a strong increase of *cyp19a1b* expression that, in contrast, remains low in controls at early developmental stages (185). This means (i.) that radial glia progenitors are direct targets of xenoestrogens and (ii.) that this gene is an excellent biomarker of xenoestrogen exposure that can be used *in vitro* (182) and *in vivo* (178, 181) to address current key questions, such as the effects of mixtures and/or the monitoring of environmental samples.

A very high aromatase activity is another feature that makes the brain of adult fish so special and, in a way, similar to that of embryonic mammals (178, 186). In mammals, at least in rodents, it is believed that aromatase activity is strongly implicated in brain sexualization (187). It is believed that these effects are mediated in part through a region-specific modulation of apoptosis (188, 189). However, aromatase and estrogens are also important in the regulation of neural development, synaptic plasticity and cell survival outside the classical "reproductive brain". Aromatase knocked-out mice have documented the potential effects in the development of some brain regions, such as the cortex. A wealth of evidence now supports the view that locally-produced estrogens acting in paracrine or autocrine ways modulate neuronal survival and brain functions. Therefore, it is possible that the high aromatase activity of the permanently developing brain of adult fishes also supports their constant neurogenic activity. In this regard, the fact that aromatase is only expressed in

radial glial cells provides an anatomical substrate for such a link between aromatase expression and neurogenesis. These observations may also explain why many species of fish are sequential hermaphrodites and can change sex as adults, a skill that requires great brain plasticity (190). Our current studies now demonstrate that estrogen-like compounds not only modulate aromatase expression and activity in the radial glial cells, but also their proliferation (N. Diotel et al., unpublished data). Thus, altogether these data suggest that xenoestrogens have the potential to disturb adult neurogenesis and sex change in adult fish, which would mean that the critical window through which animals are highly susceptible to endocrine disruptors would extend throughout the entire lifespan of fishes.

### Obesogenic effects of EDCs

There is growing recognition that some EDCs can act as “obesogens” and increase the risk of developing metabolic disorders such as diabetes (191-194). One notable obesogen is DES, a synthetic estrogen initially prescribed to pregnant women to prevent miscarriage but ultimately distributed more widely before its use was discontinued in the late 1970’s because prenatal exposure was linked to a higher risk of vaginal (195). Children exposed in utero are unfortunately at higher risk for a wide range of neuroendocrine disorders including reproductive malformations, infertility and testicular cancer (196, 197). Emerging evidence now suggests that this population may also be at greater risk for obesity and metabolic disorders (193).

Organotin compounds, such as tributyltin (TBT), are also well recognized obesogens. These compounds are used in agriculture and industry as biocide, heat stabilizer and chemical catalyst (198). They may contaminate water and human foodstuffs, especially shellfish (199-201). Due to their endocrine-disruptive effects, organotin compounds are toxic to marine species, determining the development of ambiguous genitalia (200) and the increase of androgens’ levels and the decrease of estrogens in clams’ tissues (201). Organotin compounds are PPAR $\gamma$  and RXR agonists and they stimulate the differentiation of preadipocyte 3T3-L1 cells into adipocytes (201), and modulate, in vivo, the expression of PPAR $\gamma$ /RXR target genes in adipose tissue and liver, thus acting as potential obesogens (202). In particular, TBT increases body weight in mammals (203) and disturbs levels of key hormones linked to energy homeostasis (204). These data suggest a peripheral role of TBT on obesity development, but, currently, there are only a few studies on the effects of TBT on the central nervous system. In a recent study (205), we demonstrated, for the first time in an “in vivo model”, that oral administration of TBT in adult mice may specifically activate (specific increase of c-fos expression) a key region of the circuits involved in the control of food intake, the ARC nucleus. This nucleus is the source of the NPY- and of MSH-circuits that are regulating the stimulation or the depression of the food intake stimulus. Our preliminary results indicate that NPY expression is indeed affected by adult exposure to TBT (206), as well as to other EDCs (i.e., BPA and DES (207)).

### Other Substrates to Consider for Actions of EDCs

One challenge to understanding effects and mechanisms of EDCs regards their many and variable responses and/or actions of E<sub>2</sub>-sensitive targets. For example, EDCs can mediate responses of two orphan receptors of the nuclear receptor family, the constitutive androstane and pregnane X receptors (208). As well, EDCs may have actions at membrane-associated ERs (“non-genomic” actions) (209-211). Like E<sub>2</sub>, EDCs may have steroid receptor-independent actions through numerous other substrates, such as signal transduction pathways, calcium influx, and/or neurotransmitter receptors. Of particular interest is the role that EDCs have via neuropeptide systems (121). Investigations of the extent to which EDCs’ actions involve metabolism and or ER and non-ER mechanisms for behavioral responses are ongoing.

## Summary/Conclusions

Individuals may be exposed to EDCs from varied sources, including pesticides and herbicides, dust, plastics, medical and/or dietary components (Fig. 1). EDCs can influence reproductively-relevant or non-reproductive, sexually-dimorphic behaviors. Exposure to EDCs during critical phases of development (e.g. perinatal, peripubertal periods), may result in more salient effects on neurodevelopmental and/or reproductive processes. However, exposure to EDCs in adulthood can alter physiological processes including production of steroids, actions via, or independent of, classic cognate steroid receptors. EDCs may have effects through other substrates, such as the AhR, PPAR, and retinoid, androstane, or pregnane X receptors, neurotransmitters, calcium or signal transduction. EDCs, from varied sources, may organize and/or activate sexually-dimorphic, neurodevelopmental and/or reproductive processes or other functions, by mimicking, antagonizing, or altering steroidal actions.

## Acknowledgments

Preparation of this manuscript was supported in part for CAF by NIMH grant 067698, for GCP by grants from Regione Piemonte and Fondazione San Paolo (Neuroscience Project), for GC and AV by Italy/US collaborative project 11US/11 (Italian Ministry of Health) and PREVIENI project (Italian Ministry for Environment and Protection of Territory and Sea).

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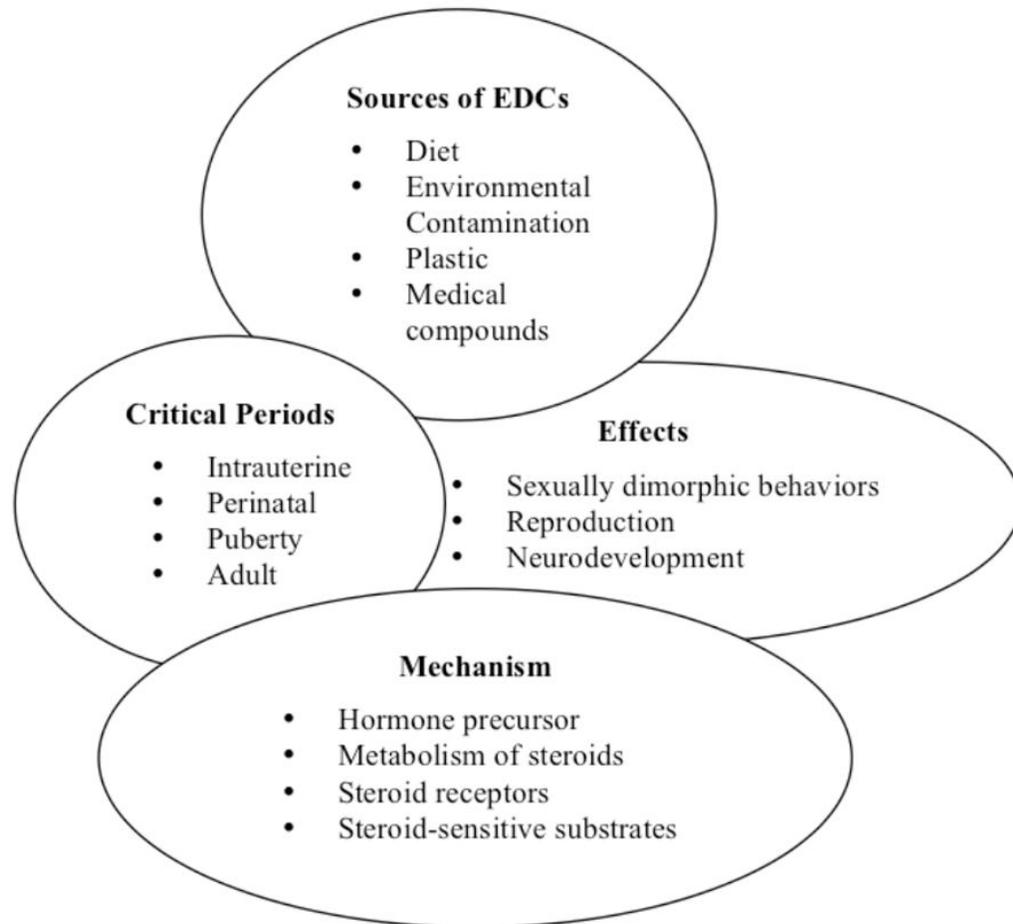
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**Figure 1.**

A schematic representation of varied sources of endocrine disrupting chemicals (EDCs) and how they may influence sexually-dimorphic, reproductive and neurodevelopmental processes, in particular through their actions during critical periods of development. Some of the steroids mechanisms that may mediate actions of EDCs are included.

Table 1

EDC	Source	Reported Behavioral Effects	Reported Neural Effects
Bisphenol A (BPA)	Polycarbonate plastics, epoxy resins (lining soup and metal cans), thermal paper receipts.  High volume production chemical. Bans or restrictions on use in some countries (not USA).	Altered explorative activity. Impaired social interaction/activity. Compromised learning and memory. Increased anxiety and aggression. Decreased male sexual behavior. Increased externalizing behaviors in girls.	Modified or lost brain sex differences. Loss of sex differences in AVPV volume and TH levels. Loss of sex difference in LC volume. Increased OT neuron number in PVN. Altered hippocampal spine density. Disrupted hypothalamic ER distribution. Altered nNOS signaling. Advanced puberty
Diethylstilbestrol (DES)	Potent synthetic estrogen (pharmaceutical) used from 1938-1971. Recognized to cause reproductive cancers, genital malformations and infertility in humans.	Decreased anxiety in females.	Demasculinization of avian AVT system.
Ethinyl Estradiol (EE)	Synthetic estrogen used in birth control pills and other pharmaceuticals.  Present at low levels in municipal water.	Decreased response to reward in females.	Masculinization of female hypothalamic development. Intersex in fish.
Genistein (GEN)	Legumes, soy and soy based food, soy infant formula, dietary supplements  Phytoestrogen produced by plants.	Increased exploratory activity in males  Altered anxiety-related behavior.	Demasculinization of avian AVT system. Disrupted hypothalamic sexual differentiation Advanced puberty.
Organophosphate Insecticides (OPs)	Pesticides including chlorpyrifos, parathion, malathion and diazinon. Also nerve gas including Sarin.	Associated with ADHD and behavioral problems in children.  Altered ultrasonic communication, aggressive behavior and social interaction in rodents.	Acute neurotoxicity (can be lethal). Neurophysiological maturation and differentiation. Disruption of serotonergic and dopaminergic transmission. Modified OT and AVP activity.

EDC	Source	Reported Behavioral Effects	Reported Neural Effects
Polychlorinated Biphenols (PCBs)	<p>Bans or restrictions for use in some countries.</p> <p>Lubricants, cooling fluids, transformer oil, adhesives, plasticizers</p> <p>Banned from US production in 1979.</p>	<p>Decreased explorative activity in females</p> <p>Compromised learning and memory.</p>	<p>Modified or lost brain sex differences.</p> <p>Disrupted hypothalamic ER distribution.</p>
2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)	<p>Most toxic of 200+ dioxins. Byproduct of combustion, burning of fossil fuels, bleaching during paper production, and PVC plastic production. Preservative for wood, textiles, paint, glue and other products. Food contaminant (highest in meat).</p> <p>Potent carcinogen, persistent, bioaccumulates, was a contaminant in Agent Orange.</p>	<p>Reduced male sex behavior.</p>	<p>Acute toxicity (can be lethal).</p> <p>Modified or lost brain sex differences.</p> <p>Compromised neurodevelopment and myelination.</p> <p>Disrupted thyroid hormone action.</p> <p>Demasculinization of the male hypothalamus.</p>