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Review Article

Endocrine-Disrupting Chemicals and Men's Reproductive Health

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Abstract

The purpose of this review is to address all agents and mechanisms lihe EDCs(Endocrine Disrupting Chemicals)capable and interfere in the development of the male's reproductive system which is regulated by hormones and other factors, and the potential consequences caused by these different chemicals.They are known to cause several effects to the male genitalia such as hypospadias, cryptorchidism,testicular cancer as well as interfering with semen quality, therefore determining its correlation with male infertility.

Keywords: Endocrine-Disrupting Chemicals; Male Genital Anomalies; Reproductive Health; Testis

Introduction

There has been a growing concern that the incidence of male reproductive disorders is increasingly higher both in humans and different animal species [1]. Over the past few years, numerous reports show a decrease in the sperm quality and even the rise of new abnormalities. They have been defined as Testicular Dysgenesis Syndrome including conditions like hypospadias, cryptorchidism, not to mention an increased incidence of testicular tumors, deserving close attention [2-5]. As described previously in Sharpe and Skakkebaek's hypothesis, Endocrine-disrupting chemicals with oestrogenic effects are considered the cause for these abnormalities [6]. Possibly, the harmful effects on Leydig cells of fetal testis contributes to the occurrence of common abnormalities like hypospadias or cryptorchidism leading to a decreased androgen production and consequently inducing alterations on the male phenotype. Among several acting agents of Endocrine-disrupting chemicals and a growing number of scientific evidence has been collected over the past few years suggesting that human reproducing capacity has been affected by a wide range of recurrent substances included in many everyday products. Several indicators are showing an increased incidence of cardiovascular disorders, obesity, hormone-dependent cancers and chronic diseases, the early puberty development, pregnancy length disorders and other reproductive health abnormalities. Among those acting agents have been defined as Endocrine-Disrupting Chemicals (EDCs).

Endocrine disruptors are chemical products that may interfere and cause adverse effects on the endocrine system at any life-stage, given their resemblance to endogenous steroid hormones.Their actions were determinated like agonist or antagonist against several hormones (estrogens or androgens). Some EDCs can disturb proteins involved in the transport of hormones and disrupt the delivery of endogenous hormones to target cells.Usually the molecular structure consist of a phenol group on the first ring and one group substitution by chlorine or bromine and mimic steroids hormones.These situations interfere with synthesis,secretion,transport and metabolism of diverses hormones and by their similarities induces in destabilization of hormonal homeostasis.They also alter the number and actions of different hormone receptors in different cell types and because that alter the concentration of circulating hormones and blocking their actions. There are many mechanisms involved and even sometimes not detected.

There are two pathways by which an EDCs can could disrupt hormone action by a direct action on a hormone-receptor protein complex or a direct action on a specific protein that control the hormone-delivery to the right place on the right time. The EDCs act like hormones and act via biding to receptors in a very low concentrations and produce synergistic or antagonistic effects. In 2013, Birnbaum showed that between 1947 and 2007,the global production of such chemicals has increased 23.5 times, whereas in 2012 only,the US produced 9.5 trillion pounds or 2.09 trillion

kilograms of such products including pesticides, plastics,chemical drugs or even personal hygene products [7]. Deserving more attention are a very old product DDT and its byproducts such as atrazine and 2,4-dichlorophenoxyacetic acid found in toys, or others containing plumb and cadmium,materials used for the production of plastic bottles containing Bisphenols A, phthalates and several other substances employed in the textile and apparel industries [7]. Among those acting agentes there are substances including a Bisphenol A and its byproducts such as Bisphenol B, Tetrabromobisphenol A and Bisphenol F and S. Some years ago, the first disruptor detected between those EDC a speciall hormone,was named Diethylstilbestrol (DES) that propitiated disorders at the genital tract of females ad males offsprings.

Our proposal is to analyze the capacity of these agents to affect the men's Reproductive life and their action to induce differents diseases in these areas (Table 1).

Atrazine/ Alachlor	Herbicides
Cadmium chloride/ Methiran	Fungicides
Carbaryl/Chlordane/DDT, etc.	Inseticides
Aldicarb/DBCP	Nematocides
Acrylamide	Water treatment/papear manufacturing
Ascarel (PCB)	Adhesives/paints/silo storage coatings
Benzoanthracene Benzopyrene	Tar/asphalt/grease/mineral oils
Bisphenols A, etc.	Epoxy resin, plastics/can coatings
Plumbs	Bateries, paints/pigments
Polichlorinated Dibenzodioxin	Pesticide-burn/residues-PVC-diesel
DBPC (Dibromochloropropane)	Nematicide
Carbon Disulfide	Celophane manufacture/rayon-solvents/wax
Sthyrene	Plastic and glasses/rubber manufacturing
Phenilphenols	Desinfecting products
Phthalates	Plastificants/varnish/cosmetics/ inseticides
HCB (Hexachlorobenzene)	Organochlorinated processes
Manganese	Iron/paint/fertilizers manufacturing
Mercury	Agrotoxics/paints/soda industry
Ethylene Chloride	Surgical equipment sterilization
Pentachlorophenol	Paints/timber conservants/fungicide
Welding	Metalsmithing and Weldings/ Boilermaking
Trichlorfon	Anthelmintics

Table 1: Several Endocrinous Disrupting-Chemicals and its Actions.

Methods

We used different sites to detect and search about different (EDC) Endocrine Disruptors and its correlation with men's reproductive life including abnormalities of testis (androgen actions) or male sexual abnormalities. A large group of papers were analyzed by consultations to PUBMED, SCIELO and Google Scholar and a great number of papers were analyzed and selected:

Endocrine Disruptors: PUBMED /SCIELO /

EDC X Testicular Steroidogenesis..... 2001-2016

Bisphenol X Male sexual development.... 2002-2017

Endocrine Disruptors X Sperm quality.... 2009-2016

Endocrine Disruptorsl X Hypospadias.... 2001-2016

Endocrine Disruptors X Cryptorchidism.. 2009-2016

Heavy Metals X Male genital anomalies(Google acad.)2014-2018..10800 papers

Were revisited a large number of papers/references and choose the most important articles for analysis by their good qualities.

Endocrine Chemicals Disruptors (Edc) and Some Historical Particularities

In 1936 the DES (Diethylstilbestrol) a nonsteroidal was sinthesized revealing a powerful estrogenic effect.Diethylstilbestrol was defined as the first "endocrine-disrupting chemical, since anomalies were found in the exposed female offsprings of pregnant women treated to prevent abortion, the former having later developed vaginal adenosis, or after that with clear cell adenocarcinoma of the vagina and/or uterus abnormalities (T Shaped uterus). Bisphenol A (2,2-bis(4hydroxyphenyl) propane was first synthesized by Dianin in 1891, but is estrogenic property was only evidenced by Dodds & Lawson in 1936 [3,4]. Later, in 1950 it was observed that BPA(Bispphenol A)could be polymerized for the manufacturing of plastics given its lightweight, moldability and impact resistency. The list of Bisphenol products available in the market has steadly increased, the most common being Bisphenol S,F,B and AF with different properties.

DDT(Dichlorodiphenyltricloroethane)-DDE(dichlorodiphenyldichloroethilene)

DDD(dichlorodiphenyldichloroethane)DDT was synthesized by Paul Muller and first employed in 1936 in Colorado potato beetles

crops. After some years it was a worldwide inseticide used during the 50's and 60's.Was banned in 1972 because its high toxicity,but was previously employed to combat the "malaria mosquito". Bysphenil Polychlorinated was first manufactured in 1927 and 1933 was detected that a direct skin contact may developed a acne-like condition named chloracne.Polybrominated-Diphenyl-ether is a flame retardant that may induce severe neurotoxic effects in humans. Atrazine was invented in 1958 by Geigy Laboratories,but due its the persistent groundwater contamination was banned in the European Union.It was prepared from cyanuric chloride and treated with ethylamine and isopropyl amine.Today near to 800 chemicals are known or are suspected to be capable and interfering on hormone receptors,hormone synthesis and their actions.

Endocrine Disruptors Are

Bisphenols: Bisphenol A (BPA)was synthesized in 1891,but evidences showed a low estrogen effect in 1936 with affinity for the nuclear estrogen receptor. Its effects will depend on the dosage,targeted tissue and tissular development where it will act. These substances can induce estrogenic or even antiestrogenic effects, or antiandrogenic and are dependent on the tissue, according to their impact at receptors [8-10]. Global production of BPA has steadly increased in the latest years given its mulptiple applications in both plastic and manufacturing industries,food packaging and toys causing a constant and permanent intoxication of food, water and the environment. In 1950, it was found Biphosphonates could be polymerized and, since then, they are used to make polycarbonate plastics. Those plastics have convenient features such as lightweight, moldability and impact and heat resistance, not being suceptible to changes over time. Around 20% of those plastics are used as a component of epoxy resin serving as internal coatings for containers and plastic bottles. Therefore, it is a liquid and food contaminant while the human serum analysis has shown variable and abnormal rates in different studies. Exposure to BPA can occur by oral ingestion or transdermal/sublingual absorption, suffering a fast hepatic breakdown [11-13]. Given its lipophilic properties, BPA can easily build-up in the adipose tissue.

Bisphenols A are rapidly metabolized to inactive forms with an average life cycle of approximately 4-5 hours in adults, presenting a relatively low metabolic rate in fetoses and children [10-12]. They can easily accumulate in adipose tissue having lipophilic properties. Measurements of human serum have determined varied and controversial toxicity rates.Currently, the United States Evironmental Protection Agency has established a safe level of 50ug/kg/day and the European Food Safety Authority has established the tolerable daily intake should remain below de 4ug/kg/day.

There are a wide range of BPA doses and is considered a "low dose" below the lowest observable adverse effect in animals is 50mg/kg/d. Five different types of Bisphenols are currently being employed in the industry such as Bisphenol B (BPB), Bisphenol F (BPF), Bisphenol S (BPS), Bisphenol AF (BPAF) and Tetrabromobisphenol (TBBPA) [14-16] (Figure 1).

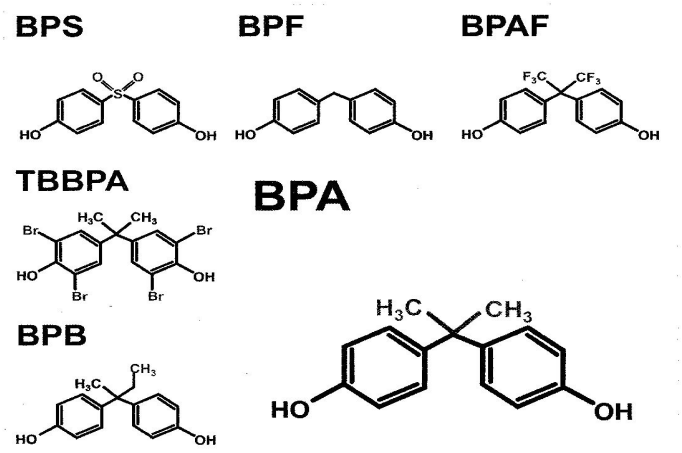


Figure 1: Comparing the Structural Formulas of different Bisphenols [16].

BPA..Bisphenol A...2.2-bis(4-hydroxiphenyl)propane

BPB..Bisphenol B... 2.2-bis(4-hydrophenyl)butane

BPF..Bisphenol F.. 4.4'-(1-phenylethylidene)bisphenol

BPS..Bisphenol S.. 4.4'-sulfonyldiphenol

BPAF.Bisphenol AF..4.4'-(hexafluoroisopropylidene

TBBPA.Tetrabromobisphenol A

Phthalates: Phthalates and their esters consist of a large group of chemical compounds frequently used in the plastic,coating,cosmetic and toy industries,including the manufacturing of medical equipment like syringes and blood bags. Phthalates are byproducts of phthalic acid and are used in the plastics industry having excellent moldability. Both in the United States and Brazil there are no restrictive regulations on their use, but the European Community has banned those products from the market. Among Phthalates, three esters are considered endocrinous disruptors having estrogenic effects such as DHEP (diethyl-hexyl phthalate),BBP (benzyl-butyl phthalate) and DBP (dibutyl phthalate).Phthalates can be found not only in serum and human urine but also in milk samples. Tolerable daily intake should remain between 3-30ug/kg/dia [13] (Figure 2).

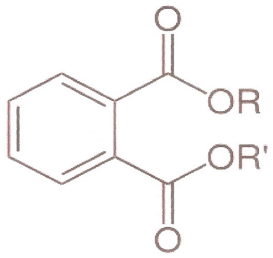


Figure 2: Structural formula of Phthalates.

Atrazine: Atrazine(2-chloro-4-ethylamino-6-isopropylamino-1,3,5-s-triazine)is largely used in agriculture as herbicide just like chlorotriazine.It has been used to reduce the growth of leaves and weeds in wheat, soy and sugar cane cultures due to the inhibition of photosynthesis [11]. Its metabolites remain active for long periods of time and, as pesticides,they cause water contamination,including water sources for human consumption [14] Atrazine remains in soil for months and the half-life in soil is 13-261 days (Figure 3).

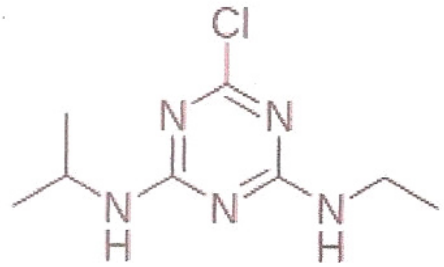


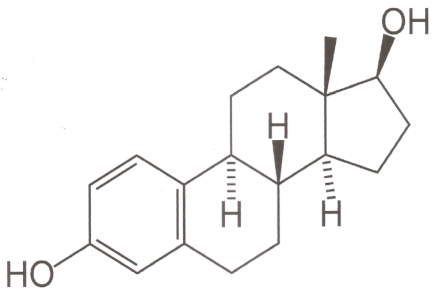
Figure 3: Structural formula of Atrazine.

Esters of Polychlorinated and Polybrominated Bisphenols: Polychlorinated Bisphenols (PCBs) are chemical substances with phenolic ring and different degrees of chlorination. They were first manufactured in 20's, being used in the rubber, resin, adhesives and paint industries [15]. Those chemicals were extensively used around the world contamining schools and constructions sites.They build up both in the environment and in adipose tissue, being considered Endocrinous Disruptors with thyroid hormone, estrogenic and anti-androgenic activity. PCBs were banned from the market in 1979 for its persistent pollutant effects. The polybrominated esters of Bysphenols were first used as flame retardants and for matresses and covers manufacturing [15-17]. Amongst all 209 synthesized products which are also polybrominated aromatic, there are the top 5 in toxicity as esters (tetra BDE-47, penta BDE99,-100,-153 and deca BDE-209 or PBDE=Polybrominated diphenyl ethers) [18,19]**.**

DDT(Dichlorodiphenyltrichloroethane)-DDE(Dichlorodiphenyldichloroethylene)–DDD (Dichlorodiphenyldichloroethane): These are chemical compounds once widely used as inseticides with long average life and strong lipophilic properties.Evidenced as contaminants to the environment, exposure to these chemicals can lead to several endocrinous diseases although it has been used to control insects that carry malaria [18]. DDT was banned from the market in 1972 due to its high degree of toxicity. In addition to DDT, other pesticides deserve to be mentioned such as hexachlorocyclohexane, chlordane and hexachlorobenzene. These products have been closely studied not only for persistently building up in nature but also for being endocrine-disrupting chemicals.However, there are new pesticides being launched in the market, with shorter average life and similar effects such as 2,4-dichlorophenol,2,5-dichlorophenol and 1-naphthol, present in 50% of pregnant women in the Salinas Valley,California,USA [20,21]. Other DDT's metabolites include DDE (Dichlorodiphenyldichloroethylene) and DDD (Dichlorodiphenyldichloroethane

Diethylstilbestrol (DES= 4.4 dihidroxiestilben): Since 1938 it was a powerful synthetic non-steroidal estrogen,used in the USA, from 1940 to 1975, to prevent abortion and/or its complications. Initially, low doses of 5mg/day were administered, which were progressively increased to 125mg/day or more, summing up to an average dose of 3650-4000mg. In 1953, Dieckmann et al proved this treatment to be ineffective [22]. In 1971, Herbst et al assessed young women having noticed a correlation between the use of DES and the appearence of clear cell vaginal adenocarcinoma,while in 1976, the same author described other abnormalities in the genital tract of these young women whose mothers had been treated with DES [23,24]. In 2012 Harris and Waring and Troisi et al in 2014 have noticed a correlation between the increased number of disorders in the reproductive system of the male and female offsprings whose mothers had been treated with DES such as crypt orchidism,hypospadias,microphallus,epididymal cysts and uterine abnormalities like T-shaped uterus and some types of hormone-dependent cancers [25-27].

Estradiol



Diethylstilbestrol

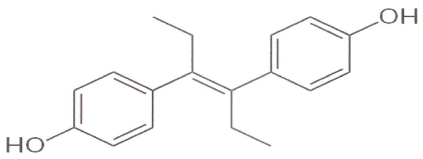


Figure 4: Structural formulas of Estradiol(E2) and Diethylstilbestrol and their similarities.

Heavy metals or organometallic: These products such as Cad mium,Plumb,Mercury,Zinc,Arsenic and Copper have been widely used in various scenarios leading to a great number of reproductive anomalies by acting as an Endocrine Disruptor and are called metalhormones. Cadmium is used fin the manufacture of batteries, metallic pigments and plastics, but exposure to this chemical may cause harmfull effects to the placental DNA and fetal umbilical cord,building up in the liver and kidneys.Cadmium can damage testis at Sertoli and Leydig cells and interfere in semen quality [28]. Plumb was once extensively used in the manufacture of paints, petrol and toys and its adverse effects include genomic methylation and a number of different abnormalities in brain development [29]. Mercury was once used in several industrial processes and charcoal combustion and human exposure can occur mainly through contaminated fish ingestion in different sites like in the Minamata Bay,Japan;Faroe Islands in the North Atlantic; and the population of Nunavik,Canada. The Mercury accumulation may causes several damages in the endocrine system and reproductive effects in male and female humans and animals and on the thyroid and adrenal systems, similar was observed anteriorly [30] .

Male Sexual Development

Male reproductive system development begins with the testis differentiation regulated by the 46,XY chromosome constitution, in the undifferentiated gonads composed of bipotential and primitive features.Development of the internal genital organs results from the continuation of the Mesonephric or Wolff ducts due to an androgenic hormonal activity and the AntiMullerian hormone production in the Sertoli cells of the fetal testis. Testosterone and dihydrotestosterone regulate the virilization of the external genital organs due to androgenic influence in the phallic growth and the anteriorization of the urethra in the penis as well as the labioscrotal union and fusion,developing the scrotal sac. Timing of hormonal action is rather accurate and sexual differentiation occurs between 8-15 weeks through gestation.Testicular descent to the scrotal sac depends on the presence of insulin-like peptide 3 and testis androgens. The production of testosterone and the development of all other male puberty features will begin later, at the beginning of puberty, by the action and stimulation of the central hypothalamic-pituitary.

Analyze and Discussion About Diffrents Edc's Actions

All these different stages of male development can be altered by many harmful chemicals as follows.

Fetal Testis Anomalies

Evidenced that low to high doses of Bisphenol A may induce fetal testis disorders, including other conditions, from birth to adult life. Increased infertility rates are associated to the harmful effects of these endocrine-disrupting chemicals such as lower sperm count, mobility and DNA damage [27-32]. Those studies are controversial, since LaRocca et al documented daily intakes of 50-1000ug/Kg/day in pregnant female rats were not harmful to the fetal testis [27-33]. On the other hand, Tanaka et al showed higher doses would have to be administered to induce a decrease in the fetal testosterone of those rats [26]. According to well established methods developed by Sharpe and Skakkebaek,in 1993 the term ´Testicular Dysgenesis Syndrome" associates Endocrine-disrupting chemicals with oestrogenic activities and multiple abnormalities is reduced sperm count, hypospadias, cryptorchidism and testicular cancer [34]. EDC with estrogenic effects could cause these disorders and the fetal testis is the major target of those substances.

Hypospadia

Is a congenital disorder in which the urethral opening is found on the ventral part and not on the end of the penis.In rats was concluded that a testosterone synthesis or action between 15,5-18,5 days after conception causes masculinization defects with hypospadias,cryptorchidism and incomplete masculinization and this was caused by EDC.This period was named as "masculinization programming window" and in human is between 6,5-14th gestational week.Topari et al described this condition is more common in a particular geographic area, however an

increased incidence has been documented in different countries [35]. Case-control studies are often used to identify hypospadias, using a small number of cases which are not statistically sufficient to allow accurate conclusions on their causing agents. Rocheleau et al in a meta-analysis suggested a correlation between the use of pesticides and an increased risk of developing hypospadias in the offspring of parents contaminated by these substances. However, since pesticides represent a great number of substances, it remains unclear if they can be associated to this anomaly [36].

No significant association has been made between a great number of different pesticides and an increased risk of developing hypospadias in further studies by Morales-Suarez-Varela et al and Rocheleau, et al. [37,38]. Akra et al in 1999 case-control study did not find any consistent support for an etiologic relationship of increased estrogenic levels for maternal origin during pregnancy and the occurrence of hypospadias and cryptorchidism [39] . In their study the babies with an increased risk for these anomalies were preterm and small for gestational age. Recent molecular approaches, including gene-targeting in mices showing that the estrogenic effects of environmental endocrine disruptors and the effects on external genitalia and depend on individual susceptibility can cause several grades of hypospadias.Kojima et al described that genes belongs the Wnt family, homeobox genes and genes for bone morphogenetic proteins and their actions regulate the external genitalia formation al [40].

Cryptorchidism

Is a common genital disorder characterized by an undescended testicle to the scrotal sac affecting about 1 to 9% of full term baby boys [41] Acerini and cols evidenced many infants are diagnosed with cryptorchidism in early childhood, where testicles might not go to the external part of the scrotal sac. Increased rates of cryptorchidism have been observed, reaching up to 7% [42]. This might be a family related condition, resulting from genetic disorders or environmental determinants. Jensen and cols documented higher incidence rates among monozygotic twins [43]. Studies in humans associating the presence of pesticides in patients with cryptorchidism showed higher concentrations of pesticides like heptachlor epoxide in the adipose tissue of male boys who underwent orchidopexy surgery-Hoise, et al. [44]. Likewise, high concentrations of chlorinated pesticides were found in the milk of women breastfeeding boys with cryptorchidism, according to Damgaard and cols, in 2006 [45]. Nevertheless, the US CPP Study made no association between cryptorchidism and DDT, DDE, chlordane or heptachlor epoxide [46]. In turn, another research completed in California by Bhatia et al found high levels of DDT in the blood of pregnant women whose male baby boys were diagnosed with cryptorchidism,although no abnormal levels of DDE (Dichlorodiphenyldichloroethylene) were found [47]. Increased levels of Dioxin and Polychlorinated Biphenyl in flame retardants were associated to higher incidence of cryptorchidism. As described previously by Virtanen and cols, in a study including Danish boys with cryptorchidism,, high levels of dioxin were found in the milk of their mothers, although no trace of this substance was observed in their placenta [48]. No correlation was made between perfluorinated compounds found in the blood of the umbilical cord and higher incidences of cryptorchidism according to a Finish-Danish study by Vesterholm and cols-2014 [49].

Another French case-control study by Brucker-Davis et al-2008, establishing DDE and Polychlorinated Biphenyl concentrations, evidenced an increased risk for cryptorchidism in the exposed group compared to the unexposed group [50]. Many other studies have been showing the authors' growing concern regarding this abnormality genesis and its potential causing agents. In a Study performed in Denmark-Finland in 2013 by Rantakokko et al was analysed the association of placenta organotin with congenital cryptorchidism in 280 newborn boys. The rapid increase in the prevalence of cryptorchidism suggest that environmental factors-endocrine disruptors may be involved even at very low concentration due to activation of the retinoid X receptor [51].

Endocrine Disruptors and Sperm quality

Many contaminating agents have been associated with their capacity of interfering with sperm quality including chemotherapy substances,ionizing agents,nicotine and a number of other chemicals (EDC). All those substances may alter spermatogenesis affecting spermatogonia,Sertoli cells and causing DNA sperm damage. Such damage might be temporary or permanent and will depend on each chemical's intensity of action. Several studies evaluating the effects of Polychlorinated Bisphenols (PCB),with variable degrees of chlorination and phenolic ring, observed its potential damage to sperm quality. Toft and cols, in 2006, and Haugen and cols, in 2011, documented both positive and negative effects of PCB to sperm quality [52,53]. Two studies by Meeker and cols, including 167 and 190 male patients recruited in fertility clinics observed lower levels of inhibin and LH, higher FSH levels and no correlation with plasma levels of total testosterone as well as free testosterone and thyroid hormones levels. Also, a reduction on the sperm concentration and great damage to the DNA sperm has been documented, although the sperms' shape and motility remained unaltered [54,55]. In 2010, Mendiola and cols observed increased levels of Bisphenol A associated to decreased free androgen levels and changes in the free androgen and LH plasma levels in the semen of 302 infertile man. Other hormones like estradiol, total testosterone and free testosterone, TSH, T3 and T4 remained unaltered [56]. In 2011, Li and cols observed low concentrations, decreased sperm count and vitality in the semen of 218 male patients [57]. A prospective study by Knez and cols, in 2014, evaluated seminal parameters of 129 men undergoing infertility treatment and found decreased sperm count

and lower sperm quality [58]. Lassen and cols, in 2014, evaluated 308 young man of a general population having and average urinary BPA concentration of 3.3ng/ml finding decreased sperm motility associated to high levels of total and free testosterone and LH and estradiol [59]. In 2015, Goldstone and cols in prospective cohort study including 418 man of participating couples willing to conceive,, assessed different sperm parameters observing a low percentage of DNA fragmentation while the other seminal parameters remained unaltered [60]. DNA sperm damage was also evidenced in the findings of Rozati and cols (2002), Rignell-Hydbom and cols (2005), Spano and cols(2005) and Stronati and cols (2006) [61-64].

As previously described by Dallinga and cols, in 2002, and Hauser and cols, in 2003, the incidence of organochlorinated bisphenols in the plasma revealed opposite reactions, although no worsening of sperm quality was evidenced in those patients [65,66]. Such reviews and many other published studies often present conflicting results showing a correlation between the harmful effects of endocrine-disrupting chemicals and alterations in the sperm quality,DNA sperm damage also affecting hormonal activity and significantly interfering with male reproductive health. The results varied considerably and included positive, inverse or no associations may times. Heavy metals can interfere on the seminal quality and spermatozoa in Finnish men study performed by Hovatta and cols (1998).In this group of patients the serum levels of aluminium,lead and cadmium were increased [29]. Pant e cols (2003)in other study analysed lead and cadmium concentration in the seminal plasma of men in fertile and infertile patients. Observed an increase in lead and cadmium levels and lead semen concentration with sperm motility and sperm concentration in oligoasthenospermic men [28]. Mocevic, et al. (2013) in Greenland Inuit group and European men concluded that environmental levels of mercury were increased and tge semen quality and reproductive hormones can be disturbed [30].

Conclusions

This broad review reveals the association between exposure to the so-called Endocrine-disrupting chemicals and a number of different disorders including hypospadias, cryptorchidism and lower semen quality; having an important role for understanding male infertility.The evidence on EDCs exposure calls attention to the idea that EDC's are responsible to the decline in male reproductive health. EDCs have been incorporated in a large serie of products like foods,plastics,clothes,shampoos,soaps,textelis, carpets,toys etc.Rehman et al described that some countries like France outlawed some products and reduced the amount of BPA in containers that have contact with foods and the use of DHEP in toys and others products to childcare [67].In the United States legislation as the Toxic Substances Control Act and the Safe Drinking Water Act of 1996 gives the Environmental Protection Agency the power to regulate about substances that may act as an EDCs. WHO(World Health Organization) by Summary for decision Makers established that a very large of substances increase susceptibility to a variety of diseases and disorders and that exposure to EDCs even during the development are capable to induce several damages [68,69].

However, contradicting results obtained from other studies require further research comprehending evaluations that include epidemiological data in order to reach appropriate conclusions. Better information on how and when EDCs act is needed to reduce exposure and prevent diseases.It is important that a large number of diseases have their origin during the development and there are multiples substances like environmental factors and EDCs that interact with our genetic background and increase more and more susceptibility to a variety of disorders and diseases. The WHO recommendations is improve global knowledge of these chemicals,reduce potential disease risk and cut related cost. Include:

- testing known EDCs and more testing methods to identify possible endocrine disruptors;
- research more scientific evidence is needed to identify the effects of mixtures of EDCs on humans and wildlife;
- reporting many sources of EDCs that are not known because insufficient reporting;
- more colaboration between scientists and countries to detect those substances [70] .

Our conclusion is that a large group of researches will be necessaries to permit a strong and definitive idea about diferents EDCs and to analyse their actions in humans and animals during prenatal and early-life periods and their possible damages to the genital area.

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