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Perinatal Exposure to Chemical Agents: Delayed Effects by the Mechanism of Imprinting (Cell Programming)

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Abstract

Tchernitchin AN. Perinatal Exposure to Chemical Agents: Delayed Effects by the Mechanism of Imprinting (Cell Programming). ARBS Ann Rev Biomed Sci 2005;7:68-126. The early reports linking the development of clear cell cervicovaginal adenocarcinoma in young women with diethylstilbestrol treatment of their mothers during pregnancy were the first evidence that perinatal exposure to several substances may induce irreversible alterations that can be detected at older ages. Current evidence suggests that these substances induce, by the mechanism of imprinting, alterations of the differentiation or programming of several cell-types that last for life and that may further result in the development of disease.

The first evidence for the induction of the imprinting mechanism was obtained by prenatal or early postnatal exposure to abnormal hormone levels or to synthetic hormonal compounds. Today it is known that several non-hormonal compounds such as heavy metals, pesticides, other pollutants, pharmaceuticals, drugs of abuse, food additives and even normal constituents present in food may induce this mechanism. The present review describes most relevant delayed effects of perinatal exposure to hormones displaying sex hormone action, several pollutants (lead, benzopyrenes, ozone, nitrogen dioxide, carbon monoxide, chlorinated organic persistent compounds, polychlorobiphenyls (PCBs), dioxins and several pesticides), maternal tobacco smoking, and illicit (tetrahydrocannabinol,

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cocaine, opiates, ketamine, toluene) and licit (nicotine, caffeine and ethyl alcohol) drugs of abuse.

It is concluded that perinatal exposure to several agents causes irreversible changes that determine health conditions during adulthood. Several diseases developing during adulthood probably were determined during early stages of life, under the effect of exposure or preferential mother's diet during pregnancy. Regulations to avoid these early exposures may contribute to an important improvement of health conditions of humankind.

KEYWORDS: Imprinting, prenatal exposure delayed effects, perinatal exposure delayed effects, cell programming, sex hormones, pollutants, drugs of abuse, maternal tobacco smoking

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1. Introduction

Acute or chronic exposure to several toxic agents, even at low doses or concentrations, may cause delayed adverse effects that are evident later in life, frequently several years after exposure, or even in the future generations of exposed individuals. The best known delayed effects are cancer development, mutations and congenital malformations. Cancer may develop several years following exposure to chemical or physical carcinogens at any stage of life. The exposure to mutagens may affect germinal cells, causing hereditary diseases that may persist in the population for many generations. The exposure to teratogens during the early stages of embryonic development may cause gross anatomic malformations such as anencephaly, non compatible with life, hydrocephalia, focomelia, tetralogy of Fallot and many others. A large number of mutagens, teratogens and carcinogens for various animal species were found and a few of them were confirmed as causing the same effects in humans.

Recently, a new kind of delayed effects was reported. The first evidence emerged from clear cell cervicovaginal adenocarcinoma development in young women whose mothers were treated with diethylstilbestrol during pregnancy (Herbst, 1981; Verheigen *et al.*, 1991). The cause-effect relationship was subsequently confirmed in experimental animals (Walker, 1983; Newbold *et al.*, 1990), suggesting that that prenatal or neonatal exposure to this synthetic estrogen induces permanent changes in some cell types. These changes become evident after puberty as an enhanced risk for malignancy development, probably under the effect of postpubertal increased estrogen levels in the blood.

Based on these findings, the Hungarian biologist György Csaba and his co-workers started an experimental study that showed that exposure of fetuses to hormones or hormone action-displaying xenobiotics during critical periods of their development induces persistent changes in the action of related hormones (Csaba & Nagy, 1976; Csaba, 1980). These changes, detected later in life, include a modification in the activity of receptors and in the intensity of responses mediated by them (Dobozy *et al.,* 1985; Csaba *et al.,* 1986). This effect of hormones during fetal or neonatal life permanently modifying the ability of the cells to react to hormone stimulation, was named by Csaba "imprinting" (Csaba, 1980; Csaba *et al.* 1986).

In addition to a change in quantity and quality of hormone receptors in affected cell-types once they reach maturity; this process also involves several biochemical, morphological and functional alterations in these cell-types. Based on the above considerations, it was proposed that the process discovered by Csaba involves a modification of the routes of normal differentiation of these cells (Tchernitchin & Tchernitchin, 1992) or of the cell programming process (Tchernitchin *et al.*, 1999).

Subsequent studies lead to the finding that not only hormones, but additionally several pharmaceutical agents, pollutants, stress, food additives, some natural components of food, and several substances present in plants, display the ability to induce imprinting or cell reprogramming following interaction with the different cell-types at precise stages

of their fetal or neonatal development (Tchernitchin & Tchernitchin, 1992; Tchernitchin *et al.*, 1999; Tchernitchin & Lapin, 2005).

It was proposed that the changes in cell differentiation/programming induced by this mechanism may favor, later in adulthood, the development of various diseases, such as neoplasias, endocrine abnormalities, infertility, immune diseases, psychic alterations, or changes in personality and behavior (Tchernitchin & Tchernitchin, 1992; Tchernitchin *et al.*, 1999). The relevance of this process in the determination of health conditions later on in life takes place in the fact that it is not only generated by agents that it is easy to avoid. It is also induced by early exposure to a myriad of agents and conditions that it is very difficult to detect and avoid, such as stress, very low concentrations of pollutants and natural substances contained in food.

The present report reviews some of the best known imprinting inducing agents relevant to human pathology, especially those affecting human health during adulthood. These are: substances displaying sex hormone action, various pollutants, drugs of abuse, food additives and some natural components of food.

2. Agents Displaying Sex Hormone Action

2.1. Effect of Perinatal Exposure to Diethylstilbestrol and other Estrogens on the Female Genital Tract

The earliest information on the effect of prenatal exposure to diethylstilbestrol in humans and in experimental animals was the gynecologic malignancies that develop after puberty or during adult age in daughters of mothers treated with this compound during pregnancy (Herbst, 1981; Walker, 1983; Newbold *et al.*, 1990; Verheijen *et al.*, 1991).

In addition to increased carcinogenic activity, other alterations develop in the female genital tract in female offspring following maternal exposure to diethylstilbestrol and other estrogens during pregnancy.

In experimental animals, perinatal exposure to diethylstilbestrol, allylestrenol, estradiol-17ß or estradiol benzoate induce permanent changes in steroid hormone activity (Gellert *et al.*, 1977; Aihara *et al.*, 1980; Campbell, 1980; Csaba *et al.*, 1986; Andersson & Forsberg, 1988), histological alterations (Ennis & Davies, 1982; Andersson & Forsberg, 1988), including gross abnormalities (Ennis & Davies, 1982), development of paraovarian cysts (Gladyshev *et al.*, 1994) and infertility (McLachlan *et al.*, 1982).

In the human species, women prenatally exposed to diethylstilbestrol also display histological alterations in the genital tract (Herbst, 1981), including gross abnormalities (Berger & Alper, 1986; Menczer *et al.*, 1986), development of paraovarian cysts (Haney *et al.*, 1986), endometriosis (Stillman & Miller, 1984; Missmer *et al.*, 2004), increased frequency of abortions (Verheigen *et al.*, 1991) and infertility (Stillman & Miller, 1984; Berger & Alper, 1986; Menczer *et al.*, 1986).

We suggested that changes in steroid receptors, explaining the modifications

of the responses to hormone stimulation and most of the above changes, probably reflect the imprinting of routes of heterodifferentiation or cell reprogramming of genital tissues following perinatal exposure to diethylstilbestrol or other estrogens (Tchernitchin & Tchernitchin, 1992; Tchernitchin *et al.*, 1999).

In the mouse, the precocious appearance of estrogen receptors in uterovaginal epithelium (Andersson & Forsberg, 1988) may explain the postpubertal increase in adenocarcinomas derived from this tissue. In the human, the abnormal localization of uterine epithelium in the cervix and vagina was considered as one of the factors increasing risk of malignancy development (Robboy *et al.*, 1984). Further, the decrease in estrogen receptors in the rodent uterus following neonatal treatment with diethylstilbestrol, allylestrenol, estradiol-17ß or estradiol benzoate (Gellert *et al.*, 1977; Aihara *et al.*, 1980; Campbell, 1980; Csaba *et al.*, 1986; Campbell & Modlin, 1987; Medlock *et al.*, 1988) may explain the persistent underdevelopment of rat uterine glands and perhaps the mechanism involved in uterine hypoplasia in humans (Medlock *et al.*, 1988), in addition to a decrease in uterine responsiveness to estrogen stimulation (Gellert *et al.*, 1977; Aihara *et al.*, 1980; Campbell, 1980; Campbell & Modlin, 1987).

The existence of separate groups of estrogen receptors that mediate separate groups of estrogenic responses through independent mechanisms of hormone action (Tchernitchin, 1983; Tchernitchin *et al.*, 1985, 1989a) and the finding that perinatal exposure to other sex steroids induce selective interference with some responses to estrogens but not others (Arriaza *et al.*, 1989; Mena *et al.*, 1992) suggests that estrogenic compounds, including phytoestrogens, may selectively interfere with the development of some but not all responses to estrogen.

2.2. Effect of Perinatal Exposure to Androgens on the Female Genital Tract

Perinatal exposure of experimental animals to high levels of androgens causes changes in the normal development of fetal genitalia and mammary glands (Wolf *et al.*, 2002), failure in ovulation and corpus luteum formation (Iguchi *et al.*, 1988), development of polycystic ovary (Iguchi *et al.*, 1988; Bruns *et al.*, 2004), constantly cornified vaginal epithelium (Herrenkohl & Scott, 1984; Iguchi *et al.*, 1988), changes in uterine physiology including abnormal hormone-induced uterine growth (Herrenkohl & Scott, 1984; Schwartz *et al.*, 1986), a permanent alteration in the hypothalamic cyclic center, the "sexually dimorphic nucleus of the preoptic area" (Ito *et al.*, 1986), and sterility (Sawada, 1988).

In sheep, exposure of females to testosterone before birth produces perturbances and maltiming in periovulatory gonadotropin secretory dynamics, but these do not produce apparent defects in cycle regularity or luteal function (Savabieasfahani *et al.,* 2005). With regard to estrogen action, there was a controversy. While some investigators did not detect changes in estrogen receptor levels (Gellert *et al.*, 1977; Campbell, 1980; Campbell & Modlin, 1987) or in estrogen action (Gellert *et al.*, 1977) in the uterus of neonatally androgenized

rats, others reported a decrease in receptor levels and an impairment in hormone action (Campbell, 1980; Schwartz *et al.*, 1986; Campbell & Modlin, 1987).

The above studies used, however, biochemical techniques which do not discriminate between changes in the different uterine cell-types, explaining, at least in part, differences in results on the delayed effects of prenatal exposure to androgens.

Taking into account the possibility of dissociation of responses to estrogen under different experimental conditions (Tchernitchin, 1976; Tchernitchin *et al.*, 1976, 1985, 1989a; Tchernitchin & Galand, 1982, 1983; Galand *et al.*, 1985; Grunert *et al.*, 1986), studies were performed in our Laboratories on estrogen action in the uterus of prenatally androgenized rats, using morphometrical techniques that discriminate between responses in the different uterine cell-types. These studies demonstrated that prenatal androgenization inhibits estrogen induced luminal and glandular epithelium hypertrophy, and potentiates endometrial edema, eosinophil migration to the uterus (Arriaza *et al.*, 1989) and the mitotic response (Tchernitchin *et al.*, 1989b), but does not modify myometrial hypertrophy in the prepubertal rat uterus (Arriaza *et al.*, 1989). This dissociation of responses to estrogen can be explained by the independence between the different mechanisms of estrogen action in the uterus (Tchernitchin *et al.*, 1976, 1985, 1989a; Tchernitchin & Galand, 1982, 1983; Tchernitchin, 1983; Galand *et al.*, 1985; Grunert *et al.*, 1986) and the independent regulation of hormone action in every uterine cell-type (Tchernitchin, 1976; Tchernitchin *et al.*, 1985).

The mechanisms involved in the changes of uterine physiology following prenatal exposure to androgens are not well understood (see review in Tchernitchin & Tchernitchin, 1992). The most conspicuous effect, the selective inhibition of estrogen action in luminal and glandular epithelium cells in androgenized rats, may explain the decrease in fertility observed in these animals (see review in Tchernitchin & Tchernitchin, 1992). If this effect is confirmed in humans, it may explain changes in fertility in daughters of patients treated with androgens or other steroids during pregnancy and alert population to the possible risk of the ingestion of meet from animals grown with synthetic androgens.

2.3. Neurobehavioral Effects of Perinatal Exposure to Synthetic Androgens, Estrogens or Progestins

Adult sex behavior and other sex-dependent personality characteristics are dependent on the presence of sex hormones during precise stages of intrauterine development in some regions of the brain. These hormones determine paths of neuronal differentiation that are normal for each gender. Following prenatal exposure to abnormal levels of sex steroids or substances displaying agonist action, the most conspicuous alterations appear in the central nervous system, including biochemical changes and neurobehavioral alterations.

Prenatal exposure to low level of synthetic estrogens determine an outer-directed personality in the adult, one that is more group-oriented and group-dependent,

less individualistic and more consciously identified with its group or social environment. Exposure to synthetic progestins causes an inner or self-directed personality in the adult, one that is more independent, self-assured and self-sufficient, more individualistic and less concerned with social environment (Reinisch, 1977). Perinatal exposure to higher levels of sex steroids or non-steroidal synthetic agonists such as diethylstilbestrol imprints, in humans (see review in Tchernitchin & Tchernitchin, 1992), life-long alterations in sex-dimorphic behavior (gender role), temperamental sex differences and sexual orientations in adults, as well as sex-dimorphic play behavior in children and a decrease in orientation towards parenting in adult women.

2.4. Other Effects of Prenatal or Early Postnatal Exposure to Synthetic Estrogens or Androgens

Neonatal androgenization abolishes clock-timed gonadotrophin release in prepubertal and adult female rodents, induces changes in tuberoinfundibular dopamine nerve activity and several biochemical alterations in the forebrain, hypothalamus and cerebellum, including alterations in opioid control of noradrenaline release in specific brain areas and changes in gonadotropin, oxytocin and prolactin secretion (see review in Tchernitchin & Tchernitchin, 1992). Prenatal exposure to estrogens affects subsequent transport of a-aminobutyric acid into rat brain (Litteria *et al.*, 1977). As in the genital tract, the above alterations reflect important changes in the differentiation and development of the central nervous system and suggests an explanation for the behavioral changes in exposed experimental animals or humans.

In women, it was been suggested that prenatal exposure to high levels of androgens determines during adulthood a shift from strictly heterosexual orientation towads a not-strictly heterosexual orientation (van Anders & Hampson, 2005).

Androgenization induces permanent alterations in testosterone metabolism in the hypothalamus-pituitary-gonadal axis in male rats. Neonatal exposure to estrogens determines developmental, structural and functional alterations in testis, prostate and seminal vesicles (see review in Tchernitchin & Tchernitchin, 1992). Prenatal diethylstilbestrol also affects the male reproductive system: it causes an inhibitory effect on testicular function as late as in offspring at 6 weeks of age (Yamamoto *et al.*, 2003).

The immune system is also affected by exposure to sex hormones. Estrogens cause changes in the development of the rat thymus gland, including premature involution of its cortex (Leceta *et al.*, 1988). Diethylstilbestrol persistently alters NK cell activity in the mouse (Kalland, 1984) and humans (Ford *et al.*, 1983). Prenatal diethylstilbestrol exposure induces long term thymic changes in a sex-related fashion, probably pre-programming the thymus to result in aberrant response to a subsequent adult exposure to an endocrine disrupting chemical (Fenaux *et al.*, 2004). Alterations in immune responsiveness (Ways *et al.*, 1987) and increased occurrence of autoimmune disease (Noller *et al.*, 1988), were reported in women exposed *in utero* to diethylstilbestrol, in addition to

the increased frequency of diseases suggesting impaired immune function, such as respiratory tract infections, asthma, arthritis, and lupus (Wingard & Turiel, 1988).

Thyroid function is also permanently affected by prenatal diethylstilbestrol; it increases thyroid function. Plasma T4 concentrations appeared increased at 1, 3 and 6 weeks after birth in prenatally exposed rats, TSH concentration at 6 weeks of age was also significantly increased, and the height of thyroid follicular epithelial cells was increased at 3 weeks (Yamamoto *et al.*, 2003).

Prenatal androgenization of male rhesus monkeys determines a decrease in insulin sensitivity and in pancreatic beta-cell compensation (disposition index). Since prenatally androgenized males do not exhibit elevated androgens during adulthood, it was suggested that insulin resistance and impaired pancreatic beta-cell function result from fetal reprogramming of key metabolic tissues (Bruns *et al.*, 2004).

3. Pollutants

Pollutants best known to induce imprinting mechanisms following perinatal exposure are lead, benzopyrenes, ozone, dioxins and several pesticides.

3.1. Lead

The most relevant delayed effects caused by prenatal, early postnatal or infant age exposure to lead by the mechanism of imprinting occur in the central nervous and the female reproductive systems. These effects persist through life. They include infertility (possibly through alterations in uterine estrogen receptors and ovary LH receptors), learning impairment, lower IQ scores and neurobehavioral changes.

3.1.1. Lead Effects in Adolescent and Adult Population

In relation to reproductive damage, chronic lead exposure at adolescence or during adult age depresses fertility and causes reproductive disfunctions in both males and females (Rom, 1976; Needleman & Landrigan, 1981; Winder, 1993). In women, it causes infertility, miscarriage, preeclampsia, pregnancy hypertension, and premature delivery (Winder, 1993), polymenorrhea, prolonged and abnormal menstruations, hypermenorrhea and important increase in spontaneous abortions incidence (Tang & Zhu, 2003). The infertility developing during adult age may recover following decrease in blood lead levels. On the contrary, the antifertility that follows perinatal or early childhood exposure usually persists through life.

The above alteration in frequent in humans under the effect of environmental or occupational exposures, and may widely affect human population, as it was hypothesized for the Roman Empire times. In fact, it was suggested that the declining birth rate and apparently increased incidence of psychoses in Rome's ruling class, which may have been at the root of the Empire's dissolution, were a result of exposure to lead in food and wine (see Tchernitchin & Tchernitchin, 1992, for a review).

The reproductive effects of chronic lead exposure during the prepubertal or adult age were also demonstrated in experimental animals, causing mainly infertility and increasing abortion rate. In monkeys, it causes inhibition of menstruation, ovulation, and follicular growth. In rodents, it was shown to cause a delay in vaginal opening (Kimmel *et al.*, 1980), a decrease in frequency of implanted ova and of pregnancies (Odenbro & Kihlström, 1977) increasing abortion rate or causing infertility (Ronis *et al.* 1996). Further, lead exposure was shown to selectively affect some but not all responses to estrogen in the uterus (Tchernitchin *et al.*, 1998a, 1998b, 2003).

Experimental studies suggest that lead affects female reproductive organs through different mechanisms. It may interact at the enzyme level (Kempinas *et al.*, 1994), may interfere with the action of reproductive hormones at the target organ by increasing the quantity of estrogen receptors in the pregnant uterus (Wide and Wide, 1980) or it may inhibit the implantation process, which is regulated by estrogens (Wide, 1980). Lead may interfere at the level of hypothalamus-pituitary, decreasing pituitary response to growth hormone releasing factor (Camoratto *et al.* 1993), affecting levels of gonadotropin-releasing hormone, somatostatin (Sierra & Tiffany-Castiglioni, 1992), FSH and LH (McGivern *et al.,* 1991) and increasing blood levels of glucocorticoids (Vyskocil *et al.* 1991).

In addition, exposure to lead causes a stress reaction (Vyskocil *et al.*, 1991); that is followed by a raise in glucocorticoid, catecholamine (Vyskocil *et al.*, 1991), and prolactin (Kinsley *et al.*, 1989) levels. Taking into consideration that increased levels of glucocorticoids (Tchernitchin, 1979; Tchernitchin *et al.*, 1976, 1985) and prolactin (Unda *et al.*, 1989) selectively inhibit some responses to estrogen in the uterus and other target organs, it may be expected that an increase of these hormones in blood levels of lead-exposed animals may affect several responses to estrogen in the uterus.

Further, the reported increase in the number of estrogen receptors in pregnant animals following acute lead exposure (Wide & Wide, 1980) provides another possible mechanism for lead-estrogen interaction. From the above considerations, these mechanisms have to be kept in mind for the analysis of the persistent changes in the various organs and systems following prenatal or early postnatal exposure to lead involving imprinting.

Besides reproductive effects, chronic exposure of adult population to lead causes progressive damage to the central and peripheral nervous systems (Needleman *et al.,* 1979; Banks *et al.,* 1997), a moderate increase in blood pressure (Staessen *et al.,* 1994), it affects the hematopoietic system (Grandjean *et al.,* 1989; Pagliuca *et al.,* 1990; Graziano *et al.,* 1991), depresses thyroid function (Tuppurainen *et al.,* 1988), it causes nephropathy (Weeden *et al.,* 1979; Ong *et al.,* 1987; Cooper 1988; Cardenas *et al.,* 1993), intestinal colic and gastrointestinal symptoms (Pagliuca *et al.,* 1990). Lead exposure damage the immune system in humans as well as in experimental animals (Jaremin 1983; Cohen *et al.,* 1989; Koller, 1990; Lang *et al.,* 1993; Tchernitchin *et al.,* 1997; Villagra *et al.,* 1997). It may also cause, in the human species, effects on chromosomes (Al-Hakkak *et al.,*1986), increase in mortality rate (Cooper, 1988) and a decrease in the life expectancy.

3.1.2. Imprinting Induced by Perinatal Exposure to Lead

Lead may induce an imprinting mechanism (Tchernitchin & Tchernitchin, 1992; Tchernitchin *et al.*, 1999) causing a persistent decrease in the concentration uterine estrogen receptors (Wiebe & Barr, 1988) and of ovary luteinizing hormone (LH) receptors (Wiebe *et al.*, 1988) following perinatal exposure.

In the experimental animal model, it was found that prenatal exposure of female rats cause a persistent alteration of ovary gonadotrophin receptors and of steroidogenesis that can be detected later in life (Wiebe *et al.*, 1988). These findings may explain the delay in puberty that occurs with very low increases in blood lead levels from dietary origin in mice. In fact, while modest increases in blood lead concentrations from a normal background of 2-3 to 13.2 μg/dL delayed the onset of puberty by 15-20% to about 40-43 days, reducing blood lead from 2-3 to 0.7 μg/dL was associated with an acceleration of puberty to 21 days, an enhancement by over 30% (Iavicoli *et al.*, 2004). This dose-response relationship represents novel findings of possible ecological as well as public health significance that indicates that lead is able to induce biologically significant changes at blood lead levels previously thought to be without effect.

In prenatally exposed animals, the number and characteristics of uterine estrogen receptors differ from that found in non-exposed animals (Wiebe & Barr, 1988). Work in progress in our Laboratory shows that prenatal exposure to lead causes selective changes in some responses to estrogens but not others (Tchernitchin *et al.*, unpublished observations). These alterations explain, at least in part, the known fertility inhibition in lead exposed experimental animals and humans (Rom, 1976; Needleman & Landrigan, 1981).

In experimental animals, prenatal exposure to lead causes a permanent increase in the affinity of δ- (McDowell & Kitchen, 1988) and μ-opioid (Kitchen, 1993) receptors, but not κ–opioid receptors (Kitchen, 1993) in the rat brain. This change parallels the impairment of opioid but not non-opioid stress-induced antinociception in developing rats (Jackson & Kitchen, 1989), and a depression-like behavior (de Souza Lisboa *et al.*, 2005). It has not been investigated whether these changes also occur in humans; if they do, they may explain behavior changes that occur in exposed population (Bellinger & Needleman, 1985; Rothenberg *et al.*, 1989; Needleman *et al.*, 1990), and perhaps may explain increased frequency of addiction to opioid or other abuse drugs in high lead contaminated environments (Tchernitchin & Tchernitchin, 1992).

The finding that the dopamine and 5-hydroxyindoleacetic acid response to amphetamine is enhanced in lead-exposed animals (Lasley *et al.*, 1985), suggests that the response to other stimulant abuse substances may be enhanced as well (Tchernitchin & Tchernitchin, 1992).

Our hypothesis on the role of early exposure to lead on abuse drug addiction (Tchernitchin & Tchernitchin, 1992) was confirmed by the finding of opiate deprivation syndrome that occurs in prenatally exposed rats but not in those were not exposed (Kitchen & Kelly, 1993).

In experimental animals, exposure to lead impairs learning (Massaro *et al.*, 1986).

In humans, it causes deficits in central nervous system functioning that persists into adulthood, including learning impairment, deficit in psychometric intelligence scores, lower IQ scores, poorer school performance, increased school failure, reading disabilities and poorer eye-hand coordination (Bellinger & Needleman, 1985; Rothenberg *et al.*, 1989; Needleman *et al.*, 1990). According to the U.S. Department of Health & Human Services, a deficit in the IQ scores can already be detected in children with lead blood levels as low as 9 μg/dL (Royce, 1990). The inhibition by lead of brain protein kinase C at early stages of brain development may explain persistent lead effect in memory damage (Xu *et al.*, 2005).

A recent report from our Laboratory describes neurological damage (measured as sums of scores of the different neurological signs and symptoms from anamnesis and physical examination, which included learning deficit and behavioral alterations) with blood lead levels 10 to 19 μg/dL or higher in children 1 to 10 years living near a lead mineral storage site in Antofagasta, Chile (Tchernitchin *et al.*, 2006). It was also shown a delay in response to auditory stimulus in children with lead blood levels $\geq$ 10 μg/dL in children 8 or 9 years old living in a lead polluted area in Arica, Chile; this delay occurs at much lower levels than those causing a decrease in the velocity of nerve conductance through motor myelinated nerve (Tchernitchin *et al.*, 2006).

Similarly to what was described in the rat (De Marco *et al.*, 2005), in humans perinatal or infant exposure to lead causes the development of a hyperactive and aggressive behavior (Tchernitchin *et al.*, 2006). Imprinting or programming in central nervous system cells may explain at last in part the above alterations. A correlation between bone lead levels and history of delinquent behavior in an American population was reported (Needleman *et al.*, 1996). It was suggested that the hyperactive or aggressive behavior induced by early lead exposure, which is irreversible, is a risk behavior for antisocial or delinquent behavior development later in adolescence (Tchernitchin *et al.*, 2006). If this aggressive behavior could be channeled, under psychological treatment, to socially-positive aggression-like activities, such as sports, dance, hobbies, or many other activities, it will be possible to avoid the transformation of these children into a delinquent population (Tchernitchin *et al.*, 2006).

Maternal lead exposure causes permanently elevated blood levels of corticosterone in the offspring; this effect is potentiated by maternal stress. Such increases could suggest a potential mechanism by which lead exposure could enhance susceptibility to diseases and dysfunctions and induce cognitive deficits (Cory-Slechta *et al.*, 2004).

Taking into consideration the proposed role of lead in the Roman Empire dissolution, through the declining birth rate of the ruling class and increased incidence of psychoses (see Tchernitchin & Tchernitchin, 1992, for a review), it is necessary to pay attention to the widespread lead contamination that currently affects many human communities throughout the world. Besides its effects on reproductive functions, it is relevant its damage to central nervous system, impairing mental abilities, inducing aggressive behavior, favoring delinquent behavior and a tendency to addition to drugs of abuse. This

way, lead may also cause an enormous damage to our societies.

We previously proposed (Tchernitchin & Tchernitchin, 1992) that during the second part of this century, an important epidemic of addiction to drugs of abuse developed, first, in large cities from the U.S.A., then, in large cities from Western Europe, and currently in most large cities from the developing Third World. It does not affect rural or small town population localized far away from large cities. This addiction to drugs of abuse paralleled a simultaneous increase in criminality. According to our hypothesis, these changes can be explained, at least in part, by the increase in lead pollution in large cities, but not in small towns, that followed the massive use of leaded gasoline in these places. Perinatal exposure to lead would have originated changes in brain opiate, estrogen and other receptors and subsequent neurobehavioral alterations.

3.2. Benzopyrenes

These are present in air particulate material, and are mainly originated from the combustion of diesel gasoline. Benzopyrenes are carcinogens that are responsible of a high mortality of lung cancer in highly polluted areas (Rivara & Corey, 1995; Pope *et al.*, 2002) as well as in smokers (Denissenko *et al.*, 1996; Matter *et al.*, 2004).

It has been shown that prenatal exposure to benzopyrenes increases risk of child cancers and leukemia development (Knox, 2005). Prenatal exposure also induces, by the mechanism of imprinting, a persistent decrease in glucocorticoid receptors in thymus (Csaba & Inczefi-Gonda, 1984). Exposure to benzopyrenes during the adult age also causes a persistent decrease in glucocorticoid receptors in thymus, which is the first documentation of imprinting mechanisms induced during de adult age (Csaba & Inczefi-Gonda, 1996). These findings mean an alteration in glucocorticoid regulation of the immune function in lymphoid organs. They explain the relative decrease in the immune defense mechanisms against bacterial and viral infections and their increased severity in population exposed to high particulate pollution in cities like Santiago, Chile (Schwartz *et al.*, 1996). Further, this mechanism may explain the increase in premature mortality and the correlation between mortality and PM10 particulate air concentration in the three subsequent days following increased particulate pollution in Santiago (Ostro *et al.*, 1996).

3.3. Ozone

Ozone is an air pollutant affecting many large cities. It is originated by a photochemical process from nitrogen oxides, under catalysis by ultraviolet light and volatile hydrocarbon compounds. The first finding of the delayed effects of prenatal exposure to ozone in rats were reported by Kavlock *et al.* (1980), who described a substantial impairment in somatic and neurobehavioral development in the postnatal life, following exposure of their mothers during pregnancy to 1 and 1.5 ppm ozone. These findings were not confirmed in CD-1 mice by Bignami *et al.* (1994), who found, under the effect of prenatal exposure to 1.2 ppm ozone a slight depression in postnatal body weight gain and a delay in eye

opening only, but not other neurobehavioral changes under the effect of exposure.

Further studies by Dell'Omo *et al.* (1995a) of prenatal and early postnatal exposure to increased ozone concentrations demonstrated delayed selective neurobehavioral effects, and confirmed a long-lasting reduction in body weight without modification of sex differences. Among the selective effects reported on neurobehavioral development, attenuation of the sex differences in several responses (rearing and sniffing in the open-field, activity in the final conditioned place preference test session); a change in response choices in the final conditioned place preference test, in the absence of a main effect on conditioning, a reduction of grooming in the activity test on postnatal day 29, and impairment of passive avoidance acquisition limited to the initial period of training. The above effects were found in the absence of changes in reproductive performance (proportion of successful pregnancies, litter size, offspring viability, and sex ratio).

Other neurobehavioral changes in adult mice following early postnatal exposure to 0.6 ppm ozone (from birth to weaning) were reported by Dell'Omo *et al.* (1995b), such as higher swimming speed, which was unrelated to differences in body weight and to navigational performances. Mice exposed to ozone had a strong tendency to make turns to the left while the controls, preferred clockwise turns, reflecting alterations leading to behavioral asymmetries at adulthood.

Petruzzi *et al.* (1995) described subtle or borderline persistent behavioral deficits in mice prenatally exposed to 0.2 to 0.6 ppm ozone. They suggested that these findings should be considered both in further animal experiments and in the assessment of risk to developing humans. Later studies demonstrated that exposure to O_3 slightly but selectively affected neurobehavioral performance in rodents (Sorace *et al.* 2001). It consistently impaired reversal learning in the Morris water maze test in both prenatally and adult exposed mice. Longer latency to step-through in the first trial of the passive avoidance test and a decrease in wall rearing in the hot-plate test were also recorded in ozone prenatally exposed mice.

In another study that suggest subtle central nervous system changes affecting mouse behavioral responses following ozone perinatal exposure, Petruzzi *et al.* (1999) investigated in mice the effects of exposure to ozone (0.3, 0.6, or 0.9 ppm), during foetal and neonatal life until the time of weaning. On postnatal day 70 mice were tested for handedness using a paw preference task assessing both the animals' capability to reach a food pellet in a feeding tube and the individual preference for the use of one of the other forepaw. Ozone exposure did not affect the animals' capability to learn the task but caused changes in handedness. The females exposed to the intermediate ozoned concentration showed a reduced preference for the right paw than both their same-sex controls and 0.6 ppm males. Additionally, on postnatal day 100, both male and female mice exposed to the 0.9 ppm ozone revealed a reduced sensitivity to the analgesic effect of morphine HCl (10 mg/kg) in a hot plate test.

Rivas-Manzano & Paz (1999) described morphological alterations in

cerebellum at different ages in rats prenatally exposed to ozone. Among them, cerebellar necrotic signs at postnatal age 0, diminished area of the molecular layer with Purkinje cells with pale nucleoli and perinucleolar bodies at postnatal age 12, and Purkinje cells showing nuclei with unusual clumps of chromatin in the periphery at age 60. Further studies from other authors confirmed that prenatal exposure to ozone affects the postnatal development of cerebellum (Romero-Velazquez *et al.*, 2002).

Although the above effects of perinatal exposure to ozone were not confirmed in the human species, the findings warn on a possible damage of the central nervous system in exposed population, which can be detected later in life and could be responsible of behavioral alterations or damage to mental abilities.

3.4. Nitrogen Dioxide

Exposure of pregnant rats (from gestational day 7 to delivery) to total diesel-engine exhaust containing 1.71 mg/m^3 particulate matter and 0.80 ppm nitrogen dioxide (high dose) or 0.17 mg/m^3 particulate matter and 0.10 ppm nitrogen dioxide (low dose), or exposure to filtered exhaust without particles containing 0.80 (high dose) or 0.10 (low dose) ppm nitrogen dioxide, determines in the male offspring, at day 96 after birth, a decrease in the daily production of sperm due to an insufficient number of Sertoli cells (Watanabe, 2005). In the reported experiment, the ratio of spermatids/Sertoli cells and the follicle-stimulating hormone levels in the exposed groups were significantly higher. The similarity of results in the groups with filters and without filters suggested that the gaseous phase but not the particulate matter is responsible of the effects of prenatal exposure.

3.5. Carbon Monoxide

Sartiani *et al.* (2004) reported in the rat that prenatal exposure to carbon monoxide affects the postnatal cellular electrophysiological maturation of the rat heart, and proposed that in humans is a potential substrate for arrhythmogenesis in infancy. They proposed that a prolonged myocyte repolarization induced by prenatal exposure to carbon monoxide may establish a period of vulnerability for life-threatening arrhythmias in infancy.

In humans, various air pollutants were associated to a decrease in birth weight in São Paulo, Brazil, a reduction of 23 g in birth weight was estimated to result from a 1 ppm increase in mean exposure to carbon monoxide during the first trimester (Gouveia *et al.*, 2004). A decrease in the birth weight was, in turn, proposed to cause many alterations in various organs and systems (Edwards *et al.*, 2003; Gray *et al.*, 2004; Jones *et al.*, 2004; Seckl, 2004).

3.6. Chlorinated Organic Persistent Compounds

Various chlorinated persistent organic compounds display a very strong toxicity. Most of these compounds are extremely stable and persistent in the environment, and are not metabolized by living organisms, therefore they may be bio-concentrated through alimentary chain and found in human food at much higher concentrations that in the

environment. Most of these compounds are very potent carcinogens, specially dioxins, furans and polychlorobiphenyls (PCBs). 2,3,7,8-tetrachlorodibenzodioxin is considered as the most potent carcinogen, that was assumed to be responsible for more than 10% of all cancers affecting humans. Besides their carcinogenic activity, they were found to increase the potency of other carcinogens (Desaulniers *et al.*, 2001; Birnbaum & Fenton, 2003).

Scarce information is still available on the perinatal exposure delayed effects of these compounds through the mechanism of imprinting. The mostly investigated compounds are dioxins, PCBs and a few organic chlorinated compounds. Most organic polychlorinated compounds share many of these effects, and there are many epidemiological studies that report their combined action.

Although the effects of perinatal exposure to dioxins, furans and PCBs are grossly similar, some conspicuous differences were found. For instance, while prenatal human exposure *in utero* to dioxins or furans causes in male children feminization of play behavior, and in female children further feminization of play behavior, prenatal exposure to PCBs causes in male children feminization of play behavior but in female children causes masculinization (Vreugdenhil *et al.*, 2002b). Further, studies of the mechanism of thyroid homeostasis disruption by prenatal exposure to dioxins (Kuriyama *et al.*, 2003) indicated that there exist different mechanisms for the toxicity of dioxins: arylhydrocarbon receptor-dependent and arylhydrocarbon receptor-independent mechanisms. Therefore, it was suggested that, in addition to TEQ (toxic equivalence factor) for dioxins and other polychlorinated organic compounds, toxicity should be evaluated for arylhydrocarbon receptor-independent effects (Kuriyama *et al.*, 2003), and that the indicator TEQ for dioxins and PCBs is not valid for all polychlorinated organic compounds.

3.6.1. Polychlorobiphenyls (PCBs)

In experimental animals, it was shown that perinatal exposure to polychlorobiphenyls causes persistent behavioral changes in rats (Pantaleoni *et al.*, 1988), a decrease in fertility in *Peromyscus polionotus* (McCoy *et al.*, 1995), and a permanent disruption of the hypothalamus-pituitary-thyroid axis (Kuriyama *et al.*, 2003). Perinatal exposure to a low dose of PCB 118 permanently disrupted the hypothalamo-pituitary-thyroid axis leading to a significant increase in thyroxin levels in offspring, as a "thyroid resistance syndrome". The mechanism of thyroid homeostasis disruption seems to be arylhydrocarbon receptor-independent, suggesting a different mechanism of toxicity from that of dioxins (Kuriyama *et al.*, 2003).

In humans, a number of epidemiological studies have shown predictive relationships between prenatal or perinatal exposure to polychlorinated biphenyls (PCBs), a delay in cognitive development (Lai *et al.*, 1994) and subtle cognitive deficits in infancy through the preschool or school years (Jacobson *et al.*, 1985, 1990; Patandin *et al.*, 1999; Stewart *et al.*, 2000; Vreugdenhil *et al.*, 2002a, 2004). For instance, in 9-year-old children of the Rotterdam PCB—dioxin cohort, higher prenatal PCB levels were associated with

longer response times, more variation in response times, and lower scores on the "Tower of London" (Vreugdenhil *et al.*, 2004).

Prenatal exposure to PCBs following large-scale poisoning occurred in central Taiwan in 1979 from ingestion of cooking oil contaminated by polychlorinated biphenyls (PCBs) and polychlorinated dibenzofurans, showed alteration in male reproductive function. Sperm of exposed children have increased abnormal morphology, reduced motility, and reduced capacity to penetrate hamster oocytes (Guo *et al.*, 2000). Further, prenatal exposure to PCBs determines feminization of in 7-8 year-old male children play behavior, while in female children it causes masculinization (Vreugdenhil *et al.*, 2002b).

Perinatal exposure to PCBs causes immune depression (increase in lymphocytes and T cells, changes in markers and decrease in antibodies) that persist through childhood and that may be related to increased susceptibility to infectious diseases (Weisglas-Kuperos *et al.*, 2000); the immunological and hematological alterations persist up to the age of 8 years (ten Tusscher *et al.*, 2003).

Alterations in nail development were also reported in prenatally exposed human population (Hsu *et al.*, 1995).

3.6.2. Dioxins

Prenatal exposure of experimental animals to 2,3,7,8-tetrachlordibenzo-p-dioxin (TCDD) cause persistent effects in the immune system. Thymus gland atrophy and immune suppression was described and explained by an alteration of the differentiation of the lymphocyte stem cells (Fine *et al.*, 1989). Persistent suppression of contact hypersensitivity and altered T-cell parameters (increase in CD4+) was also reported in F344 rats exposed perinatally to 2,3,7,8-tetrachlorodibenzo-p-dioxin (Walker *et al.*, 2004).

In the human species, perinatal exposure to dioxins causes immune depression (increase in lymphocytes and T cells, changes in markers and decrease in antibodies) that persist through childhood and that may be related to increased susceptibility to infectious diseases (Weisglas-Kuperos *et al.*, 2000). It has been reported that it causes hematological and immunological persistent alterations, which were detected in Dutch children at the age of 8 years (ten Tusscher *et al.*, 2003).

Exposure to TCDD during development permanently alters reproductive function in male Long Evans rats and hamsters. It causes a reduction in ejaculated and epididymal sperm numbers and sex accessory gland weights in offspring with normal testosterone blood and androgen receptor levels (Gray *et al.*, 1995). It also determines in males a morphologic and behavioral demasculinization and feminization, and a decrease in fertility (Gray *et al.*, 1995). Ohsako *et al.* (2001) reported in prenatally exposed rats an inhibition of further development of male genitalia, and a decrease in weight of the urogenital complex and in the anogenital distance, with no change in serum testosterone or luteinizing hormone. Tetrachlorodibenzodioxin exposure resulted in both a dose-dependent increase in 5alpha-reductase type 2 (5alphaR-II) mRNA level and a dose-

dependent decrease in androgen receptor mRNA level.

Ohsako *et al.* (2001) suggested that low-dose dioxin exposure had a greater effect on the development of the external genital organs and ventral prostate than on development of the testis and other internal genital organs and that the decrease in the size of the ventral prostate by maternal dioxin exposure might be due to decreased responsiveness of the prostate to androgen due to an insufficient expression level of androgen receptor during puberty. Further reports from Ohsako (2002) confirmed decreases in the urogenital complex and ventral prostate weights, in urogenital-glans and in penis length of male rat offspring at postnatal day 70, from rats exposed at gestational day 15 but not in rats exposed on gestational day 18 or postnatal day 2. Testicular and epididymal weights were also lower than control group in dioxin-exposed animals at gestational day 15 only. Anogenital distance was significantly reduced in the animals exposed at gestational days 15 and 18 but not in the postnatal day 2 group. PCR analysis showed that androgen receptor mRNA levels were decreased in the dioxin-exposed gestational day 15 group only, suggesting the presence of a critical window during development with regard to impairments of male reproductive organs by *in utero* and lactational exposure to a low dose of dioxin (Ohsako *et al.,* 2002).

Another study revealed that prenatal dioxin exposure determines impaired growth of the rat seminal vesicles, which is associated with a dramatic decrease in the development of the epithelium (Hamm *et al.*, 2000). Seminal vesicle weights were not significantly decreased until postnatal day 32, and androgen receptor mRNA expression in postnatal day 25 seminal vesicles was not different from control. Dioxin exposure, however, decreased seminal vesicle epithelial branching and differentiation. In addition, immunolocalization of proliferating nuclear antigen, which in controls was confined to undifferentiated basal epithelial cells, in dioxin-exposed animals was found in both basal and luminal seminal vesicle cells (Hamm *et al.*, 2000).

Lin *et al.* (2003) investigated the inhibition of prostate development in prenatally dioxin-exposed mice. They found that *in utero* tetrachlorodibenzodioxin exposure causes an aryl hydrocarbon receptor-dependent inhibition of prostatic epithelial bud formation commensurate with its inhibitory effects on ventral and dorsolateral prostate development, and that the inhibition of budding is not due to insufficient dehydrotestosterone. They suggested that inhibited bud formation appears to be the primary cause of abnormal prostate development in dioxin-exposed mice. In this context, Moriguchi *et al.* (2003) investigated the effect of dioxin exposure in homozygous mice for human type aryl hydrocarbon receptor gene and reported that these animals were less sensitive to dioxin-damage; in fact, human-type gene exposed animals developed hydronephrosis but not cleft palate, while mouse-type gene developed both abnormalities.

Hurst *et al.* (2000) reported that prenatal dioxin exposure of male fetuses at gestational day 15 (13.2 pg tetrachlorodibenzodioxin per gram of fetal tissue) caused a delay in puberty and decreased epididymal sperm counts. The authors warned that low-

level dioxin exposure during the perinatal stage of life can produce adverse effects within the developing pups.

In humans, changes in 7-8 year-old children gender-related play behavior was reported following prenatal exposure to dioxins or furans: it determines feminization of male children play behavior and it causes further feminization of female children play behavior (Vreugdenhil *et al.*, 2002b).

In females, morphological genital congenital malformations were reported following prenatal exposure to dioxins (Hurst *et al.*, 2000). *In utero* and lactational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin and 2,3,4,7,8-pentachlorodibenzofuran reduces growth and affects reproductive parameters in female rats (Salisbury & Marcinkiewicz, 2002); exposure disrupts regular estrous cycles, inhibits ovulation rate, and serum estradiol following chorionic gonadotrophin (hCG) stimulation is lower in exposed animals. The dioxin-like PCB congener 3,4,3',4'-tetrachlorobiphenyl (PCB 77) has estrogenic and anti-estrogenic properties, and has been shown to affect brain chemistry and behavior of developing rats when administered during gestation, especially affecting offspring maternal behavior (Simmons *et al.*, 2005). Perinatal plus adult exposure to tetrachlorodibenzodioxin increases the size of endometriotic lesions surgically induced in mice (Cummings *et al.*, 1999).

Prenatal exposure to dioxins affects the development of the mammary gland in experimental animals (Fenton *et al.*, 2002). It irreversibly inhibits the development of the mammary gland (reduced primary branches, decreased epithelial elongation, and fewer alveolar buds and lateral branches). This phenomenon persisted through postnatal day 68 when, unlike fully developed glands of controls, dioxin-exposed rats retained undifferentiated terminal structures. Gestational day 15 was a critical period for consistent inhibition of epithelial development.

Experiments using mammary epithelial transplantation between control and dioxin-exposed females suggested that the stroma plays a major role in the retarded development of the mammary gland following tetrachlorodibenzodioxin exposure (Fenton *et al.*, 2002). In this context it was proposed that stromal tissue regulates hormone effects of epithelial tissue via stimulating in the epithelium synthesis of hormone receptors which in turn respond to hormone strimulation; these mesenchymal-epithelial interactions may explain very weak epithelial response to hormone stimulation or a very strong response and even carcinogenesis of epithelial tissues depending on the degree of its stromal development (Cunha *et al.*, 1983). In agreement with this proposal, it was suggested that dioxin exposure prior to migration of the mammary bud into the fat pad permanently alters mammary epithelial development in female rat offspring (Fenton *et al.*, 2002). The glands, however, retain their ability to respond to estrogen stimulation inducing the synthesis of progesterone receptor and undergoing differentiation under hormone stimulation (Lewis *et al.*, 2001).

Prenatal exposure to dioxins increases their sensitivity to estrogens to induce, by the imprinting mechanism, mammary cancer development in adult females (Birnbaum & Fenton, 2003). Dioxin effects on the developing breast involve delayed proliferation

and differentiation of the mammary gland, as well as an elongation of the window of sensitivity to potential carcinogens. Authors suggest, based on these findings, that causes of endocrine-related cancers or susceptibility to cancer may be a result of developmental exposures rather than exposures existing at or near the time of tumor detection.

Prenatal exposure to dioxin increases mammary gland sensitivity to the carcinogen metilnitrosourea to induce breast cancer development (Desaulniers *et al.*, 2001).

Perinatal exposure to dioxins also imprints neurobehavioral delayed effects in experimental animals as well as in humans.

In the rat, Markowski *et al.* (2002) provided evidence that prenatal exposure to dioxin inhibits the development of attentional processes. Some of the behavioral effects evoked by prenatal exposure of laboratory animals were reported to be sexually dimorphic (Hojo *et al.*, 2002). The anatomical and biochemical substrate for these alterations seem to be a decrease in serotonergic neurons in prenatally exposed animals in all raphe nuclei as well as a decrease in the intensity of immunostaining (Kuchiiwa *et al.*, 2002). Approximately a quarter to half of immunoreactive neurons were detected in dioxin - exposed offspring raphe nuclei compared with control offspring.

Further, it has been shown that perinatal exposure to dioxin affects the expression of both subunits of the N-methyl-D-aspartate in the neocortex and hyppocampus at postnatal day 49, without changes at postnatal day 5 (Kakeyama *et al.*, 2001). The alteration consists in an enhancement of the nuclear receptor 2A subunit mRNA expression in the neocortex and hippocampus, and an inhibition of the 2B subunit mRNA expression. Similar alterations were found in the first postnatal months (Nayyar *et al.*, 2003), supporting the finding of Kakeyama *et al.* (2001) that provided evidence that the perinatal exposure to dioxin can alter the molecular basis of brain of offspring in adulthood.

In humans, the only evidence reported for the effects of prenatal exposure to dioxins are feminization of male children play behavior and further feminization of female play behavior (Vreugdenhil *et al.*, 2002b).

Decreased lung function assessed by spirometry in 7 to 12 year-old children, was associated with perinatal exposure to Dutch background levels of dioxins: a decrease in lung function in relation to both prenatal and postnatal dioxin exposure and a clinical association between chest congestion and perinatal dioxin exposure (ten Tusscher *et al.*, 2001).

3.7. Pesticides

Several pesticides were reported to induce perinatal exposure delayed effects. Among them, organochlorine pesticides (DDT and its metabolite DDE, methoxychlor, chlordecone), organophosphate pesticides (parathion, malathion), pyrethroid insecticides (cyhalothrin, cypermethrin) and the herbicide paraquat.

Perinatal exposure to DDT induces changes in muscarinic acetylcholine brain receptors (Johansson *al.,* 1995) and altered behavior during adulhood following neonatal

exposure to low doses (Eriksson *et al.*, 1990). It was recently demonstrated that mothers exposure to DDT is able to activate offspring brain estrogen receptors, suggesting an explanation for the above finding (Mussi *et al.*, 2005). Based in reports that it displays estrogenic action (Galand *et al.*, 1987; Bustos *et al.*, 1996), it is possible to expect similar effects to that displayed by estrogens.

The DDT metabolite p,p-DDE displays high affinity for androgen receptors and potent anti-androgenic action (Kelce *et al.*, 1995). The decrease in sperm cells count in Denmark and a smaller penile size in a Florida Lake (U.S.A.) alligators were attributed to this agent (Sharpe, 1995).

Perinatal exposure to methoxychlor, a pesticide with estrogenic action, increases the number of atretic follicles and induces early vaginal opening (Swartz & Corkern, 1992), prolonges the days exhibiting cornified vaginal smears during the estrous cycle, and suppresses both the lordosis reflex and preovulatory LH surge on the presumptive proestrus evening (Suzuki *et al.*, 2004). In males, perinatal exposure to methoxychlor decreases serum LH and FSH but it does not affect testosterone levels and neither affects copulatory behavior (Suzuki *et al.*, 2004).

Perinatal exposure to chlordecone causes masculinization (Sierra & Uphouse, 1986) and persistent changes in blood corticosterone levels (Cranmer *et al.*, 1984).

Prenatal exposure to the organophosphate pesticide parathion causes a persistent inhibition of Mg-dependent renal ATPase, which is possible to detect later in life (Jaramillo-Juárez *et al.*, 1989). Malathion, in turn, causes changes in cholinesterase activity and facilitates addiction to ethanol during adulthood (Ivashin *et al.*, 1991).

Perinatal exposure to the pyrethroid cypermethrin causes a decrease in thymus CD4 and CD8 subtypes, decreases the thymocyte proliferating ability and affects thymocyte differentiation (Santoni *et al.*, 1998). It also increases blood NK cells and blood cytotoxic activity dependent of antibody (Santoni *et al.*, 1997). The pyrethroid cyhalothrin causes a delay in testis descent (Gomes *et al.*, 1991).

Prenatal exposure to the herbicide paraquat causes a delayed increase in hepatic peroxidation (Gladyshev *et al.*, 1994), and counteracts, during adulthood, paraquat-induced increase in liver glutathione reductase (Semeniuk *et al.*, 1991).

4. Maternal Tobacco Smoking

Maternal cigarette smoking during pregnancy can result in a wide variety of adverse fetal outcomes, ranging from preterm delivery and low birth weight, to sudden infant death syndrome. In addition, *in utero* tobacco smoke exposure is associated with delayed or impaired neuropsychological development. Although the causative agent in tobacco smoke that leads to these aberrations is not known, some studies have concluded that nicotine may play an important role.

4.1. Birth Weight Decrease and Associated Risks

Maternal smoking during pregnancy increases the relative risk of low weight at birth (Magee *et al.*, 2004). Birth weight, in turn, is strongly associated with lung function in adulthood, supporting the hypothesis that impairment of fetal growth displays a significant effect on adult lung function (Edwards *et al.*, 2003). It was also reported that maternal smoking during any trimesters increased the risk of preterm birth, and that maternal smoking during the third trimester reduced the body length of both full-term and preterm neonates and the birthweight of the full-term neonate in a somewhat dose-dependent manner (Ohmi *et al.*, 2002).

4.2. Stillbirths and Infant Mortality

Wisborg *et al.* (2001) reported that exposure to tobacco smoke *in utero* was associated with an increased risk of stillbirth, and infant mortality was almost doubled in children born to women who had smoked during pregnancy compared with children of nonsmokers. Among children of women who stopped smoking during the first trimester, stillbirth and infant mortality was comparable with that in children of women who had been nonsmokers from the beginning of pregnancy. Approximately 25% of all stillbirths and 20% of all infant deaths in a population with 30% pregnant smokers could be avoided if all pregnant smokers stopped smoking by the sixteenth week of gestation. Further, Ernst *et al.* (2001) reported a consistent finding of a dose-response relationship between maternal smoking rates and spontaneous abortion.

4.3. Sudden Infant Death Syndrome (SIDS)

It is well known that maternal smoking is an important dose-dependent risk factor for sudden infant death syndrome (Daltveit *et al,.* 2003). This association may find an explanation in the recent finding that maternal smoking impairs infant arousal from sleep along with changes in control of autonomic cardiac function (Horne *et al.*, 2004). Indeed, maternal tobacco smoking significantly impairs both stimulus induced and spontaneous arousal from quiet sleep when infants sleep in the supine position, at the age when the incidence of sudden infant death syndrome is highest (Horne *et al.*, 2002).

In this context, it was also found that preterm infants exposed prenatally to cigarette smoke have increased respiratory events during active sleep, predominantly due to obstructive apnea, and possibly a higher arousal threshold during apneic events. These alterations in respiratory and arousal patterns in preterm infants born to smoking mothers may lead to significant vulnerability in this population (Sawnani *et al.*, 2004). Other authors found that prenatal exposure to nicotine significantly increased enkephalin mRNA levels in the rat adrenal medulla prenatally, and postnatally the normal up-regulation was obliterated (Wong *et al.*, 2003). They suggested that these changes may lead to a disturbed modulation or regulation of catecholamine release in the adrenal and may be one factor contributing to the attenuated capacity of nicotine-treated pups to survive severe

hypoxia, and speculated that this may be part of the mechanism underlying the relation between maternal smoking and sudden infant death syndrome.

In this context, current evidence suggests that maternal smoking is associated with decreased respiratory drive and blunted hypoxic ventilatory response in the newborn. In a study intended to evaluate the possible role of nicotine exposure on each component of biphasic hypoxic ventilatory response, Simakajornboon *et al.* (2004) found that prenatal exposure of rats to 6 mg nicotine/kg of body wt, from minipumps delivering the compound to pregnant mothers, was associated, at day 5, with attenuation of peak hypoxic ventilatory response. It was also associated with a selective increase in the expression of protein kinase C-beta and protein kinase C-delta within the caudal brain stem of developing rats.

Further, measurements undertaken prior to any postnatal exposure have consistently demonstrated significant changes in tidal flow patterns in infants whose mothers smoked in pregnancy (Stocks & Dezateux, 2003). While there is, as yet, no convincing evidence from studies in human infants that smoking during pregnancy is associated with increased airway responsiveness at birth, many studies have demonstrated a reduction in forced expiratory flows (on average by 20%) in infants exposed to parental smoking (Stocks & Dezateux, 2003).

4.4. Immune Depression and Increase in Infectious Diseases

Yuan *et al.* (2001) reported that maternal smoking during pregnancy is associated with a higher risk of hospitalization with infectious disease during early childhood. This association is independent of fetal growth indicators. For instance, maternal smoking is associated with increased risk of meningococcal disease (Sorensen *et al.*, 2004). These findings may reflect an immune deficit resulting from prenatal exposure to tobacco smoke.

4.5. Respiratory Diseases in Prenatally Exposed Children and Adults

Maternal smoking during pregnancy is associated with respiratory diseases in prenatally exposed children and adults. An association or tobacco smoke exposure during pregnancy with a higher risk of wheezing was reported by Cano Garcinuno *et al.* (2003). Multivariant analysis with logistic regression was performed for children bronchiolitis, and the only variable that remained statistically significant was smoking during pregnancy (Cano Fernandez *et al.*, 2003). From that study, it was concluded that maternal smoking during pregnancy seemed to be the main risk factor for the subsequent development of bronchiolitis.

4.6. Bronchial Asthma

Maternal smoking is associated with offspring bronchial asthma (Yuan *et al.*, 2003). A population-based cohort study (Jaakkola & Gissler, 2004) has shown that maternal

smoking increased the risk of asthma during the first 7 years of age, and only a small fraction of the effect seems to be mediated through fetal growth.

Studies in experimental animals explained the increased risk of asthma following prenatal exposure to maternal smoking by an increase in bronchial hyper responsiveness in the offspring (Singh *et al.*, 2003), which was in turn explained by biochemical changes that occurring in the lung following prenatal exposure. Animals exposed prenatally but not postnatally to cigarette smoke exhibited increased airway hyperresponsiveness after a single intratracheal injection of *Aspergillus fumigatus* extract. The increased airway hyperresponsiveness was not associated with increased leukocyte migration or mucous production in the lung but was causally related to decreased lung cyclic adenosine monophosphate levels, increased phosphodiesterase-4 enzymatic activity, and phosphodiesterase-4D isoform-specific messenger ribonucleic acid expression in the lung (Singh *et al.*, 2003).

In the human species, it was shown that children at school age from mothers had smoked during pregnancy, showed increased bronchial reactivity after cold air challenge compared to children whose mothers had not smoked during pregnancy (Nuesslein *et al.*, 2002). Similar differences were found, when the study population was divided according to the maternal smoking status during the first six months of life (Nuesslein *et al.*, 2002), suggesting that pregnancy and early infancy are periods of increased vulnerability of the airways to tobacco products.

4.7. Opiate Receptors

Maternal smoking causes biochemical changes in fetal central nervous system, probably in opiate receptors containing neurons. It was reported that infants born to heavy smoker mothers had significantly stronger and longer lasting opioid neonatal abstinence syndrome than in infants born from light smokers (Choo *et al.*, 2004).

4.8. Obesity

An association between maternal smoking during pregnancy and offspring obesity has been reported (von Kries *et al.*, 2002; Toschke *et al.,* 2003); this association was found to be independent from weight at birth, and may be attributed to specific effects of cigarette smoke (Wideroe *et al.*, 2003).

4.9. Age at Menarche

The mean age at menarche was a few months earlier among daughters from mothers smoking during pregnancy, as compared to unexposed girls (difference = -0.22 years). Girls with both high prenatal and childhood passive smoke exposure had an adjusted mean age at menarche about 4 months earlier than those unexposed (Windham *et al.*, 2004).

4.10. Sex Hormones and Endocrine Changes in Females

It has been shown in the rat that prenatal nicotine exposure increases plasma testosterone levels chronically in adolescent female rat offspring (measured at the age of 30 days), but not in males (Smith *et al.*, 2003).

4.11. Sex Hormones, Reproductive and Endocrine Alterations in Males

In the rat, it was reported that prenatal exposure to maternal nicotine at similar concentrations in the blood occurring in smoking women, decreases efficiency of the copulation along with a decrease in plasma testosterone levels [(Segarra & Strand, 1989) see under "nicotine"]. This effect has suggested the possibility of similar effects in the human species, i.e., male sexual impotence caused by prenatal exposure to tobacco smoke (Tchernitchin *et al.*, 1999). Although the possibility was not investigated in humans, it was recently reported that adult smoking is a risk factor of male sex impotence (Sanchez de la Vega *et al.*, 2003; Lyngdorf & Hemmingsen, 2004; Rowland *et al.*, 2005). Further, in the rabbit it was found that secondhand tobacco smoke impairs neurogenic and endothelium-dependent relaxation of *corpus cavernosum* smooth muscle (Gocmez *et al.*, 2005).

In the human species, prenatal exposure to maternal tobacco smoking causes additional adverse effects in the male reproductive system. Pettersson *et al.* (2004) reported an association between maternal smoking and the incidence of testicular cancer in prenatally exposed offspring. Jensen *et al.* (2004) found an association of *in utero* exposure to maternal smoking with reduced semen quality and decreased testis size in adulthood in a cross-sectional study of 1770 young men from the general population in five European countries. These changes may suggest an explanation for the decrease in testosterone levels and changes sex behavior found in experimental animals (Segarra & Strand, 1989).

4.12. Neurobehavioral Changes

Prenatal exposure to maternal smoking causes persistent delayed neurobehavioral effects. Prenatal tobacco exposure was significantly associated with deficits in learning and memory. Specifically, prenatal tobacco exposure was associated with deficits in verbal learning and design memory, as well as slowed responding on a test of eye-hand coordination (Cornelius *et al.*, 2001). In addition, these children demonstrated a reduced ability for flexible problem solving and more impulsivity, as indicated by an increase in perseverative responses on a card-sorting test.

Maternal smoking during pregnancy appears to show an association with offspring attention deficit hyperactivity disorder symptoms that is additional to the effects of genes and not attributable to shared rater effects, clinical referral biases, or covariation with antisocial behavior (Thapar *et al.*, 2003). In this context, child hyperactivity-impulsivity and oppositional behaviors were associated with a DAT genotype polymorphism but only when the child also had exposure to maternal prenatal smoking (Kahn *et al.*, 2003). Batstra

et al. (2003) reported that children of mothers who smoked during pregnancy showed more signs of attention deficit and displayed higher levels of troublesome (externalising) behaviour than non-cigarette-exposed children. Also, children of smoking mothers performed worse on arithmetic and spelling tasks. Spelling problems were more pronounced when the mother continued to smoke after the child's birth. Excessively withdrawn (internalising) behaviour was not related to maternal smoking but to factors like the mother's use of psychotropic drugs and bottle-instead of breastfeeding.

Another study has shown, in 13 to 16 years-old children, that their exposure to prenatal maternal cigarette smoking was associated with deficits in overall intelligence and aspects of auditory functioning while prenatal exposure to marihuana was negatively associated with tasks that required visual memory, analysis, and integration (Fried *et al.*, 2003).

It was also reported that maternal prenatal smoking is related to criminal and substance abuse outcomes in male and female offspring. Higher rates of index arrests for female offspring may be related to their substance abuse problems (Brennan *et al.,* 2002).

A review of several epidemiological studies suggested that there is a relationship between maternal smoking during pregnancy and adverse neurobehavioral effects later in life. Prenatal exposure to tobacco seems to increase the risks for cognitive deficits, attention deficit/hyperactivity disorder, conduct disorder, criminality in adulthood and a predisposition in the offspring to start smoking and alcohol abuse (Hellstrom-Lindahl & Nordberg, 2002). As a matter of fact, Piquero *et al.* (2002) provided evidence documenting the relationship between maternal cigarette smoking and offspring criminal behavior.

4.13. Cardiovascular Disease

Various epidemiologic studies suggested that *in utero* exposure to maternal smoking is associated with elevated blood pressure later in life (Pausova *et al.*, 2003). An experimental study in rats, performed to verify this possibility, has shown that intrauterine exposure to nicotine increases blood pressure and serum cholesterol levels later in life, depending on the genetic background and, as such, supported the notion that the intrauterine environment interacts with genes in determining an individual's health later in life (Pausova *et al.*, 2003).

4.14. Miscelaneous Effects

It was recently shown in humans, using magnetic resonance imaging, that the size of the lumbar vertebral canal, a risk factor for spinal stenosis in adult life, was reduced by both low birth weight and maternal smoking as an added adverse factor (Jeffrey *et al.*, 2003).

4.15. Prenatal Exposure Delayed Effects that are not Mediated by the Imprinting Mechanism

Cleft palate increases in mothers smoking during first trimester of pregnancy; this effect is mediated most probably through an increase in glucocorticoid hormones in the mother, unless they are exposed to anti-prostaglandin drugs which antagonize this effect (Little *et al.*, 2004).

5. Drugs of Abuse

5.1. Illicit Ones

5.1.1. Tetrahydrocannabinol

Prenatal exposure to delta 9-tetrahydrocannabinol, the active agent from *Cannabis sativa*, causes biochemical and functional modifications in the central nervous system, that lasts through life. Among them, alterations in brain tyrosine hydroxylase expression (Bonnin *et al.*, 1995), in the pituitary-adrenocortical axis (Rubio *et al.*, 1995) and neurobehavioral changes (Navarro *et al.*, 1994; Rubio *et al.*, 1995), mainly impaired sustained attention (Noland *et al.*, 2005).

5.1.2. Cocaine

Prenatal exposure to this active substance from *Erythroxylon coca*, determines a persistent reduction in dopamine release in the mesocortical region (Wang *et al.*, 1995), causes neurobehavioral changes (Heyser *et al.*, 1994a) and selectively decreases the sensitivity to cocaine for some but not all responses to the drug during the adult age (Heyser *et al.*, 1994b). Noland *et al.* (2005) reported that maternal pregnancy use of cocaine was associated with increased commission errors, indicative of inferior selective attention. Prenatal exposure to cocaine also causes a persistent alteration of norepinephrine release from cardiac adrenergic nerve endings (Snyder *et al.*, 1995).

5.1.3. Opiates

Prenatal exposure to morphine, active agent from *Papaver somniferum*, determines changes that persist through life. In the rat, affects noradrenaline and dopamine turnover rate in various central nervous system regions (Vathy *et al.*, 1994, 1995); in humans imprints sequellae in the area of attention (Hickey *et al.*, 1995).

5.1.4. Ketamine

This pharmaceutical is an anesthetic drug used in veterinary. It has been used by youth as drug of abuse ("special K"), and also by offenders to anesthetize victims for antisocial purposes. It has been reported that ketamine causes apoptotic neurodegeneration in the developing brain, through competitive inhibition of NMDA glutamate receptor inhibition or GABA-A receptor activation (Olney *et al.*, 2002), explaining the reduced brain mass and neurobehavioral disturbances following prenatal exposure to this agent.

5.1.5. Toluene

This solvent, found in glues and cleaners, is among the most commonly abused inhalants, causes persistent effects in offspring when inhaled by their mothers during pregnancy. Besides, it may cause similar effects through occupational exposure of pregnant women.

In rats, prenatal exposure to high concentrations of toluene can cause growth restriction, malformation and impairments of biobehavioral development (Bowen *et al.*, 2005), as well as an increased pups mortality until weaning (Thiel & Chahoud, 1997). In the brain, it was found that prenatal exposure to toluene induces long-lasting changes in oxidative status (increased level of oxidative stress when brain tissue is submitted to various toxic agents) and membrane function (Edelfors *et al.*, 2002). It also causes caused a poor performance in various behavioral tests (da Silva *et al.*, 1990; Jones & Balster, 1997) and damage to cognitive functions, the latter seemed most marked in female than in male offspring (Hougaard *et al.*, 1999). These findings are in agreement with the persistent reduction in forebrain myelination described at postnatal day 21 in prenatally toluene-exposed pups (Gospe & Zhou, 1998).

For humans, there are reports that link increased spontaneous abortion and fetal malformations with occupational exposure to toluene (Jones & Balster, 1998). Authors review of more than 100 cases reported in the literature of children born to solvent-abusing mothers, describes that many of these children were small at birth, and some have craniofacial abnormalities. In the few studies reporting the findings of follow-up in these children, some evidence was obtained for retardation in growth and development and for residual deficits in cognitive, speech, and motor skills. (Jones & Balster, 1998).

Arai *et al.* (1997) reported two cases of patients with severe motor and intellectual disabilities syndrome, who were born to mothers having inhaled organic solvents during pregnancy. They had microcephaly, cerebral palsy, mental retardation, seizures, growth failure and minor craniofacial anomalies, variable growth deficiency including a small midface, narrow bifrontal diameter, low-set ears, thin upper lips and micrognathia. One of these patients deceased, and authopsy revealed revealed marked cerebral atrophy and destruction of bilateral temporal lobes with ventricular enlargements. Microscopic examination revealed migration disorders with polymicrogria at the remaining cerebrum and the cerebellum as well as very thin white matter. Other reports describe microcephalia, various morphological facial changes and developmental delays in children born from toluene-abuser mothers (Hersh, 1989; Arnold *et al.*, 1994).

5.2. Licit Drugs of Abuse

5.2.1. Nicotine

In the rat, nicotine is the agent responsible of the addictive effect of tobacco smoking. It is transported across the placenta, affects fetal tissues and causes delayed effect that may persist for life (*vide infra*).

5.2.1.1. Neurobehavioral Effects

In the rat, prenatal exposure to nicotine causes an increase in spontaneous locomotor activity (Fung, 1988), which can be explained by the changes in striatum

dopamine binding sites (Fung & Lau, 1989). It causes persistent alterations in the functional state of catecholaminergic neurons, evidenced by a persistent decrease in MOPEG and, in male rats only, an increase in noradrenaline content (Ribary & Lichtensteiger, 1989).

A treatment of pregnant rats with nicotine (1 mg/kg daily from gestation days 4 to 20) determined, at postnatal day 30, a significant increase in acetylcholinesterase activity in the brainstem, cerebellum of male offspring, an increased neuronal cell death in the cerebellum granular cell layer of female offspring and a rise in glial fibrillary acidic protein immunostaining in the hippocampus and cerebellum in female and male offspring (Abdel-Rahman *et al.*, 2003).

Further studies demonstrated in the rat that prenatal nicotine exposure sensitize the brain to further nicotine-induced neurotoxicity during adolescence (Abreu-Villaca *et al.*, 2004a) and caused a persistent acetylcholine hypoactivity (Abreu-Villaca *et al.*, 2004b), suggesting that prenatal nicotine exposure alters the subsequent response to nicotine in adolescence, effects that may contribute to the association between maternal smoking during pregnancy and subsequent adolescent smoking in the offspring (Abreu-Villaca *et al.*, 2004b). In this context, in a long-term prospective investigation from pregnancy through adulthood, it was shown that offspring of mothers who smoked a pack or more of cigarettes during pregnancy are at elevated risk of developing nicotine dependence but not marijuana dependence as adults (Buka *et al.*, 2003). Authors concluded that maternal smoking during pregnancy is a risk factor for subsequent nicotine dependence among offspring.

5.2.1.2. Genderdependent Changes in Behavior and Sensitivity to Nicotine

Oral nicotine delivery to pregnant mice causes persistent, gender-dependant changes in behavior and sensitivity to nicotine (Pauly *et al.*, 2004). On PN40 and PN60, male mice exposed to *in utero* nicotine demonstrated significant locomotor hyperactivity in an open filed arena. Although female animals did not show any signs of hyperactivity, they did have a significant attenuation of their hypothermic response to acute nicotine challenge (Pauly *et al.*, 2004).

5.2.1.3. Neuroendocrine Effects

Prenatal exposure to nicotine also alters adult rat neuroendocrine response (ACTH and prolactin) to nicotine (Poland *et al.*, 1994) and increases sensitivity to nicotine analgesic effect (Zbuzek & Chin, 1994).

5.2.1.4. Male Reproductive and Endocrine Alterations

Prenatal exposure to nicotine also alters subsequent sexual behavior in males, increasing the latency before the physiological changes that occur during intercourse and decreasing the efficiency of the copulation (Segarra & Strand, 1989). These alterations may be caused by the decrease in blood testosterone levels observed in adult prenatally exposed

animals, due to a decrease in hormone synthesis in the testis (Segarra & Strand, 1989). These effects of nicotine suggested the possibility that nicotine fetal exposure from maternal tobacco smoking may contribute to favor the development of sexual impotence in men (Tchernitchin *et al.*, 1999). Although the possibility was not investigated in humans, recent reports on the effect of tobacco smoke support this possibility (*vide supra*).

5.2.1.5. Respiratory Effects

In lambs, experimental prenatal nicotine exposure appears to have long-term effects on the postnatal breathing pattern, suggesting altered lung function, e.g., increased airway resistance, decreased lung compliance, or both (Hafstrom *et al.*, 2002). The increased inspiratory drive is most likely secondary to increased impedance of the respiratory system. These changes are most marked close to birth but persist during at least the initial postnatal period when they were investigated (Hafstrom *et al.*, 2002).

5.2.1.6. Miscelaneous Effects

Prenatal nicotine exposure elicits up-regulation of adenylate cyclase activity in membrane preparations of kidney and heart, not accompanied by ß-adrenergic receptor up-regulation, which can be explained by changes in enzymes involved in membrane receptor signal transduction, leading to altered responsiveness independently of changes at the receptor level (Slotkin *et al.*, 1990).

5.2.1.7. Prenatal Exposure Delayed Effects that are not Mediated by the Imprinting Mechanism

One of the effects of maternal smoking during pregnancy on fetal development, is a higher incidence of persistent pulmonary hypertension. The recent identification of nicotinic acetylcholine receptors on cells of the pulmonary vessel walls suggests that maternal smoking during pregnancy may produce morphological alterations in fetal pulmonary vasculature. Following nicotine treatment, total wall and tunica adventitia thickness of airway associated vessels increased significantly. Nicotine exposure significantly increased collagen I and III mRNA and protein in tunica adventitia in all airway associated vessels but not in tunica media. By contrast, levels of elastin protein were significantly decreased. Alpha7 nicotinic acetylcholine receptors were detected in airway associated vessels fibroblasts that expressed collagen mRNA. Choline acetyltransferase, the enzyme which synthesizes acetylcholine, the ligand for alpha7 nicotinic acetylcholine receptors was also detected in endothelium and fibroblasts. These findings suggest that with smoking during pregnancy, nicotine is transported across the placenta and directly interacts with nicotinic acetylcholine receptors in pulmonary vessels to alter connective tissue expression and therefore produce vascular structural alterations (Sekhon *et al.* 2004).

5.2.2. Caffeine

This active agent from *Coffea arabica*, is present in coffee and is also used as food additive in several cola drinks. Prenatal exposure of experimental animals to low caffeine doses (0.23 mg/mL in drinking water, 28 mg/kg/day) determines an increase in activity and a decrease in emotionality during the adult age (Hughes & Beverdige, 1990). The exposure of pregnant rats to caffeine (30 mg/kg/day) inhibits the differentiation of fetal testis interstitial tissue and Leydig cells, thus reducing fetal testis testosterone synthesis (Pollard *et al.*, 1990); the latter causes changes in cell programming in several organs through the mechanism of imprinting.

In mice, coffee exposure during pregnancy determined in offspring, a delay in eye opening, a slow down of body weight gain and affected all parameters of locomotor behavior (Ajarem & Ahmad, 1996).

In humans, it was reported that drinking coffee during pregnancy is associated with an increased risk of stillbirth but not find any association with infant death (Wisborg *et al.*, 2003). Other authors, however, reported an increased risk of sudden infant death syndrome in offspring of heavy coffee drinking women during their pregnancy (Ford *et al.*, 1998).

It is necessary to take into consideration that, in humans, exposure to caffeine may not only come from coffee drink. Caffeine is added to some soft drinks such as cola drinks or to "energetic" drinks, where it may act as an addictive substance. Pregnant women are usually not warned about it, as well as children at the early stages of their development, and may be subjected to persistent changes through the mechanism of imprinting, that can be the root of the development of diseases at later stages of their life.

Finally, coffee, besides caffeine, also contains estrogenic agents that may induce imprinting mechanisms. It was reported that roasted *Coffea arabica* beans as well as in instant coffee powder contain a yet unidentified estrogenic compound (Kitts, 1987).

5.2.3. Ethyl Alcohol

Its prenatal exposure from maternal ethanol intake during pregnancy was shown to cause several irreversible alterations, mainly in the central nervous system, that persist through life.

5.2.3.1. Hypotheses Explaining Delayed Effects Caused by Prenatal Ethanol Exposure

Many hypotheses were drawn to explain persistent alterations caused by prenatal exposure to ethanol. Among them, it was proposed that ethanol can produce neuroteratogenic effects by its interactions with molecular regulators of brain development (Goodlett *et al.*, 2005). It was suggested that alcohol produces many of its damaging effects by exerting specific actions on molecules that regulate key developmental processes (e.g., L1 cell adhesion molecule, alcohol dehydrogenase, catalase), interfering with the early development of midline serotonergic neurons and disrupting their regulatory-signaling

function for other target brain structures, interfering with trophic factors that regulate neurogenesis and cell survival, or inducing excessive cell death via oxidative stress or activation of caspase-3 proteases (Goodlett *et al.*, 2005). Other hypothesis considered changes in enzymes such as carboxipeptidase H, which altered the rate of proteolytic processing of neuropeptide precursors (Mukhina *et al.*, 2005).

In addition to direct effect of ethanol on fetal tissues, maternal alcohol consumption during pregnancy may interfere with fetal development indirectly, by disturbing the functions and interactions of maternal and fetal hormones (Gabriel *et al.*, 1998). In both the mother and the fetus, alcohol exposure can impair the functioning of the hypothalamic-pituitary-adrenal axis, which regulates the body's response to stress; the hypothalamic-pituitary-gonadal axis, which controls reproductive functions; and the hypothalamic-pituitary-thyroid axis, which regulates the metabolism of almost all tissues.

In addition, alcohol can interfere with the activities of growth hormone and insulin-like growth factors, which promote body growth and activity (Gabriel *et al.*, 1998). In this context, it was reported that prenatal ethanol exposure-induced increase in pregnenolone sulfate levels in fetal brain (but not in other fetal or maternal tissues) at embryonic day 14, and this effect lasted until post-natal day 5; explaining the decrease both cellular and behavioral responsiveness to neurosteroids in prenatally exposed animals, since this neurosteroid may play an important role in brain maturation (Caldeira *et al.*, 2004).

In addition, alcohol exposure during pregnancy alter hormone levels in the pregnant mother, and these hormones may cross placental barrier and affect the fetus. For instance, exposure of pregnant animals to ethanol causes an increase in blood estradiol levels (Hilakivi-Clarke *et al.*, 2004), thyroid hormones (Wilcoxon & Redey, 2004), and glucocorticoids (Zhang *et al.*, 2005). Changes in hormone levels in fetal tissues may in turn induce, by the mechanism of imprinting, irreversible changes that persist through life and may be the root for the development of various diseases later in life (Tchernitchin & Tchernitchin, 1992).

5.2.3.2. Effects in Central Nervous System

In the rat, prenatal ethanol exposure causes a decrease in the thickness of brain cortex and changes in glucose metabolism in certain brain areas, mainly affecting neurons from the thalamus and corpus callosum connections (Miller & Dow-Edwards, 1988). It causes permanent changes in brain benzodiazepine (Kruglikov & Zhulin, 1990) and serotonergic 5-HT1 (Tajuddin & Druse, 1988) and GABA(A) (Iqbal *et al.*, 2004) receptors as well as change in enkephalin levels (McGivern *et al.*, 1984a) and norepinephrine secretion destabilization (Bazian, 1988). In mice, it causes a decrease in serotonin neurons in the brainstem that persist upt to 45 days of age (Sari & Zhou, 2004). It causes alteration in the sensitivity of dopaminergic central receptors (Becker *et al.*, 1995), enhancement of the reactivity of the dopamine D1 but not D2 or D3 receptors in offspring (Sobrian *et al.*, 2005), and reduction in the spontaneous electrical activity of dopamine neurons in the

ventral tegumental area of adult animals (Choong & Shen, 2004). It increases nitric oxide synthase levels in the brain of prenatally ethanol-exposed postnatal rats (Dizon *et al.*, 2004).

Prenatal exposure to ethanol induces changes in astrocyte enzymes which may cause neuronal alterations (Guerri *et al.*, 1989), decreases in neuron number (Miller & Potempa, 1990) and morphology (Clemens *et al.*, 1979; Popova, 1989), impairment in hippocampus pyramidal cell dendrites development (Lolova *et al.*, 1989) and pyramidal and granular cell loss in various hippocampus regions (McGoey *et al.*, 2003; Tran & Kelly, 2003).

Prenatal alcohol exposure permanently alters both presynaptic and postsynaptic brain-derived neurotrophic factor and its receptor tyrosine kinase B in the hippocampus (Feng *et al.*, 2005). It causes a persistent decrease in neurotrophin receptor in hippocampus, septum and cerebellum, and a persistent increase in cortex (Moore *et al.*, 2004). Prenatal ethanol exposure causes a persistent alteration of the phospholipid profile in the hippocampus (Wen & Kim, 2004), and a suppression in infant rats of c-Fos expression, a marker of hippocampal neuronal activity that is induced by a variety of stimuli (Jang *et al.*, 2005). Prenatal exposure to ethanol reduces, in the dentate gyrus of adult offspring, the expression of glutamate GluR5 receptor, suggesting that the presynaptic nerve terminal is one site where prenatal ethanol exposure has reduced this receptor number and function; contributing to the hippocampal synaptic plasticity and behavioral deficits (Galindo *et al.*, 2004).

In the neocortex, ultrastructural changes, mainly in the layer V pyramidal neurons with cell pyknosis and broken dendrites, astrogliosis and astrocyte immunohistochemical changes were reported in adult rats prenatally exposed to ethanol (Fakoya, 2005). In the adult guineapig somatosensory cortex prenatally exposed to ethanol, a selective loss of GABAergic interneurons or failure to express glutamic acid decarboxylase in layers II/III is observed (Bailey *et al.*, 2004).

The above changes may be the biochemical and morphological substratum of the behavioral changes observed in experimental animals after prenatal exposure to ethanol (Kruglikov & Zhulin, 1990), among which it is important to mention the increase in aggressivity (Davis *et al.*, 1984) and attention deficit (Hausknecht *et al.*, 2005), and a reduced behavioral adaptation to stress (Schneider *et al.*, 2004).

In humans, prenatal exposure to ethanol causes cognitive impairment (Korkman *et al.*, 2003) and attention deficit (Lee *et al.*, 2004). It was shown that working memory may be the most important aspect of attention that is adversely affected in 7.5 year-old children by prenatal alcohol exposure (Burden *et al.*, 2005). Prenatal ethanol exposure impairs intellectual function, causing IQ deficit in children from moderate or heavy drinking mothers; intellectual performance is more severely affected as the mothers are older during pregnancy (Jacobson *et al.*, 2004).

Neuroanatomical and behavioral evidence indicate that the cerebellum is particularly vulnerable to the toxic effects of prenatal alcohol exposure. It was suggested that children prenatally exposed to alcohol have deficits in cerebellar processing similar to those with dyslexia, and that these functional deficits are related to disabilities in learning

(Coffin *et al.*, 2005).

Prenatal exposure to alcohol in children slows down peripheral nerve conduction velocity and affects nerve electrical properties (Avaria *et al.*, 2004).

It is possible to propose that the increase in locomotor system sensitivity to ethanol stimulation under the effect of prenatal exposure to ethanol, particularly under conditions affecting serotonin (Tajuddin & Druse, 1988) or adrenergic (Becker *et al.*, 1995) receptors, may explain the increased prevalence of alcoholism in offspring from alcoholic parents. This increased prevalence was attributed, up to present, exclusively to genetic and psychological factors (Devor *et al.*, 1988; see Rothhammer *et al.*, 1994, for a review). Recent results seem to support the hypothesis of a conditioned preference learned in utero as a consequence of the association between the orosensory characteristics of ethanol and its reinforcing properties, apparently mediated by the opioid system (Chotro & Arias, 2003).

5.2.3.3. Effects in the Immune System

Prenatal exposure to ethanol determines permanent immune depression in humans (Johnson *et al.*, 1981) as well as in experimental animals (Gottesfeld *et al.*, 1990). This effect may find an explanation on an alteration by ethanol of both maternal and fetal hypothalamus-pituitary-adrenal axis, as well as in the fetal testosterone role in immune cell development.

It was proposed that maternal alcohol consumption during pregnancy can reprogram hypothalamus-pituitary-adrenal axis increasing its activity in both the maternal female and the offspring, increasing glucocorticoid levels for life, which in turn can alter behavioral and physiologic responsiveness, cause immune depression and increase vulnerability to various pathologies later in life (Zhang *et al.*, 2005). Indeed, it was reported prenatal exposure to ethanol causes in 7.5 months-old mice hyperresponsive response to stress (measured as corticosterone secretion) (Park *et al.*, 2004). It was reported that the ability of increased brain nitric oxide levels to release ACTH and stimulate the paraventricular nucleus neuronal activity is enhanced in adult male rats exposed to alcohol prenatally, supporting the hypothesis that alterations in hypothalamus-pituitary-adrenal axis activity in adult offspring of alcohol-exposed dams may be related to changes in hypothalamic responsiveness to nitric oxide (Lee *et al.*, 2003).

Experimental data reveal a link between *in utero* alcohol exposure and significant reduction of thymic size together with impaired immune surveillance (Gottesfeld *et al.*, 1991; Gottesfeld *et al.*, 1992). These observations suggest an altered process of thymic development in fetuses exposed to alcohol *in utero*, leading to immune suppression in the offspring.

Fetal alcohol exposure (FAE) leads to marked, long term suppression of T cell-dependent functions, such as splenocyte proliferation in response to mitogens (Weinberg & Jerrels, 1991; Redei *et al.*, 1993). These latter effects are observed primarily in the male offspring and are abolished by maternal adrenalectomy (Weinberg & Jerrels, 1991; Redei *et al.*, 1993). It was suggested that long term effects of alcohol exposure *in utero* on the T

cell function of male offspring (Redei *et al.*, 1993) support the hypothesis that alcohol interferes with certain critical androgen-dependent steps in lymphoid development (Revskoy *et al.*, 1997).

Changes in level of hormones regulating immune processes, mainly glucocorticoids, under the effect of prenatal ethanol exposure, may be reflected in hypersensitivity diseases. For instance, it was reported that alcohol during pregnancy was associated with a significant and dose-dependent increased risk of topic dermatitis in early infancy; this effect was mainly seen in high risk infants (two parents with allergic disease) (Linneberg *et al.*, 2004).

5.2.3.4. Effects in the Reproductive System

Several effects of prenatal exposure to ethanol in the reproductive system were reported. Alteration in sex dimorphic behavior (McGivern *et al.*, 1984b) and reproductive changes such as a decrease in hypothalamic sensitivity to testosterone feedback (Jungkuntz-Burgett *et al.*, 1990), increase in fetal testosterone levels (Dahlgren *et al.*, 1989), a persistent reduction in testicular weight and an alteration of the morphology of the seminiferous tubules of adult male rats, as well as an inhibition of spermatogenesis, implying a depression of male fertility (Fakoya & Caxton-Martins, 2004). Further, in contraposition to effects of prenatal exposure to ethanol in non-stressed rats that slightly increases testosterone prenatally (Ward *et al.*, 2003) without alteration of normal male copulatory behavior (Ward *et al.*, 2002), a combined exposure to prenatal ethanol and stress causes a severe failure in copulatory behavior (Ward *et al.*, 2002) and completely blocks the rise of prenatal testosterone (Ward *et al.*, 2003). Prenatal exposure to stress alone causes a partial failure in copulation only and an attenuated prenatal testosterone surge.

Prenatal exposure to ethanol was shown to decrease postnatal testosterone increase in male rats (McGivern *et al.*, 1993); this effect, however, seems not to have adverse effects in the development of normal male copulatory behavior, at least during adult age (McGivern *et al.*, 1998).

In pregnant rats exposed to alcohol at doses generating alcoholemia corresponding in humans to low and moderate alcohol consumption (and are lower than those inducing fetal alcohol syndrome), an increase in blood estradiol levels was reported (Hilakivi-Clarke *et al.*, 2004). When adult, female offspring from alcohol-exposed dams developed more 7,12-dimethylbenz[a]anthracene -induced mammary tumours than controls, their mammary epithelial tree was denser, contained more structures susceptible breast cancer initiation, and contained elevated levels of oestrogen receptor-alpha (Hilakivi-Clarke *et al.*, 2004), suggesting a possible cause relationship to mammary tumorigenesis.

In addition, in the female, prenatal exposure to ethanol determines estrus cycles disruption (Dahlgren *et al.*, 1989) and a delay in puberty (Wilson & Handa, 1997). This effect may find an explanation on the reported increase in estradiol blood levels in the in alcohol-exposed mothers during pregnancy, (Hilakivi-Clarke *et al.*, 2004) and

hormone-induced changes in fetal tissues by the mechanism of imprinting. The delay in puberty may find an explanation in the alteration of gonadotropin secretion in infantile life in male and female rats; the delay in FSH secretion in females may ultimately play a role in the delay in puberty observed in the prenatally ethanol exposed female rat (Wilson & Handa, 1997).

5.2.3.5. Endocrine Effects Non-Related to the Reproductive System

Other endocrine changes were found in offspring of alcohol exposed pregnant mothers. An increase in osmotic threshold for vasopresin release, a reduction in pituitary vasopresin and of hypothalamic vasopresin mRNA was reported in prenatally exposed rats, suggesting as result a permanent condition of a mild partial central diabetes insipidus (Knee *et al.*, 2004), that is in agreement with the reduction in vasopresin producing neurons and changes in their morphology, both in humans and in experimental animals (Madeira *et al.*, 1993; Harding *et al.*, 1996). Alcohol-induced decrease in maternal thyroid function imprints in offspring changes in thyroid hormone regulation by the hypothalamic-pituitary-thyroid axis that can be observed during offspring adult age as a decrease in triiodothyronine (T3) and increase in TSH levels (Wilcoxon & Redei, 2004). It was reported that similar changes in triiodothyronine and TSH are caused, by the mechanism of imprinting, by neonatal treatment with thyroid hormones (Csaba & Nagy, 1985).

Exposure to ethanol during prenatal life or during lactation determines during adulthood insuline resistance. In addition, but in growth restricted rats only, it causes persistent dyslipidemia (Chen & Nyomba, 2004).

5.2.3.6. Miscellaneous Effects

The circadian rhythm may also be affected by fetal exposure to ethanol. It was reported that prenatal exposure to ethanol has a long-lasting effect on the light responsiveness of the deep body temperature circadian rhythm (Sei *et al.*, 2003).

Alterations in the development of beta-1 adrenoceptor development in brown adipose tissue were reported under the effect of prenatal ethanol exposure. These alterations may mean a decrease in plasticity in peripheral nervous system development (Zimmerberg *et al.*, 1995).

6. Concluding Remarks

Prenatal exposure to a myriad of compounds, among them abnormal levels of hormones or synthetic hormones, pharmaceuticals, pollutants, tobacco smoking, drugs of abuse, food additives, several normal food components, and maternal diseases or abnormal situations, determines irreversible morphological, biochemical and functional changes in various cell-types through the mechanism of imprinting or cell programming. These alterations that persist through life include changes in hormone receptors and action

that alter the mechanisms of cellular homeostasis, and favor the development of diseases later in life. Taking the above into consideration, it is clear that these prenatal or early postnatal exposures determine the future health conditions during adulthood. It can be assumed that an important number of adult age diseases were determined during early stages of life, under the effect of these chemicals or of agents present in the preferential mother's diet during pregnancy. It is possible to foresee that knowledge of prenatal exposure delayed adverse effects will allow to avoid exposures during sensitive stages of human development, i.e., late fetal and early neonatal ages. Further, the finding of mechanisms for antagonizing the effects of imprinting opens the possibility to interfere with prenatal exposure delayed adverse effects, in situations where it is not possible to avoid the contact with the imprinting-inducing agent. This new field of environmental pathology and medicine may therefore contribute to an important improvement of health conditions of humankind.

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