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Clinical Pharmacodynamics of Endocrine Disruptors: A Historic Perspective

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Abstract

In this review endocrine disruptors (EDCs) are viewed from a historic perspective. A lot of them are are among us for 100 years or even more. Nevertheless research in this area is only a few decades old with a lot of conflicting data. Possible causal relationships between EDCs exposure and adverse effects on human health are dependent on the critical window between exposuer in utero and early childhood. This critical window can be 20 years or more As history predicts definite conclusions can only be drawn after replacing or eliminating some EDCs by law It will take another few decades to observe the effect of these necessary measures.

Keywords

Endocrine disruptors; Pharmacodynamics; Phthalates; Bisphenol A; Sex hormones; Breast cancer miscarriages; Birth weight; Obesity; Cardiovascular disease; Childhood asthma

Introduction

Endocrine-disrupting chemicals or EDCs are synthetic or naturally occuring compounds that can interfere or mimic the body's hormones. EDCs such as flame retardants, pthalates and bisphenol A are known for their potential effects on reproductive, neurological and immune functions

Animal studies also suggest that early life exposure to some EDCs can cause weight gain in later life. These are called"obesogens". The history of EDCs starts in 1958 when the endocrinologist Roy Hertz proposed that certain chemicals in feedlots could find their way into the human body and mimic hormone activity [1].

Effects of EDCs on early development in wildlife and in humans are often irreversible and may not become evident until later in life. At the moment 87.000 chemicals are screened by the EPA (Environmental Protection Agency) for their possible endocrine disruptimg effect. EDCs can be classified by their mechanism of action interfering with the different or same target organs as the natural hormone by altering their synthesis, metabolism, binding and cellular action. Pharmacodynamics studies the ligand (drug)-receptor binding which shows similarities with the natural hormone-receptor binding. In this case the drug or ligands are the EDCs. This review will focus on the clinical pharmacodynamics of endocrine disruptors in a historic perspective. In the early 1970s the dramatic health impacts of diethylstilbestrol (DES), an estrogen based drug that was thought to prevent miscarriages, introduced the possibility of hormone disruption as a threat to human health and devolopment, that sparked intensive study of estrogens in the environment. Since the second part of the last century the phytoestrogens have been studied most widely.

Phytoestogens-Natural Disruptors

Phytoestrogens are dietary plant derived estrogen-like compounds found in a variety of plant foods such as beans, seeds and grains, though they are concentrated in soy Foods and flax.

It is important to realize that plants are not the only dietary source of xenoestrogens. There is also estrogen content in animal foods such as meat, dairy, eggs, fish and seafood.

Most research has focused on the plant derived versions and little research has been conducted on animal sources, which is leading to an underestimation of intake [2].

The phytoestrogens are structurally related to 17-beta estradiol as is shown by the chemical sructure of the isoflavones genistein and diadzen present in soybeans. The isoflavones belong to a large group of substituded natural phenolic compounds as the coumestans and prenylflavanoids. Phytoestrogens exert their effect primarily through binding to the estrogen receptor (ER). There are two variants of the ER, the alpha (ER) and beta (ER). Many phytoestrogens and also mycoestrogens have somewhat higher affinity for the beta (ER) compared to the alpha (ER). The ER is a nuclear receptor that is activated by the sex hormone estrogen. Ligands and agonists are the non-selective endogenous estrogens (e.g, estradiol, estrone, estriol, estetrol), natural and conjugated estrogens and synthetic estrogens (eg ethinylestradiol). A selective agonist of the alpha (ER) over the beta (ER) is propylpyrazolestriol (PPT). Mixed agonists are the phytoestrogens (e.g., coumestrol, daidzein, genistein, miroestrol) and the selective estrogen modulators (e.g. tamoxifen, clomifene, raloxifene). The ER antagonists include the non-selective anti-estrogens fulvestrant and ethamoxytriphetol. A selective ER antagonist is methylpipiridinepyrazol (MPP). Estrogen insensitivity syndrome is a very rare condition charachterized by a defective alpha(ER) that is insensitive to estrogens. Estrogen receptors (ERs) are present in a variety of tissues. Alpha (ER) is most abundant in the uterus and smaller quantities are present in the ovary, testis, skin and gut. High amounts of beta (ER) are present in the ovaries, testes, adrenals and spleen [3]. The ER has important interrelelationships with the progesterone receptor(PR) system as well with insulin-like growth factor (IGF-1). The harmful or benificial effects of soy have been a dispute for decades. Evidence of isoflavones possibly having harmful effects appeared in the 1940s spurring one of soy's first controversies. A 1946 in the Australian Veterinary Journal indicated that sheep that grazed on a subterranean isoflavone-rich clover in Western Australia experienced fertility issues and breeding problems [4].

About 80% of the soy currently produced in the United States is used as animal food. By 1959 soybean meal was described an "excellent source of growth promoting" for young farm animals as turkeys [5].

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By the early 1970s more studies shed light on the use of soy proteins in baked foods and the functional properties of soy proteins [6-7]. In the 1980s two animal studies suggested that soy diets caused an enlarged pancreas and were assiociated with the growth of pancreatic cancer in those animals [8,9]. However in 1989 a report by the National Cancer Institute wrote there was no evidence that soybean derived foods had adverse effects on the human pancres [10]. Rather it was observed that human populations with high levels of soy in the diet had decreased rates of pancreatic cancer [10]. In the 1990s the breast cancer, soy connection came up. In 1991 the first of many studies to suggest that soybeans contain potentially anti- carcinogenic benefits appeared [11]. Things changed in 1996 when a study suggested that consuming soy protein might actually stimulate the growth of breast cancer cells [12]. In 2001 another study suggested that soy isoflavones stimulated the growth of human estrogen-dependent breast cancer cells [13].

The confusion about whether soy increases breast cancer risk is related to the fact that the ER has an alpha and a beta receptor, as mentioned before. When a compound binds to the alpha (ER) receptor the cancer risk rises and when it predominantly binds to the beta (ER) the cancer risk decreases. Isoflavones bind to the the beta (ER).

A review paper in the journal Cancer suggested an apperant lack of association between soy and cancer [14].

Benefits of soy were also reported. Replacing junk food in your diet by soy can aid in avoiding weight gain as research published in 2004 and 2009 reported [15,16]. Around that time soy protein and isoflavones also gained attention for having a potential role in improving cardiovascular health [17]. In 2008 the AHA (American Heart Association) stated there was not enough evidence to claim a strong link between soy and reduced risk of coronary heart disease [18]. Soy has the antioxidant properties that can lower LDL-cholesterol. It doesn't increase our good HDL-cholesterol [19]. In the mid 2000s research offered more information on how soy intake may impact thyroid function. The evidence suggests soy can interfere with the body's ability to absorb L-thyroxine, usually used in the treatment of hypothyroidism. Generally it is recommended to wait four hours before consuming any soy products after taking thyroid hormone medication [20]. Some studies have suggested that eating soy foods can help reduce menopausal symptoms [21]. But others have suggested otherwise. The effects on midlife women are mixed [22]. Meanwhile the types of soy foods being consumed by Americans continued to expand and diversify. The way soy was being eaten impacted how benificial it could be for your health. That means is it natural, processed or fermented? [23]. Now as Americans are gaining a better understanding of soy, uncertainty over the cancer and soy connection have been settled in new research Soy may not pose a risk for women with breast cancer after all according to a recent study in the journal Cancer [24].

Despite the mixed effects of soy and isoflavones the use of the commercially available supplements has grown fast. Isoflavones market size is expected to reach USD 50, 06 billion by 2025 [25]. Postmenopausal osteoporosis prevention is claimed on the base of some small studies, that were of short duration. In addition postmenopausal symptoms as hot flushes, cardiovascular benefits, breast cancer prevention are advertized. There are many kind of soy, isoflavones supplements. Comparison is difficult because they differ in content of the isoflavones and in doses. A study of the commercialy available soy suppements suggests that less than 25% of products contain within 90% of labeled isoflavone content [27]. Much of the research on soy and isoflavones have focused on adults but infants fed soy based protein infant formulas are exposed to substantial levels of soy isoflavones. The potential hormonal effects of soy isoflavones on later reproductive health outcomes are not known [28].

The phthalates

Phthalates are a diverse and wide class of industrial chemicals. Since the 1940s they are used as plasticizers to make plastic more flexible and as stabilizing or solubilizing agents. They are non-natural EDCs.

Phthalates were first introduced in the 1920s when they replaced camphor as the favoured plasticizer for cellulose nitrate. The commercially availability of polyvinylchloride and the development of di (2-etylhexyl) phthalate started the boom of the PVC industry. Glycerol phthalate was the first synthetic polyester. It came already into use in World War 1 when it was used for waterproofing [29].

The phthalates or phthalate esters are esters of phthalic acid. Phthalates are made by reacting phthalic anhydride with alcohols that range from methanol and ethanol to tridecyl alcohol. They are divided in two distinct groups with very different toxicology, applications and classification based on the number of carbon atoms in their alcohol chains. Low molecular weight (LMW, 3-6 carbon atoms) are being gradually replaced for reasons of health concerns. They are replaced by high molecular weight (HMW) with more than 6 carbon atoms with increased permanency and durability. Since 2010 producers are increasingly forced to use non-phthalate plasticizers [29]. The phthalates also called the "everywhere chemicals" are released in the environment. Due to this ubiquity of plastics most Americans have metabolites of multiple phthalates in their urine. Finding a detectable amount of phthalates in the urine does not imply that the levels of one or more will cause an adverse health effect. The levels can be used for biomonitoring of populations. People are exposed to phthalates by eating and drinking foods that have been in contact with containers. Enteric coated pharmaceuticals are another source. To a lesser extent exposure can occur from breathing air that contains phthalates vapors or phthalate contaminated dust. Children have a greater risk because of their "hand to mouth" behavior and by playing with soft children toys. Epidemiological studies at the population level as in Denmark and other countries observing adverse trends in male reproductivity together with declining sperm counts has led to the hypothesis of environmental contaminants being harmful to reproduction [30]. It was in the 2000s more epidemiological studies then questioned a link between the rising incidence in cryptorchidism, hypospadia, testes cancer and sexual precocity [31,32]. Although the presence of phthalate metabolites in urine does not imply an adverse health effect the above mentioned epidemiological studies, having the DES scandal in mind, resulted in extensive research on the effects of phthalates on the endocrine system [33,34].

Conclusions about EDC related health effects have to be made from epidemiological studies which can only reveal associations. By making inferences about human risk from experimental data from animal-or cell based models additional information is gathered. Traditional chemical testing of EDCs is inadequate to determine endocrine disrupting activity. They often test individual chemicals one at a time and assume individual chemicals have a "safe or acceptable" level of exposure. Tests are focused on adult animals, often mice and rats of different strains. They don't reflect that endocrine disruptors can have an effect in very low concentrations in various tissues life-time long. Concentrations in safety studies are mostly expressed in

parts per billions (PPBs) that can be ssubstantially higher than levels of the natural hormones however [35]. Phthalate exposure is linked to genital abnormalities in boys, reduced sperm counts, decreased "male typical" play in boys, endometriosis and the metabolic syndrome including obesity. The androgen[receptor (AR) is believed to play a central role in this.

In 2009 a small Taiwane study in humans showed that phthalates passed from mother to fetus through the placenta, long be held as a natural barrier, affect female babies sometimes resulting in abnormal sexual development [36]. Pregnant women exposed to phthalates in the workplace were found to be two to three times more likely to deliver boys with the reproductive birth defect known as hypospadia [37]. Boys who are exposed to higher levels of certain types of phthalates in the womb may show less masculine behavior, measured by playng with trucks and play fighting, than boys who are exposed to lower levels [38]. A 2007 study found that higher levels of phthalates detected in the urine of adult males was assiociated with increased waist circumference and insulin resistance [39]. A 2009 study determined that phthalate exposure correlated with premarure breast devolopment in young Taiwanese girls [40]. The health risks of medical devices containing phthalates were reviewd for the first time in 2001 [41]. Several associations were identified with short term and long term health dangers mainly subfertility, bronchopulmonary dysplasia, , parenteral nutrition associated cholestasis, necrotising enterocolitisand neurodevelopment disorders. These data were mainly based on anima lor human observational studies. In 2006 and 2007 the metabolism of the phthalates in humans was studied [42,43]. In 2010 and 2011 reports about the health risks of phthalate containing blood bags appeared [44-45]. The use of alternative plasticizers is recommended. In 2015 blood bags became "EHDP free" [46]. Pharmaceuticals that are enteric coated contain phthalates too. It took to 2017 before a Chinese study adressed this subject [47]. Definite associations couldn't be found in this heterogenous study population. The phthalates, EHDP and dibutiryl phthalate have profound impacts on the male reproductive system similar to flutamide, an antiandrogen or androgen receptor antagonist. DEHP has a toxic effect by the metabolite monoethylhexylphthalate (MEHD) on th Sertoli cells in the testes of the developing animal. Sertoli cell damage results in decreased sperm production which may be permanent even if the toxic agent is discontinued. The normal Sertoli cell development is under the influence of FSH (Follicle Stimulating Hormone) The Sertoli cell has FSH receptors on its cell membrane. Probably these receptors are blocked by phthalates. Granulosa cells of the ovary resposible for producing estrogen are also dependent on FSH stimulation for normal function. Phthalates decrease estrogen production in female animals. In the testis the Leydig cells secrete testosterone and estradiol while the Sertoli cell, responsible for spermatogenesis, secretes Inhibin B. The phthalate DEHP does not bind to the androgen receptor (AR) but in animals in utero exposure to phthalates disrupts the differentiation program of the androgen dependent tissues [48]. Phthalates have been shown to reduce testicular testosterone levels in fetal and neonatal rats. The decreased testosterone production has been assiated with the downregulation of genes involved in steroidgenesis [48,49]. Concerns among the public and professional medical societies about the phthalates as endocrine disruptors are seriously. Recently four advocacy groups claimed that the phthalate concentrations in powder of Mac and cheese were more than four times higher than in block cheese and other natural cheeses in all 30 investigated samples. The article appeared however in the New York Times and was not peer reviewed therefore. Concentrations of phthalates were not revealed0 [50]. The Endocrine Society urged the EU parliament recently in a press release to be transparent around EDC criteria [51].

Bisphenol A

Bisphenol A (BPA) was first synthesized in 1891. Edward Charles Dodd identified the estrogenic properties when he was in search of an estrogen. Later he succeeded in discovering diethylstilbestrol (DES), which he called "the mother substance" [52]. BPA never found use as a drug. Its future was in plastics. Early in the 1950s the First epoxyresins were synthesized using BPA [53]. BPA's safety profile was defined by its commercial use in plastics and accordingly by its toxic rather than hormone- like properties. Because BPA migrates from epoxyresins and polycarbonates used in food packaging and production the FDA (Food and Drug administration) considered the chemical an indirect food additive until now [54]. In 1993 endocrinologists at Stanford University determinated that BPA was leacking from polycarbonate flasks in their laboratory, while searching fora n endogenous estrogen in yeast [55]. Vom Saal et al. exposed pregnant mice to "physiologically" doses of BPA under the safety levels of 50 microgram/kg/day. He showed a higher than expected and a stimulating effect on the mammary glands. In male mice he reported increased prostate weight. These new low dose studies challenged the concept that BPA was only a weak estrogen [56,57] The phenol group is essential for the estrogen mimicking effect of BPA because of the similarity of the phenol group of both BPA and estradiol. Typically phenol containing molecules similar to BPA are known to exert weak estrogenic activity [58]. BPA has been found to bind to both of the nuclear estrogen receptors, alpha (ER) and beta (ER). It is 1000-2000 fold less potent than estradiol. BPA can both mimic the action of estrogen and antagonize estrogen, indicating that it is a selective estrogen modulator (SERM) or partial agonist of the ER. At high concentrations BPA also binds and antagonizes the androgen receptor (AR) . In addition to receptor binding the compound has been found to affect Leydig cell steroidgenesis in the testes including 17-alphahydroxylase, 17, 20 lyase and aromatase expression and interfering with LH receptor-ligand binding [59]. The major human exposure route is diet, including ingestion of contaminated food and water [60]. In the workplace inhalation and dermal exposure are the most probable routes [61]. Free BPA is found in high concentrations in thermal paper and carbonless copypaper. Popular uses of thermal papers include receipts, tickets and labels [62]. BPAs have been linked or associated with numerous body functions.

Sexual function

A 2010 study of 427 male workers in regions where high levels of BPA exposure existed showed a relationship between high urinary BPA levels and worsening male sexual function. There were significant decreases in sexual desire, erectile function, ejaculation strenght and overall satisfaction [63]. Meeker et al. concluded in 2010 that urinary BPA may be associated with declined semen quality and increased DNA damage in patients recruited through an infertility clinic, but conirmatoty studies were needed [64]. BPA can decline testosterone levels in mice and inhibit their sexual behavior [65]. Mendiola et al. foud urinary BPA levels correlated negatively with seminal fluid volume [70].

Fertility

BPA has been shown to affect many endpoints of fertility [66]. Several studies examined individuals undergoing infertility

treatments as in vitro fertilisation (IVF) and measured BPA in relation to various reproductive endpoints such as ovarian response, fertilisation success, embryo quality and implantation failure. In a cohort of women recruited from the Massachusetts General Hospital (MGH) Fertility Center, who were undergoing IVF treatment a higher urinary BPA was associared with a poorer ovarian response (fewer oocytes per cycle and decreased E2) In another population of women from the MGH Fertility Center Ehrlich et al. found that higher urinary BPA again sinificantly correlated with lower serum E2 and oocyte yield. In this study oocytes matured less and there were fewer fertilized oocytes [67,68]. In a Californian study higher unconjugated urinary BPA also correlated with a lessened ovarian response after hyperstimulation [69].

Sex hormones

Many studies have found changes in endogenous sex hormone concentrations as well as in sex hormone binding globulin (SHBG). Workers exposed to BPA had higher total urinary BPA levels in the presence of lower FSH in contrast to a study by Meeker et al. who found higher FSH levels as well as lower Inhibin B levels [71]. Takeuchi et al. tested healthy women and men as well as women with the polycystic ovary syndrome (PCOS) for serum BPA and hormone concentrations. Total testosterone (T) and free testosterone (FT) were significantly higher in men and PCOS women with high BPA levels than in normal women. Men had also sinificantly higher FSH and dehydroepiandrostenedione (DHEAS) l and lower E2 levels than non-PCOS women, while the PCOS women had significantly higher E2, LH and androstenedione concentrations. Both PCOS women and men had higher BPA serum concentrations than non-PCOS women [71]. Takeuchi et al also studied sex hormone concentrations in non-obese and obese women with and without PCOS as well in and women with women wth hyperprolactinemia and women with hypothalamic amenorrhea. In all women BPA was positively correlated with total T, FT, androstenedione and DHEAS [72-73]. Kandaraki et al also found a ssgnificant correlation between BPA and elevated androgen concentrations in women with and without PCOS [74]. The studies in PCOS are difficult to interpret as elevated androgens are a hallmark of PCOS and also associated with increased BPA levels. Thus there is no way to attribute an association solely to either factor as they are correlated with each other.

Endometriosis

Studies of BPA and endometriosis have yieded inconsistent results and were limited by the participant sampling framework, small sample size or use of serum BPA, which has very low and transient concentrations compared to urinary BPA concentrations. However a 2014 study by Upsen et al. suggests increased urinary BPA levels are associated with pelvic but not ovarian endometriosis [75]. Serum BPA was sinificantly lower in endometrial cancer patients [75].

Breast cancer

Although studies showed a stimulating effect of BPA on the mammary gland in animals and high BPA showed higher mammary densities a definite relationship between BPA and breast cancer can not be determined [79,80]. As breast cancer most likely take years to develop may be longitudinal studies measuring BPA in utero should be done.

Miscarriages

A 2003 study by Sugiura et al. showed some evidence of a relationship between recurrent miscarriages and BPA exposure in women. The authors suggested the increased incidence of miscarriages from BPA exposure may be due to an increase in chromosomal abnormalities due to meiotic disruption. However the study sample size was small [81].

Recent epidemiological studies showed a more definitly association between BPA exposure and miscarriage risk. Sample size was relatively large, urinary BPA was adjusted for creatinine and there was a low limit of BPA detection [84]. Though two studies reprted an association between BPA exposure the conclusion is inconsistent [82,83].

Premature deliveries

Only a few studies were done They show little evidence of a relationship between BPA exposure and prematurity [85-87].

Birth weight

Studies looking for a possible relationship between birth weight and BPA exposure have shown divergent results probably due to great variations in study design. Positive as well as negative correlations were found. Recalling of birth weight by parents was also a problem [88-91].

Male genital abnormalities

Male genital abnormalities such as shorter anogenital distance (AGD) have been associated with exposure to antiandrogenic disruptors in humans [92-94]. Studies linking cryptorchidism to BPA exposure are less convincing [95,96]. Based on the current evidence there does not seem to be a link betweeen BPA exposure and cryptorchidism.

Liver function

Many questions remain to be adressed about the causal link between acute and chronic EDC exposure and the development of non-alcoholic hepatic steatosis (NAFLD) in humans This is ptimarily because NAFLD is multifactorial parallelling the increase in the incidence of obesity and diabetes mellitus [97]. In two other studies weak associations between BPAs and disturbed liver function tests were found [98,99]. Overall the evidence is not convincing.

Type 2 DM

In the NHANES 2003-2006 cohort no significant associations between diabetes were found [99]. Some animal studies show glucose intolerance and insulin resistance [100]. Wang et al found a correlation between urinary BPA and obesit and insulin resistance [101].

Obesity

Various studies showed BPAs to interfere with adipogenesis, but few human studies are available [102,103]. Tese data are conflicting. Takeuchi et al. found increased BPA levels were associated with an increased BMI [Body Mass Index] in non PCOS women. In an earlier study, however there was no association between BMI and serum BPA [72,73]. In a puberty study Wolff et al. found significantly lower urinary BPA levels in girls with a high BMI [104]. Studies of the NHAENES cohorts showed higher urinary BPA was strongly associated with higher BMI and waiste circumference, When race ethnicity was examined the relationship between BPA exposure and obesity was only seen in Caucasians [105,106].

In the CHAMACOS study, examining mother-child pairs pre- and postnatal BPA exposure and its association with fat and BMI was studied. . In girls they found that increased prenatal BPA exposure was associated with decreased body fat at 9 years old. However Total urinary BPA in boys at 9 years old was positively correlated with increased BMI, waist circumference, fat mass, overweight and obesity [107]. It is clear that a "might be"link between obesity and BPAs need more longitudinal prospective studies.

The thyroid

Brücker-Davis et al studied thyroid function in mothers exposed to BPA and healthy newborns. There was a non–significant correlation between maternal BPA and TSH in newborns merely indicating a trend to hypothyroidism [96]. In the CHAMACOS cohort a higher maternal urinary BPA concentration was significantly associated with lower maternal T4 and negatively associated with TSH in boys, but not in girls. Other studies resulted in even more confusing offspring results ranging from a trend to hyperthyroidism, no effect or a trend to hypothyroidism after maternal BPA exposure but all without clinical significance [108,109].

Cardiovascular disease

Much of the literature about BPAs and cardiovascular health stems from the NHANES data. Lang et al found that a higher urinary BPA concentration was more frequently associated with a diagnosis of cardiovascular disease [110-113]. Higher urinary BPA concentrations were associated with hypertension, stable angina pectoris, coronary artery disease peripheral artery disease etc. . OLsen et al found weaker connections between BPA exposure and coronary artery disease [114]. Hard cardiovascular endpoints as cardiovascular mortality were not tested.

Childhood behavior neurodevelopment

Several studies have reported altered behavior in children exposed to BPA in utero or before puberty, indicating disruption of the brain during critical windows. In the HOMES study Braun et al. tested pregnant woman at 16, 24 weeks and at birthgiving for urinary BPA. When the offspring was 2 years their behavior was evaluated using the validated Behavioral Assessment System for Children. In girls but not boys there were significant associations between high maternal BPA and increased externalizing behavior (hyperactivity, aggression) these associations were only significant for prenatal BPA values. These studies indicate disruption of neurodevelopment caused by in utero BPA exposure, especially in girls that seem to have long lasting effects [115].

In contrast Yolton et al used the HOMES cohort too but didn't find a correlation between maternal BPA and neurobehavioral abnormalities at the age of 5 weeks [116]. Poreire et al. studied African-American and Dominican woman in the US. Spot urine samples were collected at 34 weeks gestation and fom children 3-4 years old. High maternal urinary BPA was significantly associated with higher scores (i. e more problems) for boys (agressive, emotianal) with trends of poorer scores in withdrawal and sleep problems. In girls higher urinary BPA was associated with lower scores [117]. In studies of resin-based dental composites werefound to affect behavioral in pubertal children. BPA fillings were leaking BPA at the start and possibly longtime [118-120]. On the whole these studies s uggest BPA exposure is associated in some way with neurobehavioral problems in children.

Childhood asthma

Higher prenatal exposure was associated with increased odds of wheeze in the child at 6 months of age when BPA exposure was high in the First 16 weeks of pregnancy. At 3 years of age the association had gone [121-123]. This suggests a critical window.

Immune function

Immune function was also shown to be negatively associated with BPA exposure. Clayton et al. found that urinary BPA was significantly correlated with antibodies to cytomegalovirus (CMV). Increased CMV antibody titers indicate a depressed immune system and can be an early marker of immune dysfunction in humans [124].

Oxidative stress and inflammation

Tarantino et al. looked at endpoints of chronic inflammation in women with PCOS and without in relation BPA exposure. PCOS women with higher BPA concentrations had increased markers of chronic inflammation as higher C reactive protein (CRP) and interleukin-6 (IL-6) [125]. Hong et al. examined a large Korean population. There was a positive correlation between urinary BPA and oxidative stress as measured by the reactive oxygen species malondialdehyde (MDA) and 8-hydroxydeoxyguanosine (8-OHJG) However this was not significant after adjustments [126,127]. In contrast Yi et al. found a positive correlation between conjugated urinary BPA but not (8-OHJG). The sample was very small. Lastly Yang et al studied men and pre- and pstmenopausal women. Only in postmenopausal women urinary BPA was associated with higher MDA, 8-OHJG and CRP suggesting that postmenopausal women may be more sensitive to the effects of BMA than premenopausal women and men [128].

Epigenetics

A few studies have found that BPA can change the epigenome or gene expression. Some of these effects may be more immediate than the long term development of other diseases. Increased BPA levels in serum or urine were associated in general with decreased methylation in these studies [129-133].

PCBs

The first polychlorinated bisphenyl (PCB)-like chemical was found as a by-product of coaltar. A year later in 1881 German scientists synthesized the first PCB in a laboratory. In 1935 Monsanto took over commercial production of Swan Chemicals. The electric industry used PCBs as non-inflammable replacement for mineral oil to cool and insulate industrial transformers and capacitors. PCBs were also used as heat stabilizers in cables and electronics to enhance the heat and fire resistance of PVC.

In the 1930s the toxicity of PCBs and other chlorinated hydrocarbons were recognized because of a variety of industrial accidents. In 1966 PCBs were determined as environmental contaminants [134,135]. Despite active research to its likely carcinogenic effect and an efficiënt ban on their production in the 1970s PCBs still persist in the environment because they are not biodegradable. PCBs belong to the group of organic pollutants (POPs). Other members of this group are DDT and the dioxines. People are still being exposed to PCBs from various sources such as caulk, some oil based paints and Floor finish used between 1950 and 1979 in schools. Eating PCB contaminated fish is the most common route of exposure to PCBs [138,139]. PCBs are called "possible

carcinogenic"by the EPA. Studies of PCBs in humans have found increased rates of melanoma, liver cancer, gallbladder cancer, billiary tract cancer gastric, intestinal cancer and brain cancer. PCBs are known to cause a variety of cancer types in rats, mice and other study aninals [136,137]. PCBs also cause neurodevelopmental abnormalities after exposure in utero with detrimental effects on neuropsychology [140].

The endocrine effects of PCBs are largely due to their effect on the thyroid. Many of the hydroxylated PCBs which are also biologically active have a high degree of structural resemblance to thyroxine (T4). Animal studies showed conflicting results regarding the influence of PCBs on the thyroid metabolism [146,147].

Zoeller et al provides the strongest " evidence to date" that PCBs present in flame retardants, clothes , paint, adhesives and electric transformers can interfere with with thyroid hormone action in pregnant women and may travel the placenta to affect the fetus. PCBs interfere with the way thyroid hormones function but don't actually change the amount of hormone in the body. Although these effects are largely invisible in scientific studies that only measured thyroid hormone levels they may be having a real impact on the infant's brain development. In this prospective birth cohort study he andcolleagues looked at the effects of low-dose chemical exposure in 164 women. Tissue from their placenta's was analyzed for a specific enzyme (CYP1A1) which change endocrine disruptors into a form that can interfere directly with the thyroid hormone receptor. It suggests that endocrine receptors should be studied more on the cellular level [140, 141]. CYP1A1 levels are higher in cigarette smokers. PCBs increase adipocyte differentiation in vitro and might increase body weight. They increase hepatic steatosis and visceral adiposity in the context of a lipid enriched diet [142,143] they belong to the "obesogens" PCBs affect female reproductive development in female test animals due to downregulation of essential genes such as Wut7alpha [144]. Turtles are sex reversed by PCBs . They showed estrogenic activity in this study [145]. There are over 259 PCBs, some with dioxine-like properties depending on their congeners. They can have estrogen agonist as well as estrogen antagonist effects [146-148]. Studies on the risk of endometrial cancer and PCBs have been rather elusive despite decades of research. THeir carcinogenic effect would be due to the fact that they can induce potent epithelial cell activation, enhance celluar oxidative stress, stimulate increased permeability across the vascular endothelium and induction of adhesion molecules [149,150]. Epidemiological studies in humans don't support an increased incidence of endometrial cancer despite the weak estrogen activity of PCBs [151].

In epidemiological studies the risk of breast cancer for PCBs exposure can t be demonstrated. An Inuit study showed no change in the risk for breast cancer and POPs including PCBs in the abscence of other risk factors for breast cancer [152-154].

In the male negative associations between PCBs and sperm count and circulating testosterone levels have been found [153]. A proven association between PCBs and testicular germ cell cancer have not been found [155]. For prostate carcinoma no increased risk for PCB scan be established. Neither due to the multifactorial origin of these tumors [156].

PCBs are believed to influence the immune system negatively [157,158]. In Dutch school children this resulted in a higher incidence of middle ear infections [159]. Children exposed to PCBs have also a reduced antibody response to vaccinations [160].

PCBs are thought to influence neurobehavior. The relationship between PCBs and neurodevelopment in later childhood are strongest for motor, cognitive, usual recognition and executive functions including ADHD and ASD-like behaviors [162]. There is an inverse correlation between PCBs exposure and IQ [161].

Dioxin and dioxin-like compounds

Dioxin and dioxin-like compounds are environmental persistant organic pollutants (POPs). The POPs consist of the polychlorinated dibenzo- p dioxins or simply dioxins, the polychlorinated dibenzofurans and the polychlorinated polybrominated phenyyls. The history of dioxin production and dioxin poisining is nearly 200 years old and dates back to a production plant in the state Hessen, Germany [163]. Chloracne, a persistent cystic and hyperkeratotic skin condition was First identified in German industrial workers and remains a hallmark od dioxin exposure [164]. The use of PCBs began in the early 20th century with commercial production inevitably also of mixtures that contain dioxin-like PCBs. The history of diox knows many accidents and disasters.

In 1947 X-disease a hyperkeratotic skin condition akin to chloracne was First reported in American cattle. A decade off X-disease a massive die off of commercially raised chickens in the US occured due to a condition referred as "chicken edema" later found to be caused by TCCD contamination of chicken food supplies [166]. Between these two animal poisenings an explosion in a Monsanto plant resulted in the exposure of workers in the dioxin-contaminated herbicide 2, 4, 5, T and persistent chloracne was observed [167]. Later studies on these and other occupational dioxin exposed workers demonstrated an increase in all cancers combined in the most highly exposed workers [168]. Between 1962 and 1970 "Agent Orange" containing the same herbicide contaminated with TCDD was used as a defohant in the Vietnam War. The use of "Agent Orange" was associated with an increased risk of diabetes and multiple cancers with increased duration of exposure [169]. The Institute of Medicine found sufficient evidence for a connection between "Agent Orange" exposure and soft tissuesarcoma, nonHodgkin lymfoma, Hodgkin disease and chronic lymfocytic leukemia [170]. In 1968, in Kyushu, Japan a rice bran oil company supplies became contaminated with PCBs and PCDFs. And contaminated with dioxins The contaminated oil resulted in the death of hundredsthousands of birds. In humans skin lesions, fatigue and altered reproductive and immunologic function were symptoms of what was referred to as "Yusho" (oil) disease and development delays were observed in children [171]. Unfortunately this incident was repeated in Taiwan and was referred to "Yucheng disease" (oil) In this event the association between gestational or lactational exposure was associated with impaired cognitive development and behavioral problems and altered reproductive parameters post puberty among the exposed males [172]. In the late 1970s the Great Lakes region noticed greatly diminished reproduction among lake trout and mink which has persisted until now [173]. Humans living in the area have shown signs of both developmental and immunologic consequences of these persistant organic pollutant via dietary fish intake and breast milk [174]. In 1976 an explosion occured at an Italian chemical plant in Seveso producing 2, 4, 5-T. Skin lesions as chloracne occured in several weeks. In the years that followed continuing studies of the population showed TCCD acts as a carcinogen in humans and increased the risk for diabetes, adverse cardiovascular effects and altered endocrine function [175,176]. U. S'EPA issued its First health assessment of TCDD in 1985 and 1991 [177]. After these reports the last events were a contaminated live stock food supply

and a contaminated chocolate withdrawal in Belgium. The murder at the Ukrain politician Victor Yushencko was the last incident that draw massive public attention [178-180]. Dioxins and dioxin-like compounds exert their biochemical effect through activation of the Acryhydrocarbon receptor [AhR], a ligand activated transcription factor and member of the PAS superfamily of transcription factors [180]. In the abscence of dioxin signalling the AhR may be involved in cell cycle control and tumor suppression in the stomach, prostate and hematopoietic tissues [181,182].

Adverse effects of dioxins on human health may include

cardiovasculardisease, diabetes, cancer, porphyria, endometriosis, early menopause, reduced thyroid hormones and testosterone, altered immunological response, skin , tooth and nail abnormalities, altered growth factor and altered metabolism [183]. A study in men 30 years after the Seveso disaster found that men with pre-puberty exposure had reduced sperm count and motility while those with post- exposure puberty had increased sperm counts and motility suggesting a critical window [184-188].

Thyroid stimulating hormone (TSH) levels were elevated in neonates born from mothers with persistently elevated plasma dioxin levels nearly 30 years after exposure, indicating hypothyroidism [185]. This illustrates again the significance of the timing of dioxin exposure with respect to the outcomes [189,190].

DDT–pesticides

DDT is the best known of several chlorine containing pesticides used in the 1940s and 1950s. DDT was first synthesized in 1874 by Othmar Zeidler and Adolf von Bayer [191]. DDT's insecticidal properties were not discoverd until 1939 when the Swiss chemist Paul Hermann Müller reported this. For this discovery he was awarded the Nobel Prize in Physiology and Medicine in 1948. DDT was used during World War2 to control the insect vectors of typhus, nearly eliminating the disease in Europe and the South Pacific. It was sprayed aerally for malaria and dengue control with spectacular effects [192,193]. In 1945 DDT was made available to farmers as an agriculture insecticide [192-194]. A WHO program directed at eliminating malaria with DDT only succeeded in areas with high socio-economic status and well organized healthcare systems [195]. For this reason DDT was not used in sub-Saharian Africa which still has the greatest malaria burden now [195]. DDT was less effective in tropical regions due to the continous life cycle of mosquitoes and the poor infrastructure. Resistance to drug treatment evolved rapidly. Eradication programs were abandoned in 1969. Spraying programs using DDT were curtailed due to to concerrs over safety and environmental effects [195,196]. DDT is a persistent organic pollutant (POP) that is readily absorbed in soils and sediments which can both acts as sinks or as long term exposure affecting organisms. DEpending on conditions its soil half life ranges from 22 days to 30 years [197]. Because of its lipophilic properties DDT can bioaccumalate especially in predatory birds [198]. The chemicals and its breakdown products DDD and DDE caused egg shell thinning and populations of predator preys, including the Bald Eagle, rapidly declined in Noth America and Europe [199]. The mechanism of egg shell thinning is not known [200]. DDT is an endocrine disruptor that acts as a weak androgen receptor antagonist but not as an estrogen [201]. In the 1970s and 1980s agriculture use of DDT was banned in most developed countries. In 2004 the Stocholm Convention put a global ban on DDT and several other POPs [202]. Despite the world wide ban agriculture use of DDT continues in India, North Korea and possibly elsewhere [203-205].

The organochlorine pesticides have been associated with endocrine disorders Multiple observations in animals in polluted areas demonstrated a sinificant increase in goiter and thyroid imbalance. In humans exposed to background levels of chemicals DDT had no significant effect on thyroid function [204]. There is no clear association between breast cancer and DDT or DDE [206]. DDT is rated as "possible carcinogenic" by the International Agency for Research on Cancer (IARC:199). This rating was largely based on the induction of liver tumors in experimental animal studies. Most human studies reviewed by the IARC in 1991 did not show an association between DDT and cancer risk. Research has not supported an association between DDT or DDE and the incidenceof colorectal, lung, bladder, prostate, endometrial and stomach cancer [207].

The prevalence of diabetes is positively correlated with plasma DDE levels. However given the high correlations with other organochlorine exposures additional reseaerch is needed to delineate the specific contributions of DDT and DDE [208]. High DDE levels are associated with an increased rate of fetal loss [209]. Most studies found no association between maternal serum DDE levels and fetal groeth, gestational duration, premature labor, birth weight or head circumference [210]. Associations between DDE levels and early weaning of lactation are spurious and furter research is warranted [211]. The effects on urogenital birth defects are fairly consistent with a two times higher risk for cryptorchidism and hypospadia [212]. Male fertility studies showed that plasma DDE concentrations were negatively correlated with sperm motility and decreased sperm count [213]. Female fertility studies show that DDT exposure may delay time to pregnancy [214]. Neurodevelopmental have shown that high DDT exposure was associated with poorer psychomotor development, poorer cognitive memory and poorer quantitative verbal and executive functions [215]. DDT and particularily DDE have demonstrated the potential for modulating the human immune response as measured by multiple markers such as interleukin 4, 13 and plasma levels of interferon-gamma, white blood cell counts, various lymphocytic phenotypes anf immunoglobulin (Ig) A, G and E levels [216]. Associations with aplastic anaemia, otitis media, farmers lung and asthma were reported [217]. POPS including DDT may be released from fat tissues during weight loss crash diets [218].

Glycophosphates

Glyphosate is a broad spectrum herbicide and crop dissecant. It is an organophosphorus compound madeto kill weeds, especially broad leafs, weeds and grasses that compete with crops. It was first synthesized in 1950 by the Swiss chemist Henry Martin, who worked at the Swiss company Cilag. The work was never published. In 1970 glyphosate was reinvented by the Monsanto chemist John E. Franz. Monsanto brought it to the market in 1974 [219]. It is also a chelator binding calcium, magnesium. manganese, copper and zinc. Glyphosate kills plants by interfering with the synthesis of the aromatic amino acids Phenylalanine, tyrosine and tryptophan in the shikimate pathway. By inhibiting this pathway energy and resources of the plant are diverted away. Growth stops within hours and it takes several days for the leaves to begin turning yellow [221]. The half life of glyphosate in soil ranges between 2 and 197 days. The median half life in water varies from a few days to 91 days [222]. Gyphosate formulations contain a number of adjuvans which are trade secrets [223].

Despite a review article in 2014 that reported a two fold increased

risk for glyphosate exposure and B cell lymfoma the discussion about its possible carcinogenic potential isstill going on widely [224]. Several studies have not found mutagenic effects of glyphosate while others did. Because the EPA lists glyphosate as non-mutagenic it is also not listed in the EPA International Research on Cancer Data Bases [225]. The IARC (International Agency for Research on Cancer) finalized a meeting at March, 2015 with the statement that glyphosate is "probably carcinogenic" to humans. The EPA is supposed by law to review the data once in a 15 years time and should do this again in 2017. The WHO has declared glyphosate as "possible carcinogenic" and theState of California recently put glyphosate under Proposition 65 as "Known to the State to Cause Cancer" [226]. In 2007 the EPA selected glyphosate for futher screening through its Endocrine Disruptor Screening Program (EDSP) and concluded there was no convincing evidence of potential interaction with the estrogen, androgen or thyroid pathway [227]. However some researchers found a weak estrogenic activity at the estrogen receptor depending on the assays used [228].

Neonicotinoids

The neonicotinoids are known since 1970. The precursor to nithiazine was first synthesized by Henry Feuer, a chemist at Purdue University [229]. In 1984 niathiazines mode of action was settled as a postsynaptic acetylcholesterol receptor agonist. [230]. Niathiazine is not photostable and became therefore not commercially available. In 1985 Bayer patented imidaclopid as the first commercial neonicotinoid. A dramatic rise inthe annual number of bee hives losses spurred interest in 2006 in factors potentially affecting bee health. Neonicotinoids may be responsible for detrimental effects on the bumble bee and Queen production [232-233]. In the July issue of the journal Nature it was demonstrated that the level of neonicotinoids correlated significantly with the decline in insect-eating birds [234]. Adverse human health effects are associated with respiratory diseases [235]Although animal studies suggest that neonicotinoids can affect the hypothalmic-pituitary-thyroid axis no human studies indicating neonicotinoids as an endocrine disruptor in man are available until now [236].

Heavy metals as EDC

Potential candidates are cadmium[Cd], mercury[Hg], arsenic [As], lead [Pb] manganese[Mn] and Zinc[Zn]. The mechanisms of action are largely to be elucidated Cadmium and arsenic have been studied mostly. Cadmium could be a metalloestrogen but this not proven. Animal studies use frequently toxic levels and the co-occurence with other EDCs is not studied well. Further studies to delineate the role of heavy metals are needed therefore [237,238].

Conclusion

Endocrine disruptors are for a long time among us, some for more than 100 years. Reaearch in this area has been performed only for a few decades Central in this research is the time of exposure, in utero and early childhood which is of critical importance . The critical window is often 20 years or more The research trusts on associations and correlations which suggest a plausible cause. For a proven more definite causal relationship EDCs should be eliminated or replaced by law. Observing a declining incidence of of testes cancer or an improvement of sperm quality in the next 20-30 years would make the circle round [239].

References

1. Gassner FX, Reifenstein EC, Gassner O (1958) Effects of hormones on growth fattening and meat production of live stock. Recent Prog Horm Res 14: 183-217.
2. Kahn GG, Dell Aquilla C, Aspinall SW (2008) Phytoestrogen content of Foods of animal origin: dairy products, eggs, meat, fish and seafood. J Agric Food Chem 12: 56.
3. Brandenberger AW, Tee MK, Lee JY (1997) Tissue distribution of estrogen receptors alpha (ER-alpha and beta(ER-beta) mRNA in the midgestational human fetus. J Clin Endocrinol Metab 82: 3509-3512.
4. Bennetts HW, Underwood EJ, Shier FL (1946) A specific breeding problem of sheep on subterranean clover pasteures in Western Australia. Austr Vet J 1751-0813.
5. Pran V, Aurod JB, Gupta IS (1959) Fractionation of soy bean oil meal for growth and antiperotic factors: 2 studies with genistin and soy sterols. Poult. Sci 38: 1476-1477.
6. Hoover W (1979) Use of soy proteins in baked food. J Am Oi Chem Soc 301-303
7. Kinsella JE (1979) Fractional properties of soy proteins J Amer Che Soc 56: 242-258.
8. Harwood JP (1986) Effect of longterm feeding of soy based diets on the pancreas of Cebus monkeys. Adv Exp Med Biol 199: 223-237.
9. Roebuck BD, Kapilita P, Edwards BR (1987) Effects of dietary fats and soybean protein on azoserine-induced pancreatic carcinogenesis and plasma cholecystokinin in the rat. Cancer Res 47: 1333-1338.
10. Workshop Report from the Division of Cancer Etiology, National Cancer Institute,National Institutes of Health. Cancer Res 15: 499-502.
11. Messina M, Messina V (1991) Increasing use of soy foods and their potential role in cancer prevention. J Am Diet Ass 91: 836-840.
12. Petrakis NL, Bames S, King EB (1996) Stimulatory influence of soy protein isolate on breast secretion in pre- and postmenopausal women. Cancer Epidemiol. Biomarkers Prev 5: 783-794.
13. Clinton DA, Allred KF, Young H (2001) Soy Diets Containing Varying Amounts of Genistein Stimulate Growth of Estrogen-dependent (MCF-7) Tumors in a Dose Dependent Manner. Cancer Res 61: 5045-5050.
14. Michels KB, Mohljee AP, Roset-Bahmanyar E (2007) Diet and breast cancer:a review of the prospective observational studies. Cancer 109: 2712-2749.
15. Holton TL, Hu FB (2004) The effects of high protein diets on thermogenesis,satietyand weight loss: a critical review J Am Coll Nutrit 23: 373-385.
16. Westerterp-Plantenga MS, Niewenhuizen A,Tome D (2009) Dietary protein,weight loss and weight maintenance. Ann Rev Nutr 29: 21-41.
17. CFR-Code of Federal Regulations.
18. AHA Docket No 2007 N0464; American Heart Association.
19. Taku K, Umegaki K, SatoY (2007) Soy isoflavones lower serum total and LDL cholesterol in humans: a meta-analysis of 11 randomized controlled trials. Am J Clin Nutrit 85: 1148-1156.
20. Messina M, Redmond G (2006) Effect of soy protein and soy bean isoflavones on thyroid function in adults and hypothyroid patients:a review of the relevant literature. Thyroid 16: 249-58.
21. Taku K, Melby K, Kronenberg F (2012) Extracted or synthesized soybean isoflavones reduce menopausal hot flash frequency and severity: systematic review and meta-analysis of randomized controlled trials. Menopause 19: 776-90.
22. Krebs EE, Ensrud KE, McDonald R (2004) Phytoestrogens for treatment of menopausal symptoms: a systematic review. Obstet Gynaecol 104: 824-36.
23. Mackay D, (2013) Soy isoflavones and other constituents in Pizommo Textbook of natural medicine. New York, Churchill Livingstone124.
24. Zhang FF, Haslam MS, Terry MB (2017) Dietary isoflavones intake and all-cause mortality in breast cancer survivors: The Breast Cancer Family Registry. Cancer 123: 2070-2079.

25. Isoflavones Market Size to Reach USD 50, 06 Billion by 2025.Grand review Inc Newswire.

26. Lanou AJ (2011) Soy Foods: are they useful for optimal bone health? Ther Adv Muskuloskeletal Dis 3: 293-300.

27. Collison MY (2008) Determination of total soy isoflavones in dietary supplements,supplement ingredients and soy food by high- performance liquid chromatography with ultraviolet detection:collaborative study. J AOAC Int June 9: 489-500.

28. Dinsdale EC, Ward WE (2010) Early exposure to Soy Isoflavones and effects on Reproductive Health: A review of Human and Animal Studies Nutrients 2: 1156-1187.

29. Teegarden PM (2003) Polymer chemistry: introduction to an indespensible science.

30. Bay K, Asklund C, Skakakebak NE (2006) Testicular dysgenesis syndrome:possible of endocrine disruptors. Best Pract Res Clin Endocrinol Metab 20: 77-90.

31. Toppari J, Koleva M, Virtanen HE (2001) Trends in the incidence of cryptorchidism and hypospadias and methodological limitations of registry-based data. Human Reprod Update 7: 282-286.

32. Houminki K Li X (2002) Cancer risks in second generation immigrants in Sweden. Int J Cancer 99: 229-237.

33. Herbst AL, Ulfelder H, Poskanzer DC (1971) Adenocarcinoma of vagina. Association of maternal stilbestrol therapy with tumor appearance in Young women. N Engl J Med 284: 878-881.

34. Silent Spring (2002) Rachel Carson. Houghton Mifflin 1962 Manner Books.

35. Vanden Berg LN, ColbornT, Hayes TB (2012) Hormones and endocrine-disrupting chemicals. Low dose effects and nonmonotonic dose response. Endocrine Rev 33: 378-433.

36. Hang PP, Kuo P, Chou Y (2009) Associations between prenatal exposure to phthalates and the health of newborns. Endocrinol. International 35: 14-20.

37. Ommond G, Nieuwenhuysen MJ, Nelson P (2009) Endocrine disruptors in the workplace,hairspray, folate supplementation and risk of hypospadias:case-control study. Environmental Health Perspectives 19.

38. Swan SH, Liu F, Hines M (2010) Prenatal phthalate exposure and reduced masculine play in boys. Int J Androl 33: 259-269.

39. Stahlhut RN, Wijngaarden E, Dye (2007) Concentrations of urinary phthalate metabolites are associated with increased waist circumference and insulin resistance in adult U.S. males. Environ.Health Persp 876-82.

40. ChouYY, Huang PC, Lee CC (2009) Phthalate exposure in girls during early puberty. J Pediatr Endocrinol Metab 22: 69-77.

41. Tickner JA, Schettler T, Guidotti M (2001) Health risks posed by use of Di-2-ethylhexylphthalate (DEHP) in PVC medical devices:A critical review. Am J Int Med 39: 100-111.

42. Frederiksen H, Skakkebaek NE, Anderson AM (2007) Metabolism of phthalates in humans Molecular Nutr Food Res 899-911.

43. Koch H.M,Preuss R,Angerer J (2006) Di(2-ethylhexyl)phthalate (DEHP);human metabolism and internal exposure:an update and latest results. Int J Androl 29: 155-165.

44. Samson J, de Korte D (2011) DEHP –plasticised PVC:relevance to bloodservices. Transfusion Medecine 21: 73-83.

45. Shaz B, Grima K, Hilliger D (2011) 2-(diethylhexyl) phthalate in blood bags:is this a public health issue ? Transfusion 51: 2510-2517.

46. Lagerberg JW, Gouwerok E, Vlaar R (2015) In vitro evaluation of the quality of blood products collected and stored in systems completely free ofdi(2-ethylhexyl)phthalate-platizid materials. Transfusion 55: 522-531.

47. Jia LL, Lou XY, Guo Y (2017) Occurence of phthalate esters in over the counter medicines from China and its implications for human exposure. Environ Int 98: 137-142.

48. Gray LE, OstbyJS, Furr J (2000) Perinatal exposure to the phthalates DEHP,BBP and DINP but not DEP,DMP or DOPP alters seual differentiation of the male rat Toxicol Sci 58: 330-365.

49. Parks LG, Ostby JS, Lambricht CR (2000) The plasticizer diethylhexyl phthalate induces malformations by decreasing fetal testosterone synthesis during sexual differentiation in the male rat. Toxicol Sci 58: 339-49.

50. Rubin RC (2017) The Chemicals in Your Mac and Cheese. The New York Times.

51. Gingery J (2017) Society urges EU parlament to be transparant around EDC criteria. Current Press Release Endocrine Society.

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

53. Beyza S, Bristow W, Menard K (2005) Inventors University of North Texas,assignee. Halogen containing epoxy composition and their preparation.U.S Patent.

54. List of indirect food additives used in food contact substances: U.S. Food and Drug administration.

55. Krishnan AV, Stathis P, Permath SF (1993) Bisphenol A, an estrogenic substance is released from polycarbonate flasks during autoclaving Endocrinology 2279-2286.

56. Nagel SC, Saal FS, Thayer KA (1997) Relative binding affinity-serum mediated access(RBA-SMA) assay predicts the relative in vivo bioactivity of the xenoestrogens bisphenol A and octylphenol. Environ Health Perspect 10570-10578.

57. Corangle JB, Roy D (1979) Profound effects of the weak environmental estrogen like chemical bisphenol A on the growth of the mammary glands of Noble rats. J Steroid Biochem Mol Biol 60: 153-60.

58. Kwon JH, Katz LE, Lijestrand HM (2007) Modeling binding equilibrium in a competetive estrogen binding assay. Chemosphere 69: 1025-1031.

59. Hejmej A, Balak K, Magorzata-Bilinski B (2011) Antiandrogenic and Estrogenic Compounds:Effect andFunction of the Male Reproductive System. Steroids Clin Aspect.

60. Cichna-Markl M (2012) Simple clean-up by sol-gel immunoaffinity chromatography for the determination of bisphenol A in food and urine. Methods 186-191.

61. Tsai WT (2006) Human Health Risk on Environmental Exposure to Bisphenol A: A Review J Environmental Science and Health 21: 225-255.

62. Baba K, Uppu SN, Martin B (2015) Unusually high levels of bisphenol A (BPA) in thermal paper, cash register receipts: development and application of a robust LC-UV method to quantify BPA in CRs. Toxicology and Methods 410-416.

63. Li DK, Zhou Z, He Y (2010) Relationship between urinary bisphenol A level and declining male sexual function. J Androl 31: 500-506.

64. Meeker JD, Ehrlich S, Toth TL (2010) Semen quality and sperm DNA damage in relation to urinary bisphenol A among men from an infertility clinic. Reprod Toxicol 30: 532-539.

65. Zang ZH, Suyun J Xia T (2016) Effects of bisphenol A on testosterone levels and sexual behavios of male mice. Advances in Sexual Medicine 6: 41-49.

66. Wetherill YB, Akingbemi BT, Kanno J (2007) In vitro molecular mechanisms of bisphenol A action. Reprod. Toxicol 178-198.

67. Ehrlich S, Williams PL, Missmer SA (2012) Urinary bisphenol A concentrations and early reproductive health outcomes undergoing IVF. Human Reprod 27: 3583-3592

68. Mok- Lin E, Ehrlich S, Williams PL (2013) Urinary bisphenol A concentrations and ovarian response among women undergoing IVF Int J Androl 33: 385-393.

69. Bloom AS, Kim D, Saal F (2011) Bisphenol A exposure reduces the estradiol response to gonadotropin stimulation during in vitro fertilisation Fert Steril 96: 672-677.

70. Mendiola JJ, orgensen N, Anderson AM (2010) Are environmental levels of bisphenol A associated with reproductive function in fertile men? Environ Health Persp 18: 1286-1291.

71. Meeker JD, Calafat AM, Hauser R (2010) Urinary bisphenol A concentrations in relation to serum thyroid and reproductive hormone levels in men from an infertility clinic. Environm Sci Technol 1458-1463.

72. Takeuchi T, Tsutsumi O (2002) Serum bisphenol A concentrations showed gender differences possibly linked to androgen levels. Biochem Biophys Res Common 291: 76-78.

73. Takeuchi T, Tsutsumi O, Ikezuki Y (2004) Positive relationship between androgens and the endocrine disruptor bisphenol A in normal women and women with ovarian dysfunction. Endocr J 51: 165-169.

74. Kandaraki E, Chatzigeorgiou A, Livadas S (2011) Endocrine disruptors and polycystic ovary syndrome (PCOS): elevated serum levels of bisphenol A in women with PCOS. J Clin Endocr Metab 96.

75. Upson K, Sathyrogama S, de Roos AJ (2014) A population case control study of urinary bisphenol A concentrations and risk of endometriosis. Hum Reprod 29: 2457-2464.

76. Cobellis L, Colacurci N, Trabucco E (2009) Measurement of bisphenol A and bisphenol B levels in human blood sera from healthy and endometriotic women. Biomed Chromatogr 23: 1186-1190.

77. Hiroi H, Tsutsumi O, Takeuchi T (2004) Differences in seum bisphenol A concentrations in pre-menopausal women,normal women and women with endometrial hyperplasia. Endocrin J 51: 595-600.

78. Soto AM, Vanden Berg LN, Muffin MV (2008) Does Breast Cancer Start in the Womb? Basic Clin Pharmacol Toxicol 102: 1742-1743.

79. Yang M, Ryu JH, Leon R (2009) Effects of bisphenol A on breast cancer and its risk factors Arch Toxicol 83: 281-285.

80. Aschengrau A, Coogan PF, Quinn M (1998) Occupational exposure to estrogenic chemicals and the occurence of breast cancer. Am J Int Med 34: 6-14.

81. Sugiura-Ogasuwara M, Osaki Y, Sonia S (2005) Exposure to bisphenol A is associated with recurrent miscarriage Hum Reprod 20: 2325-2329.

82. Lathi RB, Liebert CA, Brookfield KF (2014) Conjugated bisphenol A in maternal serum in relation to miscarriage risk. Fert Ster 102: 123-128.

83. Chen X, Chen M, Xu B (2013) Parental phenols exposure and spontaneous abortion in a Chinese population residing in themiddle and lower reaches of theYangtze River. Chemosphere 93: 217-222.

84. Shen Y, Zheng Y jiang J (2015) Higher urinary bisphenol A concentration is associated with unexplained recurrent miscarriage risk:Evidence from a case control study in Eastern China. Plos One Mag.

85. Cantonwine D, Meeker JD, Hu H (2010) Bisphenol A exposure in Mexico City and risk of prematurity a pilot nested case control study. Environ Health 9: 62.

86. Padmanuban V, Siefert K, Ransom S (2008) Maternal bisphenol A levels at delivery;a looming problem? J Perinatol 28: 258-263.

87. Cantonwine DE, Ferguson KK, Mukherjee B (2015) Urinary Bisphenol A levels during Pregnancy and Risk of Preterm Birth Environ Health Persp 123: 855-901.

88. Philipat C, Mortamais M, Chevrier C (2012) Exposure to phthalates and phenols during pregnancy and offspring size at birth. Environ Health Perspect 120: 464-470.

89. Miao M, Yuan W, Zhu G (2011) In utero exposure to bisphenol A and its effect on birth weight of offspring. Reprod Toxicol 32: 64-68.

90. Chou WC, Chen JL Lin CF (2011) Biomonitoring of bisphenol A concentrations to birth outcomes and adipokine expression: a birth cohort study in Taiwan. Environ Health 10-94.

91. Troisi J, Mikelson C, Richards S (2014) Placental concentrations of bisphenol A and birth weight from births in the South Eastern U.S Placenta 35: 947-952.

92. Miao M, Yuan, Zhou G (2011) In utero exposure to bisphenol A and urogenital distance of male offspring Birth Defects Res a Clin Mol Teratol 867-872.

93. Marsee K, Woodruff TJ, Axelrad DA (2006) Estimated daily phthalates exposures in a population of mothers of male infants exhibiting reduced anogenital distance. Environ Health 114: 805-809.

94. Chevrier C, Petit C, Philipat C (2012) Maternal urinary pthalates and phenols and male genital anomalies Epidemiology 23: 353-356.

95. Fenichel P, Dechaux H, Harte C (2012) Unconjugate bisphenol A cord blood levels in boys with descended or undescended testes. Hum Reprod 27: 983-90.

96. Brucker-Davis F, Ferrari P, Boda-Buccino M (2011) Cord blood thyroid tests in boys orn with and without cryptorchidism: correlations with birth parameters and in utero xenobiotics. Thyroid 1133-1141.

97. Foulds CE, Lindsey S, Trerino BY (2017) Endocrine-disrupting chemicals and fatty liver disease. Nature Reviews Endocrinology 18: 445-457.

98. Lang IA, Galloway TS, Scarlet A (2008) Association of urinary bisphenol concentration with medical disorders and laboratory abnormalities in adults. JAMA 300: 1303-1310.

99. Melzer D, Rice NE, Lewis C (2010) Association of urinary bisphenol A concentration with heart disease: evidence from NHANES study. Plos One.

100. Moon MK, Jeong IK, Jung Oh T, Ahn HY, Kim HH, et al. (2015) Longterm oral exposure to bisphenol A induces glucose intolerance and insulin resistance. J Endocrinol 226: 35-42.

101. Wang T, Li M, Chen B, Xu M, Xu Y, et al. (2012) Urinary bispheno A (BPA) concentrations associates with obesity and insulin resistance. J Clin Endocrinol Metab 97: E223-227.

102. Biemann R, Fischer B, Navarette Santos A (2014) Adipogenic effects of a combination of the endocrine disrupting compounds bisphenol A,diethylhexylpthalate and tributyrin. Obesity Facts 7:48-56.

103. Biemann R, Navarrete Santos A, Navarrete Santos A, Riemann D, Knelangen J, et al. (2012) Endocrine disrupting chemicals affect the adipogenic differentiation of mesenchymal stem cells in distinct ontogenetic windows. Biochem. Biophys Res Commun 417:747-752.

104. Wolff MS, eitelbaum SL, Windham G (2007) Pilot study of urinary biomarkers of phytoestrogens,pthalates and phenols in girls. Environ Health Perspect 115:116-121.

105. Shankar A, Teppala S, Sabanayagam C (2012) Urinary bisphenol a levels and measures of obesity: results from the national health and nutrition examination survey 2003-2008. ISRN Endocrinol 2012: 965243.

106. Trasande L, Attina TM, Blustein J (2012) Association between urinary bisphenol A concentration and obesity prevalence in children and adolescents. JAMA 308: 1113-1121.

107. Harley KG, Schall RA, Chevrier J (2013) Prenatal and postnatal bisphenol A exposure and body mass index in chidhood in the CHAMACOS cohort. Environment Health Persp 121:514-26.

108. Meeker JD, Ferguson KK (2011)Relationship between urinary pthalate and bisphenol A concentrations and serum thyroid measures in U.S. adults and adolescents from the National Health and Nutrition Examination Survey (NHANES) 2007-2008. Environ Health Persp 119:1396-4020.

109. Wang F, Hu J, Chen M (2012) High urinary bisphenol A concentrations in workers and possible laboratory abnormalities. Occup Environ Med 69:679-684.

110. Lang IA, Galloway TS, Scarlett A, Henley WE, Depledge M, et al. (2008) Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. JAMA 300: 1303-1310.

111. Melzer D, Rice NE, Lewis C, Henley WE, Galloway TS (2010) Association of urinary bisphenol a concentration with heart disease: evidence from NHANES 2003/06. PLoS One 5: e8673.

112. Shankar A, Teppala S (2012) Urinary bisphenol A and hypertension in a multiethnic sample of US adults. J Environ Public Health 2012: 481641.

113. Shankar A, Teppala S, Sabanayagam C (2012) Bisphenol A and peripheral arterial disease: results from the NHANES. Environ Health Perspect 120: 1297-1300.

114. Olsen L, Lind L, Lind PM (2012) Associations between circulating levels of bisphenol A and pthalate metabolites and coronary risk in the elderly. Ecotoxicol Environ Saf 80:179-183.

115. Braun JM, Yolton K, Dietrich KN, Hornung R, Ye X, et al. (2009) Prenatal bisphenol A exposure and early childhood behavior. Environ Health Perspect 117: 1945-1952.

116. Yolton K, Xu Y, Strauss D, Altaye M, Calafat AM, et al. (2011) Prenatal exposure to bisphenol A and phthalates and infant neurobehavior. Neurotoxicol Teratol 33: 558-566.

117. Perera F, Vishnevetsky J, Herbstman JB, Calafat AM, Xiong W, et al. (2012) Prenatal bisphenol a exposure and child behavior in an inner-city cohort. Environ Health Perspect 120: 1190-1194.

118. Bellinger DC, Daniel D, Trachtenberg F, Tavares M, McKinlay S (2007) Dental amalgam restorations and children's neuropsychological function: the New England Children's Amalgam Trial. Environ Health Perspect 115: 440-446.

119. Bellinger DC, Trachtenberg F, Zhang A, Tavares M, Daniel D, et al. (2008) Dental amalgam and psychosocial status: the New England Children's Amalgam Trial. J Dent Res 87: 470-474.

120. Maserejian NN, Trachtenberg FL, Hauser R, McKinlay S, Shrader P, et al. (2012) Dental composite restorations and psychosexual function in children. Pediatrics130:328-338.

121. Spanier AJ, Kahn RS, Kunselman AR, Hornung R, Xu Y, et al. (2012) Prenatal exposure to bisphenol A and child wheeze from birth to 3 years of age. Environ Health Perspect 120: 916-920.

122. Donohue KM, Miller RL, Perzanowski MS, Just AC, Hoepner LA, et al. (2013) Prenatal and postnatal bisphenol A exposure and asthma development among inner-city children. J Allergy Clin Immunology 131:736-742.

123. Midoro-Horiuti T, Tiwari R, Watson CS, Goldblum RM (2010) Maternal bisphenol A exposure promotes the development of experimental asthma in Environ Health Perspect 118:273-237.

124. Clayton EM, Todd M, Dowd JB, Aiello AE (2011) The impact of bisphenol A and triclosan on immune parameters in the U.S. population, NHANES 2003-2006. Environ Health Perspect 119: 390-396.

125. Tarantino G, Valentino R, Di Somma C, D'Esposito V, Passaretti F, et al. (2013) Bisphenol A in polycystic ovary syndrome and its association with liver-spleen axis. Clin Endocrinol (Oxf) 78: 447-453.

126. Hong YC, Park EY, Park MS, Ko JA, Oh SY, et al. (2009) Community level exposure to chemicals and oxidative stress in adult populations. Toxicol Lett 184:139-44.

127. Ben-Jonathan N, Hago ER, Brandenbourg TD (2009) Effects of bisphenol A on adipokine release from human adipose tissue:implications for the metabolic syndrome. Mol Cell Endocrinol 304:49-54.

128. Yang YJ, Hong YC, Oh SY, Park MS, Kim H, et al. (2009) Bisphenol A exposure is associated with oxidative stress and inflammation in postmenopausal women. Environ Res 109: 797-801.

129. Baccarelli A, Wright RO, Bollati V, Tarantini L, Litonjua AA, et al. (2009) Rapid DNA methylation changes after exposure to traffic particles. Am J Respir Crit Care Med 179: 572-578.

130. Yamaguchi A, Ishibashi M, Kohra S(2005)Short term effects of endocrine disrupting chemicals on the exposure of estrogen-responsive genes in male medaka (Oryzias latipes). Aquatic Toxicology 72:239-249.

131. Hanna CW, Bloom MS, Robinson WP (2012) DNA methylation change in whole blood is associated with exposure to the environmental contamina nts,mercury,lead,cadmium and bisphenol A in women undergoing ovarian stimulation to IVF. Hum Reprodr 27:1401-1410.

132. Fernandez SV, Huang Y, Snider KE, Zhou Y, Pogash TJ, et al. (2012) Expression and DNA methylation changes in human breast epithelial cells after bisphenol A exposure. Int J Oncol 41:369-377.

133. Savastano S, Tarantino G, D'Esposito V, Passaretti F, Cabaro S,et al.(2015) Bisphenol A plasma levels are related to inflammatory markersvisceral obesiy and insulin resistance:a cross sectional study on adult male population. J Transl Med 13:169.

134. Drinker CK, Warren MF, Benett GA (1937) The problem of possible systemic effects from certain chlorinated hydrocarbons. J Ind Hyg Toxicol 71: 283-311.

135. Jensen S (1966) Report of a new chemical hazard New Sci 32:612.

136. Arcaro KF, O'Keefe PW, Yang Y, Clayton W, Gierthy JF (1999) Antiestrogenicity of environmental polycyclic aromatic hydrocarbons in human breast cancer cells. Toxicol 133:115-127.

137. Carpenter DO (1998) Polychlorinated biphenyls and human health. Int J Occup Med Environ Health 11: 291-303.

138. Bridge ES, Kelly JF (2013) Reproductive success of belted kingfishers on the upper Hudson River. Environ Toxicol Chem 32: 1855-1863.

139. Carpenter DO (2006) Polychlorinated biphenyls (PCBs): routes of exposure and effects on human health. Rev Environ Health 21: 1-23.

140. Wadzinski TL, Geromini K, McKinley Brewer J, Bansal R, Abdelouahab N, et al. (2014) Endocrine disruption in human placenta:Expression of the Dioxin- inducible enzyme CYP1A1 is correlated with that of thyroid hormone regulated genes. J. Clin Endocrinol Metab.

141. Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A (2015) The Endocrine Society's Second Scientific Statement on Endocrine Disrupting Chemicals. Endocr Rev 36: E1-E150.

142. Arsenescu V, Arsenescu RI, King V, Swanson H, Cassis LA. (2008) Polychlorinated biphenyl-77 induces adipocyte differentiation and proinflammatory adipokines and promotes obesity and atherosclerosis. Environ. Health Persp 116: 761-768.

143. Wahlang B, Falkner KC, Gregory B, Ansert D, Young D, et al. (2006) Polychlorinated biphenyl 153 is a diet obesogen that worsens nonalcoholic fatty liver diseasein male. J Nutr Biochem 24: 1587-1593.

144. McGovern V (2006) PCBs are endocrine disruptors: Mixture affects reproductive development in female mice. Environ. Health Persp 114:A 368-369.

145. Bergeron J, Crews D, McLachlan J (1994) PCB's as environmental estrogens:turtle sex determination as a biomarker of environmental contamination. Environ Health Persp 102: 780-781.

146. Crinion W (2001) Polychlorinated Biphenyls Persistent Poluttants and Immunological,Neurological and Endocrinological Consequences. Environ Medicine 16: 5-13.

147. Rylander L, Dyremark E, Klasson-Wehler E, Erfurth EM(2001) Plasma concentrations of persistent organochlorines in relation to thyrotropin and thyroid hormone levels in women. Int Arch Occup Environ Health 74: 184-188.

148. Blair RM, Fang H, Branham WS, Hass BS, Dial SL, et al. (2000) The estrogen relative binding affinities of 100 natural and xenochemicals:Structural diversity of ligands. Toxicol Sci 54:138-153.

149. Hardell L, van Bavel B, Lindström G, Björnfoth H, Orgum P, et al. (2004) Adipose tissue concentrations of p,p'-DDE and the risk for endometrial cancer. Gynecol Oncol 95: 706-711.

150. Sturgeon SR, Brock JW, Potischman N, Needham LL, Rothman N, et al. (1998) Serum concentrations of organochlorine compounds and endometrial cancer risk. Cancer Causes Control 9: 417-419.

151. Malozzi M, Leone C, Manurita F (2017) Endocrine disrupting chemicals and endometrial cancer: An overview of recent laboratory and epidemiological studies. Int J Environ Res Public Health 14: 334.

152. Wielsoe M, Kern P, Bonefeld-Jorgensen EC (2017) Serum levels of environmental pollutants is a risk factor for breast cancer in Inuit:a case control study. Environ Health 16: 56.

153. Meeker JD, Hauser R (2010) Exposure to polychlorinated biphenyls (PCBs) and male reproduction. Syst Biol Reprod Med 56: 121-131.

154. Zhang J, Wang X, Lin K (2015) Environmental Polychlorinated Biphenyl Exposure and Breast Cancer Risk: A Meta-Analysis of Observational Studies. PLOS One.

155. Beranger R, Comet CL, Schaz J (2013) Occupational and environmental exposure associated with testicular germ cell tumors: Systematic Review of Prenatal and Life-long exposure. PLOS One.

156. Benedetti M, Zona A, Becceloni E (2017) Incidence of Breast,Prostate,Testicular and Thyroid cancer in Italian Contaminated Sites with : Presence of Substances with Endocrine Disrupting Properties Int J Environ Res Public Health 14: 355.

157. Santoro A, Ferrante MC, Guida F (2015) Polychlorinated Biphenyls (PCB 101 153 and 180) impair murine macrophage responsiveness to lipopolysaccharide: involvement of NF-LB pathway. Tox Sci 147: 255-269.

158. Herz Picolotto I, Park HY, Dostal M (2008) Prenatal exposures to persistent and non-persistent organic effects on immune system development Basic Clin Pharm Toxicology 22: 1742-1743.

159. Weisglas Kuperus N, Vreugdenhil HJ, Mulder PG (2004) Immunological effects of environmental exposure to polychlorinated bipheyls and dioxins in Dutch schoolchildren. Toxicol Lett 149: 1301-1305.

160. Hellmann C, Grandjean P, Werbe H (2006) Reduced antibody response

to vaccinations in children exposed to polychlorinated biphenyls. PLOS Medicine.

161. Stewart PW, Reihman J, Lonky E (2012) Issues in the interpretation of associations of PCBs and IQ. Neurotoxicol Teratol 34: 96-107

162. Engel SM, Wolff MS (2013) Causal Inference Considerations for Endocrine Disruptor Research in Children Health Ann Rev Public Health 34:139-158.

163. Balzer W, Gaus HM, Gaus C (2007) Remediation measures in a residential area highly contaminated with PCCD, PCDF, Arsenic and heavy metals as a result of industrial production in the early 19th Century. Organohalogen Compounds 69: 857-860.

164. VandenBerg M, Birnbaum LS, Demson M (2006) The 2005 World Health Organization reevaluation of human and Mammalian toxic equivavalence factors for dioxins and dioxin-like compounds. Toxicol SCI 93: 223-241.

165. Bell WB (1953) Relative toxicity of the chlorinated naphthalenes in experimentally produced bovinehyperkeratosis (x-disease) Vet Med Sm Anim 48: 135.

166. Firestone D (1953) Etiology of chick edema disease. Environ Health Persp 59-66.

167. Suskind RR, Hertzberg VS (1984) Human health effects of 2,4,5-T and its toxic contaminants. JAMA 251: 2372-2380.

168. Steenland K, Piacitelli L, Deddens J (1999) Cancer, heart disease and diabetes in workers exposed to 2,3,7,8 tetrachloor-p-dioxin. J Natl Cancer Inst 91: 779-786.

169. Michalek JF, Pavuk M (2008) Diabetes and cancer in veterans of Operation Ranch Hand after adjustments for calendar period, days of spraying and time spent in South East Asia. J Occup Environ Med 50: 330-340.

170. Institute of Medicine, Comittee to Review the Health Effects in Vietnam Veterans of exposure to Herbicides,Veterans and Agent Orange.Update 2006. Washington National Academy Press.

171. Aoki Y (2001) Polychlorinated biphenyls, polychlorinated dibenzofurans as endocrine disruptors-what we have learned from Yosho disease. Environ Res 86: 2-11.

172. Guo YL, Lambert GH, Hsu CC (2004) Yucheng health effects of prenatal exposure to polychlorinated biphenyls and dibenzofurans Int Arch Occup Environ Health 153-158.

173. Fox GA (2001) Wildlife as sentinels of human health effects in the Great Lakes-St Lawrence basin. Environ Health Resp109: 853-861.

174. Wickizer TM Brillant LB, Copeland R (1981) Polychlorinated biphenyl contamination of nursing mother's milk in Michigan. Am J Public Health 71: 132-137.

175. Bertazzi PA, Consonni D, Bochetti S (2001) Health effects of dioxin exposure:a 20 year mortality study. Am J Epidemiol 153: 1031-1044.

176. Mocarelli P, Gerthoux PM, Patterson DG (2008) Dioxin exposure from infancy through puberty produces endocrine disruption and affects human semen quality. Environ Health Perspect 116: 70-77.

177. Fingerhut MA, Halperdin WE, Marlow DA (1991) Cancer mortality in workers exposed to 2,3,7,8-terachloordibenzene-p-dioxin (TCDD) intoxications. N Engl J Med: 324: 212-218.

178. Gensau A, Abraham K, Geisler K (2001) Severe 2,3,7,8 tetrachloordibenzo-p-dioxin (TCDD) intoxications: clinical and laboratory effects. Environ Health Persp 109: 865-869.

179. Sorg O, Zennegg M, Schmid P (2009) 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) poisining in Victor Yushenko:identification and measurement of TCDD metabolites. Lancet 3: 374.

180. Gu YZ, Hogenesch JB, Bradford CA (2000) The PAS superfamily: sensors of environmental and developmental signals. Ann Rev Pharmacol Toxicol 40: 519-561.

181. Marlowe JL, Puga A (2005) Acryl hydrocarbon receptor,cell cycle regulation,toxicity and tumorgenesis. J Cell Biochem 96: 1174-1184.

182. Singh KP, Casado FL, Opanushak LA (2008) The acryl hydrocarbon receptor has a normal function in the regulation of hematopoeitic and other cell progenitor cell populations. Biochem.Biopharmacol 77: 577-587.

183. U.S. EPA Part 2 Health assessment of 2,3,7,8 Tetrachloor-dibenzo –p- dioxin (TCDD) and related compounds. Washington D.C. U.S. Environmental Protection Agency 2003 Dioxin Reassessment Draft Exposure and Human Health Reassessment of 2,3,7,8- Tetrachloordibenzo-p- dioxin (TCCD) and Related Compounds.

184. Baccarelli A, Giacomini SM, Corbetta C (2008) Neonatal thyroid function in Seveso 25 years after maternal exposure to dioxin. PLOS Med 5: 161.

185. Lambert GH, Needham LL, Turner W (2006) Induced CYP1A2 activity as a phenotypic biomarker in humans highly exposed to certain PCBs, PCDFs. Environ Sci Technol 40: 76-80.

186. Birnbaum LS (1994) The mechanism of dioxin toxicity, relationship to risk assessment Environ HealthPersp 157-167.

187. McHale CM, Zhang L, Hubbard E (2007) Microarray analysis of gene expression in peripheral blood mononuclear cells from dioxin-exposed human subjects. Toxicology 229: 101-113.

188. Malozzi M, Leone C, ManuritaF (2017) Endocrine disrupting Chemicals and Endometrial Cancer; An overview of Recent Laboratory Evidence and Epidemiological Studies. Int J Environ Res Public Health 14: 334.

189. Dutta D, Khadgawat R (2015) Endocrine Disruptors: Can it be the missing link explaining the diabetes epidemic in India? J Soc Health Diabetes 3: 16-21.

190. Othmar Zeidler (1874) Compounds of chloral with bromine and chlorobenzene. Reports German Chem Society 7: 1180 - 1181.

191. Dunlop T (2014) DDT,Scientists Citizens and Public Policy. Princeton University Press, USA, 328.

192. de Zulueta J (1998) The end of malaria in Europe: an eradication of the disease by control measures. Parassitologia 40: 245-246.

193. CDC-Malaria-About Malaria-History. Elimination of Malaria in the United States.1949-1954.

194. Sadasivalah S,Tozan Y, Breman JG (2007) Dichloro diphenyl trichloroethane (DDT) for indoor residual spraying in Africa;how can it be used in malaria control? Am J Trop Med Hygiene 77: 249-263.

195. Rogan WJ, Chen A (2005) Health risks and benefits of bis(chloorpheny)1,1,1 trichlroethane (DDT). Lancet 366: 763-773.

196. DDT and its derivatives: Environmental Aspects: Environmental Health Criteria WHO Monograph No 83 Geneva.

197. Cornell D et al. Introduction in Endocrinology. Blackwell Science.

198. Vos JG1, Dybing E, Greim HA, Ladefoged O, Lambré C, et al. (2000) Health effects of endocrine disrupting chemicals on wildlife,with special reference to the European situation. Crit Rev Toxicol 30: 71-133.

199. Lundholm CD (1997) DDE-induced eggshell thinning in birds:effects of p-p DDE on the calcium and prostaglandin metabolism of the eggshell gland. Comp Biochem Physiol C Pharmacol Toxicol Endocrinol 148: 113-128.

200. Hejmej A, Kotula I. Balak M, Bilińska B (2011) Steroids - Clinical Aspect: In Antiandrogenic and estrogenic compounds. Effect of Development and Function of Male Reproductive System, In Tech, Croatia.

201. Stockholm Convention on Persistent Organic Pollutants.

202. Concern over excessive DDT use in JIribam Fields.

203. Brúcker Davis F (1998) Effects of environmental synthetic chemicals on thyroid function. Thyroid 9: 827-856.

204. Viljoen JM, Borman R, Bouman H (2016) DDT exposure of frogs:A case study from Limpopo Province, South Africa. Chemosphere 159: 335-341.

205. Loomis D, Guyton K, Grosse Y, El Ghissasi F, Bouvard V, et al. (2015) Carcinogenicity of lindane,DDT and 2,4 dichlorophenoxyacetic acid. Lancet Oncology 16: 891-892.

206. Cocco P, Kazerouni N, Zuhm SH (2000) Cancer mortality and environmental exposure to DDE in the United States. Environ Health Perspect 108: 1-4.

207. Bradman AS, Schwartz JM, Fenster L, Barr DB, Holland NT, et al. (2007) Factors predicting organochlorine pesticide levels in pregnant latina women:living in a United States agricultural area. J Expo Sci Environ Epidemiol 17: 388-399.

208. Longnecker MP, Klebanoff MA, Dunson DB, Guo X, Chen Z, et al. (2005) Maternal serum level of the DDT metabolite DDE in relation to fetal loss in previous pregnancies. Environ Res 97: 127-133.

209. Segiu SK, Tolbert PE, Altshui LM Korrick SA (2001) Organochlorine exposures during pregnancy and infant size at birth. Epidemiology 18: 126-129.

210. Cupul-Uicab LA, Gladen BC, Hernández-Avila M, Weber JP, Longnecker MP. (2007) DDE, a degradation product of DDT and duration of lactation in a highly exposed area of Mexico. Environ Health Perspect 115: 8-14.

211. Fernandez MF, Olmos B, Granada A, López-Espinosa MJ, Molina-Molina JM, et al. (2007) Human exposure to endocrine disrupting chemicals and prenatal risk factors for cryptorchidism and hypospadias; a nested case control study. Environ Health Perspect 115: 8-19.

212. Aneck- Hahn NH, Schulenburg GW, Bornman HS (2007) Impaired semen quality associated with environmental DDT exposure in young men living in a malaria area in the Limpopo Province. South Afr J Androl 28: 423-434.

213. Cohn BA, Cirillo PM, Wolff MS, Schwingl PJ, Cohen RD, et al. (2003) DDT and DDE exposure in mothers and time to pregnancy in daughters. Lancet 361: 2205-2206.

214. Eskanazi B, Marks AR, Bradman A, Fenster L, Johnson C, et al. (2006) In utero exposure to dichlorophenyltricloroethane(DDT) and dichlorodiphenyldichloroethane (DDE) and neurodevelopment among young Mexican American Children. Pediatrics 118: 233-241.

215. Cooper GS, Martin SA, Longnecker MP, Sandler DP, Germolec DR (2004) Association between plasma DDE levels and immunologic measures in African-American farmers in Nort Carolina. Environ Health Perspect 112: 1080-1084.

216. Ahamed M, Amand M, Kumar A, Siddiqui MK (2006) Childhood aplastic anaemia inLucknow India: incidence organo chlorines in the blood and review of case reports following exposure to pesticides. Clin Biochem 39: 762-766.

217. Jansen A, Lyche JL, Polder A, Aaseth J, Skaug MA, et al. (2017) Increased blood levels of persistent organic pollutants (POP) in obese individuals after weight loss: A review. J Toxicol Environm Health 20: 22-37.

218. U.S. patent 3799758 Franz J.E. N-phosphonomethyl-glycine phytotoxicant compositions:issued 1974-03-26 assigned to Monsanto Company.

219. United States Patent (1964) Staufler Chemical.

220. Hock B, Elener EF (2004) Plant toxicology (4th edtn), CRC Press, USA, 292-296.

221. Research Report on Global and China Glyphosate Industry.

222. Pesticide Registration Manual-Pesticide Registration, USA, EPA.

223. Schinas L, Leon ME (2014) Non-Hodgkin lymfoma and occupational exposure to agriculture pesticide chemical groups and elective ingredients:a systematic review and analysis. J Environm Resa Public Health 11: 449-527.

224. Szekaks A, Darvas B (2012) Forty years with glyphosate. In herbicides, properties, synthesis and control of weeds, In Tech, USA, 953-78.

225. Glyphosate to be Listed under Proposition 65 as “Known to the State to cause Cancer” OEHHA.

226. United States Environmental Protection Agency Draft list of Initial Pesticide Active Ingredients and Pesticide Inerts to be Considered for Screening under the Federal Food,Drug and Cosmetic Act Federal Register.

227. VandenBerg LN, Blumberg B, Antaniou M (2017) Is it time to reassess current safety standards for glyphosate-based herbicides? Epidemiol Community Health 71: 613-618.

228. Feuer H, Lawrence JR (1969) The alkyl nitrate nitration of active methylane compounds:a new synthesis of nitro-alkyl heterocyclics. J Am Chem Soc 91: 1856-1857.

229. Schroeder ME, Hattum RF (1984) The mode of action and neurotoxic properties of the nitromethylene heterocyclic insecticides. Pesticide Biochem Physiol 22: 148-160.

230. Tombizawa M Casida JE (2005) Neonicotinoid Insecticide toxicology mechanisms of selective action. Ann Rev Pharmacol Toxicology 45: 247-268.

231. Williams GR, Troxler A, Retschnig G, Roth K, Yañez O, et al. (2015) Neonicotinoids pesticides severely affect honey bee queens. Scientific Reports 25; 14621.

232. Kessler SC, Tiedeken EJ, Simcock KL, Derveau S, Mitchell J, et al. (2015) Bees prefer foods containing neonicotinoid pesticides. Nature 521: 74-76.

233. Holmann CA, Foppen RP, van Turnhout C (2014) Declines in insectivorous birds are associated with high neonicotinoid concentrations. Nature 511: 341-343.

234. Mamane A, Baldi I, Tessier JF, Raherison C, Bouvier G (2015) Occupational exposure to pesticides and respiratory health. Eur Respir Rev 24: 306-319.

235. Pandey SP, Mohanty B (2017) Disruption of the hypothalamic-pituitary – thyroid axis on co-exposure to dithiocarbonate and neonicotinoid pesticides. Study in multiple bird Amandava amandava. Neurotoxicology 60: 16-22.

236. Lavicoli L, Fontama L, Bergamaschi A (2009) The effect of metals as endocrine disruptors. J Toxicol Endocr Health Crit Rev 12: 206-223.

237. Dyer CA (2007) Heavy metals as endocrine disruptors. In Endocrine Disrupting Chemicals:From Basic Research to Clinical Practice. Hunana Press Inc, USA, 111-133.

238. Landrigan PJ, Benbrook C (2015) GMOs,Herbicides and Public Health. N Engl J Med 20: 693-695.

239. Levine H, Jørgensen N, Martino-Andrade A, Mendiola J, Weksler-Derri D, et al. (2017) Temporal trends in sperm count: a systematic review an meta-regression analysis. Hum Reprod Update

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