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Endocrine Disrupting Chemicals: Bisphenol A and the Developing Brain

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= Abstract =

내분비 교란 물질: 비스페놀 A와 발달 단계의 뇌

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목 적: 내분비 교란 물질이 인체에 미치는 영향과 플라스틱 제품에서 용출되는 bisphenol A(BPA)가 발달 단계의 동물의 뇌에 영향을 주는 여러 기전들을 살펴보고자 하였다.
방 법: PubMed, the National Library of Medicine (USA) online database 및 Index Medicus를 이용하여 내분비 교란 물질 및 비스페놀 A에 대해 기술한 100여편 이상의 논문을 고찰하였고, 이 가운데서 일상생활에서 노출되는 미량의 농도에서의 발달 단계의 신경계에 미치는 영향에 대해 조사한 58편의 논문을 참고하였다.
결 과: 내분비 교란 물질은 인체의 내분비계에 영향을 주어 장애를 일으키는 외인성 물질이다. 비스페놀 A는 플라스틱인 폴리카보네이트와 에폭시 수지의 합성 원료이다. 인체에 노출되는 양은 미량으로 생체에서의 활성도가 낮아, 플라스틱제의 사용이 건강에 직접적인 영향은 없다고 지금까지 알려져 있다. 그러나 최근의 동물 실험에서 임신이나 수유 기간 동안 미량의 농도에 노출되었을 때 발달 단계의 뇌에 영향을 미친다는 결과들이 보고되고 있다. 또한 인간의 제대혈에서 검출되는 미량의 BPA 농도에서도 실험동물에서는 영향을 보였다고 한다. 그러므로 미량의 비스페놀 A에 만성적으로 노출되었을 때 영향은 향 후 규명되어야 할 과제이다.
결 론: 태아 및 소아는 안정성이 보장되어 있지 않은 많은 종류의 물질들에 노출되어 있으며, 미성숙한 뇌는 이들 물질들에 의해 비가역적인 장애를 받을 수 있다. 인체에서 미량의 농도에 만성적으로 노출되었을 때, 그 유해성에 대해서는 아직은 규명되지는 않았으나, 임산모나 소아의 이러한 내분비교란 물질에의 노출은 최대한 억제할 필요가 있다.

Key Words: endocrine disrupting chemicals, bisphenol A

Introduction

Endocrine disrupting chemicals (EDCs) have been defined as "exogenous substances that alter endocrine functions and consequently cause adverse health effects in an intact organism or its progeny, or subpopulations." The diversity of EDCs includes natural and synthetic hormones, phytoestrogens, pesticides, and a variety of industrial chemicals and by-products (IPC, 2002). The disruption of endocrine function can have a number of neuro-

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developmental effects, including alterations in reproductive behaviors mediated by the hypothalamic–pituitary axis, hypothalamically mediated body metabolism, sexual differentiation in brain morphology, and cognitive and psychomotor development. Sexual and brain development are under the influence of estrogenic and androgenic hormones, and chemicals that interfere with these hormones can adversely affect neurodevelopment.

Relative to the adult, the developing nervous system is differentially vulnerable to chemical exposure, due to a number of factors, such as differences in forms and activity of metabolizing enzymes, rates of excretion, lack of a protective blood brain barrier, and a differential binding affinity of xenobiotics to target proteins. The nervous system is considered to have reached a steady state in adults and is not as vulnerable to neurotoxic agents as is the developing brain (Tilson, 1998).

Extensive laboratory and clinical studies of several toxicants, including lead, mercury, polychlorinated biphenyls (PCBs), alcohol, and nicotine demonstrate the unique vulnerability of the developing brain to environmental agents at levels that appear to have no lasting effects following exposures in adulthood.

Bisphenol A (BPA), which is now present ubiquitously in the environment, has the potential for exposure and subsequent effects in humans. BPA has been widely discussed as a prime candidate for endocrine disruption.

In this review, I will discuss hormonal disruption of EDC and effects of BPA on fetal and postnatal brain development at levels of low, albeit presumably environmentally relevant, exposures.

Materials and Methods

This review was performed by searching PubMed, the National Library of Medicine (USA) online database, as well as Index Medicus for earlier (prior to 1980) citations on EDCs and BPA. More than 100 peer–reviewed articles were retrieved for review of endocrine disrupting mechanisms and actions of BPA. Of these papers, 58 were chosen for this review as they are related to brain development during intrauterine life and with lactational exposure, to low dose EDCs and BPA at levels typical of everyday environmental exposures in humans. In these studies, the effects of EDCs, including BPA, were evaluated for their relationship to estrogen and thyroid hormone status, dopaminergic and several other signaling mechanisms, and measures of behavioral, physiological and pathological changes in rodents.

Results

1. Mechanisms of Endocrine Disruption

Many EDCs appear to function as estrogens or antiestrogens by interacting with estrogen receptors (ERs) (White et al, 1994; Cheek et al, 1998). Considering the widespread tissue distribution of ER subtypes and complexities of estrogenic actions, a number of mechanisms in different tissues exist in vivo for xenoestrogens to perturb normal signaling.

Most xenoestrogens are ligands for ERs and are thought to exert their actions by promoting an active ER conformation, and thereby regulate target genes accordingly. Ligand dependent activation of ERs involves dimerization and conformational changes within the receptor that allow recruitment of coactivators. Since human tissues show different expression patterns of coactivator subsets, this could explain the tissue specific activities (agonistic or antagonistic) of xenoestrogens. These estrogenic substances can also affect nongenomic ER pathways, which do not rely on gene transcription or protein synthesis but involve modulation of cytoplasmic or cell membrane-bound regulatory proteins (Singleton and Khan, 2003).

Some EDCs, such as the hydroxylated PCB metabolites, interfere with estrogen metabolism by inhibiting estrogen sulfotransferases, thus increasing the bioavailability of estradiol (Kester et al, 2002). In addition, the metabolite of dichlorodiphenyltrichloroethane (DDT), p,p'-DDE, functions as an antiandrogen by binding to androgen receptors (Kelce et al, 1995).

Prenatal and postnatal exposures to estrogenic pollutants have the potential to alter development of dopaminergic pathways. In experimental studies, octylphenol, an alkylphenolic compound widely used in industry, enhanced the uptake of ^{3}H-dopamine by rat hypothalamic dopaminergic neurons (Christian and Gillies, 1999). Intrauterine and lactational exposures to PCBs also resulted in significantly decreased concentrations of dopamine in the frontal cortex and caudate nucleus in rats (Seegal, 1997).

Thyroid hormones (THs) are important regulators of brain development during the fetal and neonatal periods. The central nervous system is especially dependent on TH for normal maturation and function. Specifically, there appears to be extensive inter-reliance between TH and acetylcholine, nerve growth factor and hippocampal function (Smith et al, 2002). In addition, a high prevalence (70%) of Attention Deficit Hyperactivity Disorder (ADHD) has been reported in children with generalized resistance to TH (Hauser et al, 1993), and in the offspring (66.8%) of mothers exposed to mild to moderate iodine deficiency (Vermiglio et al, 2004). Unlike the ERs, there is little evidence that environmental chemicals bind to the thyroid hormone receptor (TR). Because of the complexity of TH function and regulation, it is unlikely that a single assay will become available to detect chemicals that act on any or all of these pathways. Chemicals appear to alter the thyroid system by either inhibiting synthesis of THs, altering serum binding to transport proteins, or by increasing TH metabolism (DeVito et al, 1999).

In a study in Slovakia, Langer (Langer et al, 1998) described a significantly increased prevalence of thyroid peroxidase antibodies (TPO-Ab) in female employees of a factory that had previously produced PCBs. The prevalence of individuals with defined clinical or laboratory signs of thyroid disorders was significantly greater among employees than a control group. From North American and Western European evaluations, up to 0.5% of

pregnant women (1 in 200) may have overt hypothyroidism, whereas up to 2.5% of them (1 in 40) may have subclinical hypothyroidism that is undetected before pregnancy. Between 6 and 12% of women of child bearing age (1 in 16 to 1 in 8) may have thyroid antibodies, with strictly normal Free T_4 and Thyroid stimulating Hormone (TSH) (de Escobar et al, 2004), and these antibodies do pass through the placenta. Women with high levels of TPO Ab had a sixfold increased risk of presenting with relatively low Free T_4 levels in early gestation, which is also a risk factor for impaired psychomotor development in the offspring (Vulsma, 2000).

The importance of TH transfer from the mother to the fetus during the second half of human pregnancy has received increased recognition. There is also increasing awareness of the importance of maternal thyroxine for fetal brain development early in pregnancy. During this period the mother is the only source of TH for the fetus, prior to the onset of significant secretion by the fetal thyroid at midgestion. There is increasing consensus that maternal hypothyroidism, both clinical and subclinical, requires early detection and prompt treatment, because of its important negative effects for the mother, the pregnancy and child (de Escobar et al, 2004). All pregnant women should be screened for hypothyroidism as early in pregnancy as possible.

Treatment should begin as early as possible in pregnancy with the goal of maintaining Free T_4 in the upper half of the normal reference range and TSH in the lower half of the normal reference range (Mitchell and Klein, 2004). Therefore, further research is needed to investigate maternal TH status and placental transfer of T_4 in relation to PCBs/dioxins exposure and the generation of autoantibodies against thyroid tissue.

Until recently, none of studies on effects of PCBs in human pregnancy have reported data on maternal TPO Ab titers. EDCs may affect more than one component of the endocrine system, and their effects vary with different concentrations. Therefore it is difficult to predict the effects of EDCs on human health. For example, PCBs are known to activate estrogen receptors, alter TH status, affect dopaminergic signaling and related behaviors in rodents, and can affect several signaling mechanisms. The phenotypic effects of PCBs, therefore, may not be attributable solely to their perturbations of ERs, but may also combine with other effects on genetic, epigenetic or cellular processes.

2. Bisphenol A (BPA)

1) Chemistry and history

BPA (2,2-bis-(4-hydroxyphenyl)-propane) is a diphenyl compound that contains two hydroxyl groups in the "para" positon, making it remarkably similar to the synthetic estrogen diethylstilbestrol (DES). BPA was first synthesized from phenol and acetone in 1905 by Thomas Zincke of the University of Marburg, Germany.

In the early 1930s, scientists began synthesizing compounds based on the phenanthrene nucleus of steroidal estrogens in an attempt to produce substances with similar

properties and potential clinical value. Estrogenic activity was assessed by the subcutaneous administration of test chemicals to ovariectomized rats that were then observed for the onset of estrus. The first evidence of estrogenicity came in 1936, from experiments in which BPA was fed to ovariectomised rats (Dodds and Lawson, 1936)

In 1953, Dr. Hermann Schnell of Bayer in Germany and Dr. Dan Fox of General Electric in the United States independently developed manufacturing processes for a new plastic material, polycarbonate, using BPA as the starting material. Later, epoxy resins were developed. Commercial production began in 1957 in the United States, and in 1958 in Europe, and has grown worldwide along with the continued growth of uses for polycarbonate plastic and epoxy resins.

BPA is produced at over 2 billion pounds per year worldwide, and is found in many products, including polycarbonate plastic food storage containers, as well as the epoxy resin used as the lacquer lining of food or beverage cans (Brotons et al, 1995; Yoshida et al, 2001) and in some dental sealants (Olea et al, 1996). Polycarbonate is less durable than comg monly believed. The ester bond linking polymerized BPA molecules can be hydrolyzed, and hydrolysis increases dramatically at high or low pH as the temperature increases and BPA is released to food. For example, this occurs when canned food is heat processed or plastic dishes are used in microwave ovens (Brotons et al, 1995; Olea et al, 1996; Yamamoto and Yasuhara, 1999; Yoshida et al, 2001). When polycarbonate is scratched and discolored, the rate of leaching of BPA may increase (Howdeshell et al, 2003).

2) Metabolism

Most of an orally administered dose of ^{14}C-BPA to rats was excreted in the feces and urine within 24 hours; over an 8-day period, 28% of the 14C-BPA was excreted in urine and 56% in feces. The BPA was excreted in urine as the glucuronide or in feces as free BPA, hydroxylated BPA, and conjugates (Knaak and Sullivan, 1966). BPA monoglucuronide is the major metabolite in the plasma, milk, bile and urine after oral administration of BPA. Unchanged BPA is mostly detected in feces. BPA is mainly metabolized to BPA glucuronide, is excreted into feces through the bile and is subject to enterohepatic circulation in rats (Kurebayashi et al, 2003). BPA glucuronide is almost completely devoid of estrogenic activity (Matthews et al, 2001). BPA is glucuronidated by an isoform of UDP-glucuronosyltransferase in the rat liver. However, rat liver microsomal UDP-glucuronosyltransferase activities toward xenoestrogens are absent in the fetus, although they increase developmentally in the neonate. In pregnant rats, these activities are reduced to 40~60% of those in non-pregnant adult females (Matsumoto et al, 2002).

Due to the poor glucuronide conjugation capacity of the fetus, high levels of unconjugated BPA have been detected in the fetal plasma of rats (Takahashi and Oishi, 2000) and humans (Ikezuki et al, 2002; Schonfelder et al, 2002). BPA in fetal plasma concentrations were higher in male than in female

fetuses. The levels of biologically active BPA detected in human fetal umbilical cord blood are within the range of those that produce effects in toxicological studies in rats and mice (Schonfelder et al, 2002).

3) Mechanisms of endocrine disruption of BPA

BPA has structural homology with a ring of β-estradiol and, in vitro, is a rather weak estrogen, with a 5,000- to 10,000-fold lower binding affinity to the estrogen receptor (ER) than estradiol or diethylstilbestrol (DES) (Gaido et al, 1997). However, there is a discrepancy between the estrogenic potency of BPA in vitro and in vivo (Steinmetz et al, 1997). The estrogenic effects of BPA are greater in vivo compared to its weak estrogenicity in vitro (Khurana et al, 2000). Thus, even a small change in the estrogen effect due to BPA exposure during fetal life may have detrimental effects (Gupta, 2000). However, other groups were unable to reproduce effects by low dose BPA given to pregnant rodents, which has led to controversy over their potential to cause harmful effects (Ashby et al, 1999; Cagen et al, 1999; Tyl et al, 2002).

BPA also has antiandrogenic activity in vitro and may act as an antiandrogen in vivo and alter gene expression, resulting in abnormal development and function of the androgen receptor in target tissues (Sohoni and Sumpter, 1998). BPA acts as an antagonist to TH activity, binds to TR and antagonizes T_3 activation of the TR, and reduces T_3-mediated gene expression in culture (Moriyama et al, 2002). BPA also antagonizes the ability of TH to affect oligodendrocyte differentiation in vitro (Seiwa et al, 2004).

4) Effects on the developing brain

Recent experimental studies demonstrate that the developing brain may be a primary target for BPA action. There have been a number of reports of adverse effects of perinatal exposure to low dose BPA on various behavioral traits in laboratory rodents (Farabollini et al, 1999; Adriani, 2003; Kubo et al, 2003; Negishi, 2004). Behaviors may reveal subtle effects not easily detectable at each stage of brain development. Examination of both learned and unlearned behaviors may reveal subtle deficits in CNS functions, which may not be accompanied by demonstrable tissue pathology. An overall reduction in motivation to explore has been observed in all BPA-exposed rat offspring (Farabollini et al, 1999), and the behavior in BPA exposed males was more similar to typical behavior in control females (Adriani, 2003; Kubo, 2003).

Prenatal and neonatal exposure to BPA at low doses can especially influence the development of the central dopaminergic system. In the rat, reduced novelty seeking and increased neophobia was observed in BPA-exposed females, while amphetamine-induced incremental activity was significantly less marked in males (Adriani et al, 2003). Prenatal and neonatal exposure to BPA irreversibly influenced the reception of fear provoking stimuli (e.g. electric shock) in male rats, a response known to be controlled by the monoaminergic system (Negishi et al, 2004). In mice, BPA produced an up-regulation of dopamine D1 receptor function to activate G-

proteins in the mouse limbic forebrain, along with a significant increase in levels of the dopamine D_1 receptor mRNA in the whole brain. It also enhanced a methamphetamine (Suzukiz et al, 2003) and a morphine-induced abuse state, without direct changes in opioid receptor function in the lower midbrain (Mizuo et al, 2004). BPA stimulates dopamine release in a nongenomic manner in PC 12 cells through guanine nucleotide binding protein and N-type calcium channels (Yoneda et al, 2003).

Exposure to BPA during the fetal and suckling periods leads to interaction of BPA with somatostatin receptor subtypes (sst_2) (Facciolo et al, 2002). BPA also reverses the sex difference in the locus coeruleus in rats (Kubo et al, 2003), and induces tissue oxidative stress and peroxidation, ultimately leading to underdevelopment of the brain, kidney and testis in mice (Kabuto et al, 2004).

Discussion

BPA is widespread in the environment and is commonly ingested by humans through the use of consumer products. However, because of both its low estrogenic potency and low expected levels of exposure, it has also been assumed that the probability of toxic effects from BPA is negligible. Furthermore, it has been generally suggested that after oral administration, BPA is partially absorbed and rapidly excreted (its half life is less than 1 day) with no evidence of bioaccumulation in tissues. Because of its high first pass metabolism to the monoglucuronide, the active parent form of BPA cannot be found in human blood plasma.

However, concern for possible effects of BPA is increased by reported findings that biologically active (unconjugated) BPA has been detected in human fetal umbilical cord blood. These levels were found within a range typical of those used in recent animal studies in which they were shown to be toxic to the reproductive organs of the offspring (Schonfelder et al, 2002). Although there is no direct evidence that ingestion of BPA at levels estimated to occur in typical environmental exposures has adverse effects in humans, there are several indications that even small changes in the hormone levels during fetal life may have significant effects. On initial review, chemicals that act mechanistically like estradiol may also show no-threshold dose. Sheehan (Sheehan et al, 1999) reported that turtle eggs, when incubated at a temperature that normally generates a minority of females, showed sex reversal in 14.4% after the lowest single dose of 17-estradiol was added to the shells. A dose response curve suggested a no-threshold dose for addition of estradiol. Therefore, the addition of a small quantity of a xenobiotic (such as an EDC or BPA) to the body may have effects because it acts in addition to other chemicals that are already present. There may also be synergism from the combination of two chemicals that result in more that a simple additive response. Additivity and synergism can lead to no-threshold effects. Even the smallest amount of a chemical may therefore have an untoward effect under certain conditions (Sheehan, 2000).

Singleton (Singleton and Khan, 2003) has

emphasized that the most commonly studied mechanisms of xenoestrogen effects are genomic responses mediated by nuclear ERs. Because the nuclear ER-mediated gene transcription responses to xenoestrogens are very weak, some have suggested that their presence in our environment is relatively harmless. However, xenoestrogens have the potential to exert tissue specific and nongenomic actions that are sensitive to relatively low estrogen concentrations. Nongenomic effects of several weak estrogenic compounds, including low-dose BPA, also have been reported, and are well within the range of human exposure.

Xenoestrogens, therefore, may be as powerful as estrogen at producing effects such as increasing calcium influx into cells and stimulating prolactin secretion in GH_3/B_6 pituitary tumor cells, when mediated by a cell membrane surface receptor instead of nuclear hormone receptors (Wozniak et al, 2005). BPA can affect more than one hormone (sometimes in opposite directions), or different components of the same endocrine pathway, and can exert tissue specific and nongenomic actions in experimental studies, therefore making it difficult to predict its ultimate effects on human development.

BPA is not the sole source of xenoestrogen exposure in humans. Many chemicals are metabolized or undergo environmental degradation, which further complicates the association between any specific effects on neurodevelopment and a particular chemical form or species. Results emerging from research labs that test the combined effects of different weak chemicals are revealing complex interactions, and are able to act together to produce significant effects when combined at concentrations below their "no observed effect" concentrations(Payne et al, 2000; Rajapakse et al, 2001; Silva et al, 2002; Rajapakse et al, 2004).

Conclusions

Both humans and wildlife are constantly exposed to a multitude of xenobiotics. Furthermore, the production and utilization of such chemicals by humans has increased rapidly in recent years. Recent experimental animal studies have shown that various activities of BPA at levels estimated to occur with typical environmental exposures of humans exert divergent complicated adverse effects on brain development. Altered gene expression during the development of organisms can induce dramatic changes in developmental outcomes. Such disruptions are assumed to be irreversible.

Causal relationships have not yet been adequately established between the observed effects of BPA on brain development in rats, and neurodevelopmental disorders in humans. Data are insufficient to establish the shape of the dose-response curve for BPA in the low dose region, and the mechanisms and biological relevance of reported low dose effects are unclear. However, the question remains whether adverse effects occur from low-level chronic exposures, particularly during fetal, postnatal and early childhood development.

Varying definitions of endpoints, nonspecific

endpoints caused by multiple factors, lack of exposure and effect surveillance data, confounders and effect modifiers, and long latency periods between exposures and outcomes, complicate attempts to reach definitive conclusions through epidemiologic studies (Schlettler, 2001).

In order to comprehensively assess the potential endocrine-disrupting toxicities of BPA or complex mixtures of xenoestrogens, further investigation is needed. However, only a large scale, long term prospective study will show if and how brain development is influenced by prenatal and postnatal EDCs including BPA exposure, and also determine the underlying pathogenetic mechanisms. Even in the absence of clear proof of harm, the judicious reduction of exposures is needed to protect pregnant mothers and children, by modifying the use of plastic products and reducing the release of BPA and other xenobiotics into the environment.

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References

Adriani W, Seta DD, Dessi-Fulgheri F, Farabollini F, Laviola G. Altered profiles of spontaneous novelty seeking, impulsive behavior, and response to D-amphetamine in rats perinatally exposed to bisphenol A. Environ Health Perspect 2003;111:395-401

Ashby J, Tinwell H, Haseman J. Lack of effects for low dose levels of bisphenol A and diethylstilbestrol on the prostate gland of CF1 mice exposed in utero. Regul Toxicol Pharmacol 1999;30:156-166

Brotons JA, Olea-Serrano MF, Villalobos M, Pedraza V, Olea N. Xenoestrogens released from lacquer coatings in food cans. Environ Health Perspect 1995;103:608-612

Cagen SZ, Waechter JM Jr, Dimond SS, Breslin WJ, Butala JH, et al. Normal reproductive organ development in CF-1 mice following prenatal exposure to bisphenol A. Toxicol Sci 1999;50:36-44

Cheek AO, Vonier PM, Oberdorster E, Burow BC, McLachlan JA. Environmental signaling: A biological context for endocrine disruption. Environ. Health Perspect 1998;106 Suppl 1:5-10

Christian M, Gillies G. Developing hypothalamic dopaminergic neurones as potential targets for environmental estrogens. J Endocrinol 1999;160:1-6

de Escobar GM, Obregon MJ, del Rey FE. Role of thyroid hormone during early brain development. European Journal of Endocrinology 2004;151:25-37

DeVito M, Biegel L, Brouwer A, Brown S, Brucker-Davis F, et al. Screening methods for thyroid hormone disruptors. Environ Health Perspect 1999 May;107(5):407-15

Dodds EC, Lawson W(1936) Synthetic estrogenic agents without the phenanthrene nucleus. Nature 137:996

Facciolo RM, Alo R, Madeo M, Canonaco M, Dessi-Fulgheri F. Early cerebral activities of the environmental estrogen bisphenol A appear to act via the somatostatin receptor subtype sst(2). Environ Health Perspect 2002;110 Suppl 3:397-402

Farabollini F, Porrini S, Dessi-Fulgherit F. Perinatal exposure to the estrogenic pollutant bisphenol A affects behavior in male and female rats. Pharmacol Biochem Behav 1999;64:687-694

Gaido KW, Leonard LS, Lovell S, Gould JC, Babai D, et al. Evaluation of chemicals with endocrine

modulating activity in a yeast-based steroid hormone receptor gene transcription assay. Toxicol Appl Pharmacol 1997;143:205-212

Gupta C. Reproductive malformation of the male offspring following maternal exposure to estrogenic chemicals. Proc Soc Exp Biol Med 2000;224(2):61-68

Hauser P, Zametkin AJ, Martinez P, Vitiello B, Matochik JA, et al. Attention Deficit-Hyperactivity Disorder in People with Generalized Resistance to Thyroid Hormone. N Engl J Med 1993;328:997-1001

Howdeshell KL, Peterman PH, Judy BM, Taylor JA, Orazio CE, et al. Bisphenol A is released from used polycarbonate animal cages into water at room temperature. Environ Health Perspect 2003;111:1180-1187

Ikezuki Y, Tsutsumi O, Takai Y, Kamei Y, Taketani Y. Determination of bisphenol A concentrations in human biological fluids reveals significant early prenatal exposure. Hum Reprod 2002;17:2839-2841

IPC, Global assessment of the state of the science of endocrine disruptors, international programme on chemical safety(IPCS), World Health Organization, Geneva, Switzerland, 2002 http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/

Jonathan NB, Steinmetz R. Xenoestrogens: The emerging story of Bisphenol A. Trend Endo Meta 1998;9:124-128

Kabuto H, Amakawa M, Shishibori T. Exposure to bisphenol A during embryonic/fetal life and infancy increases oxidative injury and causes underdevelopment of the brain and testis in mice. Life Sci 2004;74:2931-40

Kelce WR, Stone CR, Laws SC, Gray LE, Kemppainen JA, et al. Persistent DDT metabolite p,p'-DDE is a potent androgen receptor antagonist. Nature 1995;375:581-5

Kester MH, Bulduk S, van Toor H, Tibboel D, Meinl W, et al. Potent inhibition of estrogen sulfotransferase by hydroxylated metabolites of polyhalogenated aromatic hydrocarbons reveals alternative mechanism for estrogenic activity of endocrine disrupters. J Clin Endocrinol Metab 2002;87:1142-1150

Khurana S, Ranmal S, Ben-Jonathan N. Exposure of newborn male and female rats to environmental estrogens: delayed and sustained hyperprolactinemia and alterations in estrogen receptor expression. Endocrinology 2000;141(12):4512-4517

Knaak JB, Sullivan LJ. Metabolism of bisphenol A in the rat. Toxicol Appl Pharmacol 1966 Mar;8:175-184

Kubo K, Arai O, Omura M, Watanabe R, Ogata R, et al. Low dose effects of bisphenol A on sexual differentiation of the brain and behavior in rats. Neurosci Res 2003;45:345-356

Kurebayashi H, Betsui H, Ohno Y. Disposition of a low dose of 14C-bisphenol A in male rats and its main biliary excretion as BPA glucuronide. Toxicol Sci 2003;73:17-25

Langer P, Tajtakova M, Fodor G, Kocan A, Bohov P, et al. Increased thyroid volume and prevalence of thyroid disorders in an area heavily polluted by polychlorinated biphenyls. Eur J Endocrinol 1998;139:402-409

Matsumoto J, Yokota H, Yuasa A. Developmental increases in rat hepatic microsomal UDP-glucuronosyltransferase activities toward xenoestrogens and decreases during pregnancy. Environ Health Perspect 2002;110:193-196

Matthews JB, Twomey K, Zacharewski TR. In vitro and in vivo interactions of bisphenol A and its metabolite, bisphenol A glucuronide, with estrogen receptors alpha and beta. Chem Res Toxicol 2001;14:149-157

Mitchell ML, Klein RZ. The sequelae of untreated maternal hypothyroidism. European Journal of Endocrinology 2004;151:45-48

Mizuo K, Narita M, Miyagawa K, Narita M, Okuno E, et al. Prenatal and neonatal exposure to bisphenol-A affects the morphine-induced rewarding effect and hyperlocomotion in mice. Neurosci Lett 2004;356:95-98

Moriyama K, Tagami T, Akamizu T, Usui T, Saijo M, et al. Thyroid hormone action is disrupted by bisphenol A as an antagonist. J Clin Endocrinol Metab 2002;87:5185-5190

Negishi T, Kawasaki K, Suzaki S, Maeda H, Ishii Y, et al. Behavioral alterations in response to fear-provoking stimuli and tranylcypromine induced by perinatal exposure to bisphenol A and nonylphenol in male rats. Environ Health Per-

spect 2004;112:1159-1164
Olea N, Pulgar R, Perez P, Olea-Serrano F, Rivas A, et al. Estrogenicity of resin-based composites and sealants used in dentistry. Environ Health Perspect 1996;104:298-305
Payne J, Rajapakse N, Wilkins M, Kortenkamp A. Prediction and assessment of the effects of mixtures of four xenoestrogens. Environ Health Perspect 2000;108(10):983-987
Rajapakse N, Ong D, Kortenkamp A. Defining the impact of weakly estrogenic chemicals on the action of steroidal estrogens. Toxicol Sci 2001; 60(2):296-304
Rajapakse N, Silva E, Scholze M, Kortenkamp A. Deviation from additivity with estrogenic mixtures containing 4-nonylphenol and 4-tert-octylphenol detected in the E-SCREEN assay. Environ Sci Technol 2004;38(23):6343-6352
Schettler T. Toxic threats to neurologic development of children. Environ Health Perspect 2001 Dec;109 Suppl 6:813-16.
Schonfelder G, Wittfoht W, Hopp H, Talsness CE, Paul M, et al. Parent bisphenol A accumulation in the human maternal-fetal-placental unit. Environ Health Perspect 2002;110:703-707.
Seegal RF, Brosch KO, Okoniewski RJ. Effects of in utero and lactational exposure of the laboratory rat to 2,4,2',4'- and 3,4,3',4'-tetrachlorobiphenyl on dopamine function. Toxicol Appl Pharmacol 1997;146:95-103
Seiwa C, Nakahara J, Komiyama T, Katsu Y, Iguchi T, et al. Bisphenol A exerts thyroid-hormone-like effects on mouse oligodendrocyte precursor cells. Neuroendocrinology 2004;80: 21-30
Sheehan DM, Willingham E, Gaylor D, Bergeron JM, Crews D. No Threshold Dose for Estradiol-Induced Sex Reversal of Turtle Embryos: How Little Is Too Much? Environ Health Perspect 1999;107:155-159
Sheehan DM. Activity of environmentally relevant low doses of endocrine disruptors and the bisphenol A controversy: initial results confirmed. Proc Soc Exp Biol Med 2000;224:57-60
Silva E, Rajapakse N, Kortenkamp A. Something from "nothing"-eight weak estrogenic chemicals combined at concentrations below NOECs produce significant mixture effects. Environ Sci Technol. 2002;36(8):1751-1756
Singleton DW, Khan SA. Xenoestrogen exposure and mechanisms of endocrine disruption. Frontiers in bioscience 2003;8 Suppl:110-118
Smith JW, Evans AT, Costall B, Smythe JW. Thyroid hormones, brain function and cognition: a brief review. Neurosci Biobehav Rev 2002;26: 45-60
Sohoni P, Sumpter JP. Several environmental oestrogens are also anti-androgens. J Endocrinol 1998;158:327-339
Steinmetz R, Brown NG, Allen DL, Bigsby RM, Ben-Jonathan N. The environmental estrogen bisphenol A stimulates prolactin release in vitro and in vivo. Endocrinology 1997;138:1780-1786
Suzuki T, Mizuo K, Nakazawa H, Funae Y, Fushiki S, et al. Prenatal and neonatal exposure to bisphenol-A enhances the central dopamine D1 receptor-mediated action in mice: enhancement of the methamphetamine-induced abuse state. Neuroscience 2003;117:639-644
Takahashi O, Oishi S. Disposition of orally administered 2,2-Bis(4-hydroxyphenyl) propane (Bisphenol A) in pregnant rats and the placental transfer to fetuses. Environ Health Perspect 2000;108:931-935
Tilson HA. Developmental neurotoxicology of endocrine disruptors and pesticides: identification of information gaps and research needs. Environ Health Perspect. 1998 Jun;106 Suppl 3:807-311
Tyl RW, Myers CB, Marr MC, Thomas BF, Keimowitz AR, et al. Three-generation reproductive toxicity study of dietary bisphenol A in CD Sprague-Dawley rats. Toxicol Sci 2002;68:121-146
Vermiglio F, Lo Presti VP, Moleti M, Sidoti M, Tortorella G, et al. Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: a possible novel iodine deficiency disorder in developed countries. J Clin Endocrinol Metab 2004;89:6054-6060
Vulsma T. Impact of exposure to maternal PCBs and dioxins on the neonate's thyroid hormone status. Epidemiology 2000;11:239-241
White R, Jobling S, Hoare SA, Sumpter JP Parker MG. Environmentally persistent alkylphenolic compounds are estrogenic. Endocrinology 1994:

135:175-182

Wozniak AL, Bulayeva NN, Watson CS. Xenoestrogens at picomolar to nanomolar concentrations trigger membrane estrogen receptor-alpha-mediated Ca^{2+} fluxes and prolactin release in GH3/B6 pituitary tumor cells. Environ Health Perspect 2005 Apr;113(4):431-439

Yamamoto T, Yasuhara A. Quantities of bisphenol a leached from plastic waste samples. Chemosphere 1999;38:2569-2576

Yoneda T, Hiroi T, Osada M, Asada A, Funae Y. Non-genomic modulation of dopamine release by bisphenol-A in PC12 cells. J Neurochem 2003; 87:1499-1508

Yoshida T, Horie M, Hoshino Y, Nakazawa H. Determination of bisphenol A in canned vegetables and fruit by high performance liquid chromatography. Food Addit Contam 2001;18: 69-75

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