The impact of endocrine disrupters on the female reproductive system

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Over the last decades, many tonnes of man-made chemicals have been produced and released into the environment. Many of these chemical substances have the ability to modulate the action of hormones and are called endocrine disrupters. Cell receptors that have been pure receptors for thousands of years have (due to industrialization), become susceptible to the action of exogenous chemicals. The balance of the endocrine system is very important in the human body especially in females because the menstrual cycle and fertility are very sensitive to hormone imbalances. This review considers the mode of exposure and action of endocrine disrupters and focuses on their impact on the female reproductive system, including female hormone concentrations, menstrual cycle, fertility, spontaneous abortion and the development of endometriosis. An attempt is made to elucidate the impact of endocrine disrupters on the female reproductive system, while admitting that most scientific data come from experimental animals and the conclusions cannot be applied to humans easily. The aim is to present available information, highlighting the impact of endocrine disrupters on the female reproductive system, in order to stimulate re-evaluation in identifying hormone disorders.

Key words: endocrine disrupters/endometriosis/female hormones/pesticides/reproduction

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Introduction

Over the last 50–60 years, many types of man-made chemicals have been manufactured and many of them have become widespread environmental contaminants (Simonich and Hites, 1995; for reviews, see Longanathan and Kannan, 1994; Fry, 1995; Dich et al., 1997; Longnecker et al., 1997). These substances can affect human health, by upsetting the balance of the endocrine system, and they are known as hormone-disrupting chemicals or endocrine disrupters. As a result of mankind’s use of vast quantities of such chemicals, humans and wildlife are continually exposed to endocrine disrupters (O’Shea et al., 1980).

Many of the endocrine disrupting chemicals are organochlorine substances, which means that they contain chemically combined carbon and chlorine. This binding is very strong and resists degradation by normal biochemical and physical processes. Hence, the organochlorines have a long half-life and they accumulate in the environment as persistent organic pollutants (for reviews, see Hendriks et al., 1995; Simonich and Hites, 1995; Tanabe et al., 1998; Fisher, 1999; Muir et al., 1999).

Organochlorines occur naturally in the environment, but only at very low concentrations. About 2000 compounds are known to be produced by living organisms, which contain chlorine or other halogens (bromine, iodine, or fluorine) (Gribble, 1994). Humans and wildlife have not evolved mechanisms or biochemical pathways to detoxify and excrete these chemical substances, so the organochlorines are stored and accumulated in the lipids and fatty tissue (Hall, 1992; Fisher, 1999).
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Chronic exposure to endocrine disrupters results in growing concentrations becoming bioaccumulated. The effects observed in wildlife and humans include decreased hatching in fish, birds and turtles; reproductive problems and decreased fertility in mammals (Gilbertson et al., 1991; Fry, 1995; Muir et al., 1999); decreased sperm quality in humans (Carlsen et al., 1992; Bromich et al., 1994; Auger et al., 1995); behavioural abnormalities in birds and mammals, compromised immune system in mammals; and an increase in the incidence of malformations and cancers of male genital tract (for review, see Dich et al., 1997; Longnecker et al., 1997; Palanza et al., 1999). As these substances disrupt the hormonal balance of the body and many of them disrupt the action of oestrogen, their action in the female reproductive system and female fertility is of great interest.

Exposure

Chemicals including many pesticides, polychlorinated biphenyls (PCBs), dioxins, phthalates, lead, mercury and cadmium do not necessarily remain where they are released into the environment but may be transported in water or on air currents throughout the globe (Loganathan and Kannan, 1994). These substances are bioaccumulated and biomagnified, which means that their concentration increases from one trophic level to the next, within the food chain. Humans, some animals and sea mammals, which are on the highest trophic levels, have the highest concentration of endocrine disrupters (Mossner and Ballschmiter, 1997; Fisher, 1999).

Human exposure to endocrine disrupters may occur in a variety of ways, including ingestion of food and water, inhalation of air and skin absorption. For the majority of these chemicals, the major source of exposure is via food (Hall, 1992). For example, >90% of daily intake of PCBs is through food (Theelen et al., 1993). What is remarkable is that the placenta cannot prevent the organochlorine substances from entering the embryonic circulation (Ando et al., 1986; Kanja et al., 1992). The fetus is exposed to endocrine disrupting chemicals (i.e. exogenous hormones) during the period of organogenesis, which depends on hormone balance. After birth, exposure continues via lactation. As organochlorines are lipophilic substances, they are excreted in the breast milk and ingested by the neonate. These substances are detected in breast milk in significant quantities worldwide (Koopman-Esseboom et al., 1994; van Birgelen, 1998), so that the infant has already a burden of endocrine disrupting chemicals within the first months of its life (Patandin et al., 1999).

Mechanisms of action

The endocrine disrupters modulate the hormonal function in the body and, in particular, affect the steroid hormones. Changes in the effective concentrations of hormones can occur if an endocrine disrupter binds to a specific hormone receptor. This chemical substance may then either mimic the hormone or block the normal biological response by occupying the receptor site. Alternatively, endocrine disrupters may be able to react directly or indirectly with the hormone structure to alter its function, change the pattern of hormone synthesis, or modulate the number of hormone receptors and their affinities for specific molecules (for reviews, see Safe et al., 1991; DeRosa et al., 1998; Sonnenschein and Soto, 1998). Endocrine disrupters have been also shown to modulate the action of thyroid hormones in the body (Cheek et al., 1999; Osius et al., 1999), while there is evidence that some endocrine disrupters may interact with glucocorticoid receptors (Johansson et al., 1998).

A great deal of work has been carried out on the toxicity of dioxins, especially the most potent congener 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). In-vitro and in-vivo studies have revealed that TCDD has anti-oestrogenic properties (Safe et al., 1991; Zacharewski et al., 1994). It exerts its action through binding to a receptor called the aromatic (aryl) hydrocarbon receptor (Ah receptor), which is an intracellular protein. The binding of dioxin or other endocrine disrupters to the Ah receptor causes induction of cytochrome P450 through the transcription of CYP1AI gene and other genes that influence basic cellular processes, e.g. growth, differentiation and programmed cell death (Wu and Whitlock, 1992; Schrenk, 1998; Whitlock, 1999).

Endocrine disrupters and disorders in the female reproductive system

The development and the function of the female reproductive tract depends upon hormone concentrations and balance. Endocrine dysfunction may result in many abnormalities, e.g. menstrual cycle irregularities, impaired fertility, endometriosis, and polycystic ovarian syndrome (PCOS). These abnormalities may result from modulation of the concentrations of oestrogens, thecal androgens and thyroid hormones. As endocrine disrupters have the ability to modulate these hormones, it is vital to establish whether they can affect female genital function.

Evidence for the potential effects of endocrine disrupters comes from diethylstilboestrol (DES). The results of the prescription of DES are well known. Women who were exposed in utero to DES are at a high risk of developing clear cell adenocarcinoma of the vagina (Herbst and Scully, 1970; Giusti et al., 1995) and DES is also linked with menstrual irregularities, altered uterine structure, infertility, miscarriage, premature births and breast cancer (Giusti et al., 1995). DES is a xeno-oestrogen and many of the endocrine disrupters act in a similar manner. However, conclusions drawn from studies on DES cannot be generalized because DES acted for a limited period of time, while endocrine disrupters act during the whole life, the concentrations of the endocrine disrupters are diverse and they include a variety of substances.

In-vitro studies

Results from in-vitro experiments indicate the effects of endocrine disrupting chemicals on the female reproductive system and suggest a hypothesis for their in-vivo action and their linkage with disease. The expression of Ah receptor in endometrium is necessary for the dioxin and some other endocrine disrupters to exert their action. The Ah receptor RNA and protein in endometrium of premenopausal women is expressed in 43% of the endometria studied and have been correlated with the day of the cycle. The maximum expression in endometria is around the time of ovulation and it decreases with increasing age, indicating that women of reproductive age are likely to be more vulnerable (Kuchenhoff et al., 1999). The exposure of human endometrial cells in culture to dioxin increases the induction of expression of...
interleukin-1β and plasminogen activator inhibitor-2 mRNAs in a dose-dependent manner but, in this study, expression of CYP1A1 mRNA was not detected and the amount of Ah receptor mRNA was decreased dose-dependently (Yang, 1999). This is unlike previous reports, where binding with the Ah receptor usually induces the expression of CYP1A1 gene (Whitlock, 1999). More pathways of action for dioxin need to be investigated. TCDD suppresses the gene expression of the oestrogen receptor in the ovary, uterus and liver of mice by decreasing its transcription; this response is probably mediated through the Ah receptor (Tian et al., 1998).

Granulosa cells play a significant role during the ovarian cycle and secretion of steroid hormones. The administration of TCDD in culture of granulosa cells significantly decreases oestradiol production. It has been suggested that TCDD might interrupt the endocrine function of human luteinized granulosa cells by blocking the mitotic signal, either directly, or indirectly through the interaction of protein tyrosine kinase/microtubule associated protein 2 (MAP2) kinase and protein kinase signalling (Enan et al., 1996). The effect of the fungicide, methyl-2-benzimidazolecarbamate, on the primary cultures of human ovarian granulosa cells is similar. It has been reported that methyl-2-benzimidazolecarbamate alters centrosome organization during mitosis in dividing granulosa cells. One possible mechanism of action of this agent is the impairment of spindle microtubule dynamics at the centrosome, which results in metaphase arrest and abnormal chromosome organization (Can and Albertini, 1997).

Hexachlorobenzene is another pesticide which is used worldwide. It alters the cell shape of the ovary surface epithelium of cynomolgus monkeys. Many cells become tall, columnar, highly irregular in outline, and show signs of degeneration instead of being squamous to cuboidal, and lying in a single layer. The nuclei migrate toward the apical surface instead of being in the middle. Cytoplasm contains a large number of lysosomes, and numerous vesicles, which may be swollen endoplasmic reticulum. These effects are dose-related (Babineau et al., 1991; Sims et al., 1991).

The function of placenta may also be modulated by endocrine disrupters. The CYP1A1 enzyme is induced and polycyclic aromatic hydrocarbon-related DNA adducts in placental tissue are found in the placenta of pregnant women exposed to organochlorine chemicals (Laguex et al., 1999).

Effects on female hormone production

The organochlorine pesticide hexachlorobenzene (HCB) is a worldwide persistent organic pollutant and has been detected in various tissues and human fluids including serum and ovarian follicular fluid (van der Ven et al., 1992). The exposure of cynomolgus monkeys to HCB (10.0 mg/kg body weight/day) for approximately three menstrual cycles significantly reduces the concentration of oestradiol at ovulation (Foster et al., 1995). Findings on rats indicate that the effect of HCB on steroidogenesis is indirect (Foster et al., 1992).

The effect of TCDD on the ovary of rats appears to be similar. Simultaneous in-vivo experiments in hypophysectomized rats and in-vitro experiments in granulosa cells, theca–interstitial cells and whole ovarian dispersates indicate that TCDD does not alter ovarian steroidogenesis directly (Son et al., 1999). The results are similar when the effect of TCDD on human luteinized granulosa cells in culture are examined (Heimler et al., 1998). Evaluation of the accumulation of oestradiol in the culture medium after the addition of different quantities of dioxin and androstenediene or pregnenolone indicates that dioxin alters the oestradiol secretion from human luteinized granulosa cells by depletion of androstenedione. The administration of both choriionic gonadotrophin and TCDD in immature female rats alters the concentrations of oestradiol, FSH and LH, while the expected decrease in serum oestradiol concentrations at 60–72 h after choriionic gonadotrophin treatment is not observed (Li et al., 1995a).

Heptachlor is another organochlorine pesticide with endocrine disrupting action. The treatment of rats with heptachlor suppresses progesterone and oestradiol concentrations in blood and reduces the production of oestradiol by the ovarian cells of treated rats, while production of progesterone depends on the dose of heptachlor (Oduma et al., 1995a).

Progesterone concentrations also decrease during early pregnancy in the rabbit after treatment with the pesticide dichlorodiphenyl-trichloroethane (DDT) (Lindenau et al., 1994), while treatment of pregnant cynomolgus monkeys with TCDD results in decreased concentrations of oestradiol, progesterone and choriionic gonadotrophin (Guo et al., 1999).

As far as we know, there are no published papers on the direct effect of endocrine disrupters on the concentrations of female hormones in humans. The previous experiments provide strong evidence that these chemicals may impair the balance of the endocrine system in women. However, women with prenatal exposure to DES had no alteration in hormone concentrations except for the concentration of testosterone in the post-ovulatory and perimenstrual phases of the cycle, as well as in women with irregular menses (Wu et al., 1980). On the other hand, it is known that treatment with contraceptive pills (exogenous hormones) impairs FSH and LH secretion and results in anovulation (Stubblefield, 1996). More epidemiological studies and laboratory experiments need to be performed before final conclusions on the effect of endocrine disrupters on the concentration of female hormones in humans can be drawn.

Menstrual cycle

Endocrine disrupting chemicals may affect the function of oestrogen and progesterone and/or the hypothalamic–hypophysial axes and may alter the natural menstrual cycle, ovulation and fertility. Epidemiological studies in humans have investigated the impact of endocrine disrupting chemicals on the menstrual cycle and there is a great deal of experimental data on the effect of these substances on the cycle of monkeys or oestrus in rodents.

One of the areas in the world most contaminated with persistent organic pollutants is the Great Lakes. People who eat fish from these Lakes are exposed to various chemical substances. An epidemiological study of women who consumed fish from Lake Ontario showed a link between fish consumption, PCB exposure, and a reduction in menstrual cycle length, indicating the possible impact of PCBs through food on menstrual cycle (Mendola et al., 1997).

Rats exposed to organochlorine pesticides with oestrogenic properties including atrazine (Eldridge et al., 1994, Wetzel et al., 1994, Cooper et al., 1996), heptachlor (Oduma et al., 1995b), and

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methoxychlor (Chapin et al., 1997) have oestrous irregularities and prolonged duration. The exposure of rats to different concentrations of 3,3′,4,4′-tetrachloroazoxybenzene also results in increased oestrous cycle length (van Birgelen et al., 1999). Even after a single dose treatment with TCDD, rats show cycle irregularities, e.g. longer duration of di-oestrous (Li et al., 1995b).

Another oestrogenic chemical substance is 4-tert-octylphenol. Either neonatal exposure or exposure during adulthood of rats to this chemical results in persistent oestrus in the majority of exposed animals (Blake and Ashiru, 1997). There is also a correlation between PCB exposure and oestrus in rats (Sager and Girard, 1994) or cycle of monkeys (Arnold et al., 1993).

According to epidemiological and experimental data, there is strong evidence that exposure to endocrine disrupters is associated with menstrual cycle disorders. However, more epidemiological data is needed to confirm this and to indicate the levels of exposure which result in an effect on menstrual cycle.

**Ovulation**

It is known that contraceptive pills contain hormones, oestrogen and progestins and that they block normal ovulation. In the same way, endocrine disrupters with oestrogenic properties could block ovulation, if they reach a specific concentration. This would be possible after a critical point of bioaccumulation, either early in the life of sensitive females or even later, resulting in reproductive disorders.

TCDD inhibits ovulation in rats with direct impairment of follicular rupture and not because of an alteration in ovarian steroidogenesis (Son et al., 1999). Although the effects of TCDD on ovulation of rats have been confirmed (Li et al., 1995a,b), its action was found to be via a direct effect on the ovary and on the hypothalamic–pituitary axis (Li et al., 1995a).

The exposure of neonate mice to the organochlorine pesticide, methoxychlor, results in a dose-dependent reduction of ovulated eggs in adult life after ovulation stimulation (Eroschenko et al., 1997). Ovulation defects are also observed in prenatal and neonatal exposed mice to methoxychlor (Chapin et al., 1997), and there are experimental data (Foster et al., 1992; Goldman et al., 1993; Cooper et al., 1994) that link defects of ovulation in animals with exposure to environmental pollutants. In the absence of epidemiological studies on women, we can only assume that these substances may impair ovulation in humans.

**Fertility**

In many infertile couples, no apparent cause of infertility can be found even after thorough examination. It has been suggested that spermatozoa may have molecular or biochemical disorders resulting in an inability for fertilization, although their mobility and morphology is normal (for reviews, see Sindhu and Guraya, 1989; Tulsiyani et al., 1998).

Lindane (γ-hexachlorocyclohexane) is a widely distributed organochlorine pesticide. This pesticide intercalates into the sperm membrane and alters the molecular dynamics of the lipid bilayer (Silvestroni et al., 1997). Lindane in doses as high as that found in female genital tract secretions may inhibit sperm responsiveness to progesterone in vitro, which induces the acrosome reaction at the site of fertilization (Silvestroni and Palleschi, 1999). This could be a cause of infertility in women exposed to lindane.

Exposure to pentachlorophenol (contained in wood preservatives) has also been suggested as playing a role in infertility. The effect of pentachlorophenol in women with endocrine dysfunction may be at the hypothalamic or suprathalamic level, causing mild ovarian or adrenal insufficiency (Gerhard et al., 1999).

There are already some examples of subfertility in wildlife caused by endocrine disrupters. Lake Apopka in Florida is contaminated by a previous extensive spill of dicofol and DDT. During the 1980s there was a progressive decline in the alligator population on the lake, which is presently still continuing. The population is now only a tenth of the size recorded in the 1970s. A study on the alligators (Guillette et al., 1994) found evidence of decreased reproductive ability. Oestrogen concentrations in female juveniles were twice that of alligators from an unpolluted lake and the juveniles exhibited abnormal ovarian structure. There were also adverse effects in male alligators. These data strongly suggest that the endocrine disrupter chemicals affect hormone concentrations and reproduction. Fertility problems in numerous other organochlorine-exposed wild animals, e.g. seals (Rejinders and Brasseur, 1992) and birds (Giesy et al., 1994), have also been recorded.

Other studies indicate adverse effects of organochlorines on the fertility of experimental animals; treatment with 3,3′,4,4′-tetrachlorobiphenyl (group of PCB) results in impaired fertility. The animals show a dose-dependent reduced fecundity as well as decreased fertilization after in-vitro insemination with spermatozoa (Huang et al., 1998). Similar effects on conception rates are found after treatment of rhesus monkeys with another PCB, aroclor 1254 (Arnold et al., 1995). The presence of aroclor 1254 reduces both the IVF rates and embryonic development in mice (Khikute et al., 1994a,b,c). However, trace amounts of organochlorine compounds (found in follicular fluid of women undergoing IVF), had no effect on fertilization rates and time to cleavage (Jarrell et al., 1993). Nevertheless, this result does not rule out effects of these organochlorines on fertilization in vivo.

The pesticide methoxychlor accelerates the embryo transport rate in rats and induces preimplantation embryonic loss, perhaps due to this acceleration (Cummings and Perreault, 1990). The exposure of rabbits to sparse organochlorine compounds (PCB, DDT, γ-hexachlorobenzene) has almost no effect on fertility but organochlorine compounds are detected in uterine secretions and blastocysts. A small increase in blastocyst loss after PCB exposure may be due to its embryo toxicity (Seiler et al., 1994). The results suggest that organochlorine compounds may have adverse effects on fertilization and some cases of unknown infertility may be explained by the action of these chemical substances.

**Spontaneous abortion**

The organochlorine compounds entering the embryonic circulation through the placenta could affect the pregnancy outcome resulting in many congenital disorders but also in spontaneous abortion. In southeastern Turkey during 1955–1957, women were accidentally exposed to the pesticide hexachlorobenzene after eating contaminated seed grain and, as a result, developed...
porphyria cutanea tarda. There was strong correlation between hexachlorobenzene in serum samples and the risk of spontaneous abortion in those women (Jarrell et al., 1998). However, in another epidemiological study in Italy, no correlation was found between the serum concentration of hexachlorobenzene and spontaneous abortion (Leoni et al., 1986). More than 20% of women with repeated miscarriages have higher concentrations of organochlorines than reference populations. Organochlorines may be responsible for miscarriages in a sensitive population (Gerhard et al., 1998). Another population in southern California potentially exposed to pesticides occupationally or environmentally does not appear to have increased risk for spontaneous abortion but, in contrast, has a lower risk (Willis et al., 1993). PCB concentrations are higher in the blood of women undergoing miscarriage than women at full term (Leoni et al., 1989) or in the second trimester of pregnancy (Bercovici et al., 1983).

One attempt to interpret the mechanism through which PCBs induce spontaneous abortion suggests that arachol 1242 increases the frequency of contractions of uterl via the calcium and arachidonic acid released by phospholipase A$_2$ (Baie et al., 1999a,b).

The treatment of cynomolgus monkeys with TCDD during pregnancy alters the concentrations of some hormones and increases the risk of early fetal loss. TCDD may result in endocrine imbalance, which leads to placental insufficiency, compromised embryonic circulation and finally early fetal loss (Guo et al., 1999). It seems that exposure to endocrine disrupting chemicals may increase the incidence of spontaneous abortion in sensitive or more exposed populations. A mechanism through which PCBs may increase spontaneous abortion has been proposed (Baie et al., 1999a,b). The action of other organochlorines on the uterus should also be investigated using quantities similar to those found in the human body.

**Endometriosis**

Endometriosis is the presence of endometrial tissue (glands and stroma) outside the uterus. The disease occurs naturally only in humans and non-human primates. There is strong evidence that endometriosis is a complex trait in which multiple gene loci interact with each other and the environment to produce the expressed phenotype (Kennedy, 1999). It is an oestrogen-related disease and oestrogens are known to stimulate the growth of endometriotic lesions. The medical treatment (oral contraceptives, progestins, gestrinone, danazol and gonadotrophin-releasing hormone agonists) is designed to suppress oestrogen synthesis, thereby inducing atrophy of ectopic endometrial implants or interrupting the cycle of stimulation and bleeding (D’Hooghe and Hill, 1996).

As endometriosis is an oestrogen-related disease and some endocrine disrupters in the human body mimic oestrogen, the link between endometriosis and endocrine disrupters should be investigated. In Belgium, a country heavily polluted with dioxin, the incidence of endometriosis is high (Koninckx et al., 1994). Of course, this does not prove that dioxins are the only cause. Endometriosis is a multifactorial disease and the Belgian population may have other characteristics that promote the development of endometriosis. Very strong evidence comes from a long-term study on the health effects of chronic dioxin exposure on rhesus monkeys (Rier et al., 1993, 1995). For a period of 4 years between 1977 and 1982, one group of monkeys were fed with 25 parts per trillion (ppt) per day dioxin in their diet, a second group were fed with 5 ppt dioxin and a third group acted as control and were not given dioxin. The animals were examined 10 years after the end of dioxin treatment; five out of seven animals (71%) exposed to 25 ppt dioxin and three out of seven animals (43%) exposed to 5 ppt dioxin had moderate to severe endometriosis compared with 33% of animals in the control group. This is similar to an overall prevalence of 30% in 304 rhesus monkeys with no history of dioxin exposure. The differences were statistically significant ($P < 0.05$) in both groups of exposed animals. It is concluded that chronic exposure to dioxin is directly correlated with a significant increase in the incidence of the development of endometriosis.

According to this experiment, there is strong evidence that dioxin exposure leads to development of endometriosis, but there is no epidemiological evidence from large studies on humans. The population in Seveso, Italy, which was exposed to dioxin after an accident, would be ideal for designing an epidemiological study (Bois and Eskenazi, 1994), but as far as we know, nothing has been published yet. Additional information comes from other studies. It is known that endometriosis is a major factor in female infertility, and that 18% of women with endometriosis have miscarriage but, in contrast, has a lower risk (Willis et al., 1993). PCB concentrations are higher in the blood of women undergoing miscarriage than women at full term (Leoni et al., 1989) or in the second trimester of pregnancy (Bercovici et al., 1983).

One attempt to interpret the mechanism through which PCBs induce spontaneous abortion suggests that arachol 1242 increases the frequency of contractions of uterl via the calcium and arachidonic acid released by phospholipase A$_2$ (Baie et al., 1999a,b). The action of other organochlorines on the uterus should also be investigated using quantities similar to those found in the human body.

Endocrine disrupters and female reproductive system

Endocrine disrupters are chemicals that interfere with the endocrine system, which is responsible for the production and regulation of hormones. These chemicals can interfere with the production, transport, or action of hormones, leading to changes in reproductive health. One example of an endocrine disrupter is dioxin, a byproduct of the manufacture of certain industrial chemicals. Dioxin is known to have adverse effects on human health, including reproductive problems. In the case of endometriosis, dioxin exposure has been linked to an increased incidence of the disease. This is because endometriosis is an oestrogen-related disease, and dioxin can interfere with the production of oestrogen. Additionally, dioxin can also cause placental insufficiency, which can lead to miscarriage. Therefore, exposure to dioxin can have a significant impact on female reproductive health, and the relationship between dioxin exposure and endometriosis warrants further investigation.
Experiments on mice and rats may be of questionable value, described experimental studies provide evidence that some endocrine disrupters may affect the development and promotion on the potential effects of endocrine disrupters. Current research estimate the whole exposure, as exposure to individual substances are also different from that in women. In order to results from epidemiological or laboratory studies on women and there is not sufficient data concerning humans. The limited hypothesis that endocrine disrupters impair female reproduction. These substances may alter both the hormone concentrations and the menstrual cycle of women as well as their fertility. There is also evidence that endocrine disrupters may enhance the development and promotion of endometriosis, while it would be interesting to elucidate the correlation between PCOS and the endocrine disrupters. Although PCOS is related to hormone irregularities, there is no published study investigating this correlation.

In most studies documented, animals were exposed to a few chemical substances for a certain period of time. On the other hand, humans are exposed concomitantly to a great number of chemical substances over their lifetime. These various chemical substances may enhance or have an antagonistic effect on each other. The accumulated concentrations of the chemicals in animals are also different from that in women. In order to increase the available data and information on the impact of endocrine disrupting chemicals on human health, it has been proposed that a marker of exposure should be developed (Soto et al., 1997). This marker, if developed in a screening test, would estimate the whole exposure, as exposure to individual substances may not be reliable because of the cumulative, synergistic or antagonistic effects among different substances.

It therefore appears urgent that research strategies should focus on the potential effects of endocrine disrupters. Current research investigates infertility problems with no regard for the potential effects of these relatively new chemical substances. The identification of the exact effects and role of these endocrine disrupters may help explain some cases of unknown infertility.

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