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CYP polymorphisms and pathological conditions related to chronic exposure to organochlorine pesticides

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ABSTRACT

The association between genetic variations in the cytochrome P450 (CYP) family genes and pathological conditions related to long-term exposure to organochlorine compounds (OCs) deserves further elucidation. OCs are persistent organic pollutants with bioaccumulative and lipophilic characteristics. They can act as endocrine disruptors and perturb cellular mechanisms. Prolonged exposure to OCs has been associated with different pathological manifestations. CYP genes are responsible for transcribing enzymes essential in xenobiotic metabolism. Therefore, polymorphisms in these genetic sequences a. alter the metabolic pathways, b. induce false cellular responses, and c. may provoke pathological conditions. The main aim of this review is to define the interaction between parameters a, b and c at a mechanistic/molecular level, with references in clinical cases.

1. Introduction

1.1. Organochlorines

Organochlorines are organic compounds used as pesticides highly effective in the eradication of parasitic diseases. Following World War II, discovery of dichlorodiphenyltrichloroethane (DDT) contributed enormously to malaria and typhus eradication, significantly reducing morbidity and mortality rates. This event was regarded as a landmark in pesticide history and lead to an intense industrial production of the pesticide [1]. Apart from the synthetic OCs, many of these compounds exist naturally, in plants and aquatic organisms, as a means of attack

Abbreviations: AhR, aryl hydrocarbon receptor; ARNT, AhR nuclear translocator; CYP450, cytochrome P450; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; GST, glutathione-S-transferase; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; HPTE, hydroxychlor; MXC, methoxychlor; OBP, organochlorine by-product; OC, organochlorine compound; PAA, phenoxyacetic acid; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzodioxins; PCDF, polychlorinated dibenzofurans; POP, persistent organic pollutant; ROS, reactive oxygen species; SNP, single nucleotide polymorphism; TCDD, tetrachlorodibenzodioxin; VCM, vinyl chloride monomer

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and defense. OCs belong to the extended Persistent Organic Pollutants (POPs) family, they are halogenated hydrocarbons and they present common chemical properties: persistence to decomposition (biological and chemical), lipophilicity and bioaccumulation in tissues. Some members of the OC family are apart from DDT, hexachlorobenzene (HCB), polychlorinated biphenyls (PCBs), lindane (HCH), chlorinated cyclodienes, toxaphene, mirex and chlordecone (caged structured). OCs accumulate in tissues of biota, and subsequently get magnified, as trophic levels of food chains ascend. They can be detected in soil sediments, due to their low aquatic solubility. Their half-lives vary from months to decades, and, impressively, concentrations of OCs have been found in the Arctic and other remote, non-inhabited regions of the world [2].

OCs were widely used in agriculture but several restrictions in their use have been imposed since the late 1970s [3]. For example, although the use of hexachlorocyclohexane (HCH) and DDT in China was prohibited thirty years ago, high concentrations of HCH and DDT recently were detected in Taihu Lake region [4]. Scientists concluded that remediation in uncultivated land progresses at a slower rate compared to areas with continuous cultivation.

Humans are exposed to OCs mainly through dietary uptake (orally) and direct environmental or occupational contact (via the respiratory tract, dermally) [5,6]. Usually humans are exposed to a combination of xenobiotics. Synergism or antagonism between them determines the final result [7]. Real life exposure scenario in which humans are exposed to mixtures of xenobiotics in low realistic doses are now the main concern of researchers in the field [8,9]. A new methodology for animal testing that have the ambition to answer to multiple questions related to long term toxicity of non-commercial chemical mixtures at realistic low level doses and simultaneous investigations of many key points as genotoxicity, organ toxicity, endocrine disruption and systemic mechanistic pathways like oxidative stress, have already been proposed [10,11]. Ambient exposure to OCs, either acute or chronic, has been linked with induction of pathological mechanisms, including disruption of the endocrine system [12], immune dysfunction [13], reproductive impairment [14], neurotoxicity [15–17] and possible carcinogenic/mutagenic action [18,19].

Under experimental conditions, OCs demonstrate a dual endocrine disrupting action: they possess similar potency to that of estrogens by activating the production of hepatic microsomal enzymes, which leads to hydroxylation of steroids and subsequently burdens the reproductive ability and at the same time they behave as a hindrance to hormone signaling and cell communication. Furthermore, OCs may induce reproductive dysfunction, through mutations and modifications in steroidogenesis [2,20,21].

CYP genes are responsible for transcribing enzymes essential in xenobiotic metabolism. Therefore, polymorphisms in these genetic sequences a. alter the metabolic pathways, b. induce false cellular responses, and c. may provoke pathological conditions. The main aim of this review is to define the interaction between parameters a, b and c at a mechanistic/molecular level, with references in clinical cases.

1.2. OCs and cytochrome P450 metabolism

Of the pesticides in use, the majority are metabolized in the human body by the same P450 family member, CYP1 isoenzymes [22]. The cytochrome P450 proteins are monooxygenases, which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. At low concentrations, CYP1A1 (also known as aryl hydrocarbon hydroxylase) is expressed in the liver [23]. On the other hand, at high concentrations, it is expressed extrahepatically, in pulmonary cells and lymphocytes. On the contrary, CYP1A2, which also metabolizes polyunsaturated fatty acids into signaling molecules that have physiological as well as pathological activities, resides mainly in the liver. CYP1B1, which metabolizes procarcinogens such as polycyclic aromatic hydrocarbons and 17 beta-estradiol and is also regulated by the aryl hydrocarbon receptor as CYP1A2, is expressed in many tissues, including hepatic cells and it is localized to the endoplasmic reticulum. The intestinal mucous membrane consists presumably the most significant site, regarding extrahepatic drug biotransformation [24].

Human CYP family members are not the same as CYP family members belonging to other species. Furthermore, CYP family members differ between people of different races due to CYP polymorphisms. They display, in other words, an inter-ethnic and inter-racial pattern among frequencies of genetic variations [25].

Polymorphisms in CYP genes principally influence the metabolism of substances that are substrates for these enzymes, resulting in altered response, therefore susceptibility to different pathologies [26,27]. Furthermore, overexpression of some CYP family members depends on the expression of other family members present in different organs and this interaction in expression is not identical between individuals of the same species and the same race [28].

1.3. CYP genetic variations and their clinical impact in chronic exposure to organochlorines

It is now well documented that the pathogenesis of most diseases has a mixed genetic and environmental background. The genotype affects gene expression, and therefore the susceptibility of an individual to a toxic substance [29].

The ability of OCs to disrupt endocrine signal transduction consists the premise of their biochemical actions. This event might be also linked with the ability of OCs to up-regulate a number of genes, including cytochrome CYPs. Some PCBs are known to induce the enzymes CYP1A1, CYP1A2 and CYP1B1. A genetic polymorphism in CYP1A1 was related to PCB118 serum levels and it was shown that a single nucleotide polymorphism (SNP) in the CYP1A1 gene significantly correlated to circulating levels of PCB118 [30]. Moreover, various SNPs in CYP1A2 and CYP1B1 have been correlated with PCB118 serum levels, and certain SNPs in the CYP1B1 gene have been correlated with PCB156 and PCB206 serum levels [30]. Clinical manifestations, from plain hypertrophy to dysplastic lesions and potentially tumorigenesis, could be attributed to a P450 mode of action along with mutagenic activity of various OCs [31].

At the same time, CYP1A1, CYP1A2 and CYP1B1 are enzymes that play an important role in the detoxification of xenobiotics such as PCBs [32]. CYP1A1 metabolism has been proposed as the primary mechanism, interacting with PCBs [33]. It could therefore be argued that, CYP polymorphisms (SNPs) are responsible for adverse reactions caused by exposure to PCB. Recent studies have already shown associations between CYP1A1/PON1 polymorphisms in several clinical manifestations of individuals occupationally exposed to PCBs [34].

CYPs participate in the metabolism of aromatic hydrocarbons, whose products react with DNA, and may provoke DNA mutations, alteration of gene expression profiles and tumorigenesis. Glutathione-S-transferase (GST) mediates glucuronide conjugation, a detoxification step of chemical intermediates excretion procedure [25]. Variations in CYP1A1, CYP1A2 and GST hold a particular significance in hormone-implicated cancer induction [29]. (Fig. 1)

It is confirmed that OCs up-regulate CYP1A1 enzyme activity − as well as other CYPs – promoting estrogen hydroxylation [35].

Methoxychlor (MXC) and hydroxychlor (HPTE) act by disturbing the metabolism of both endogenous, as well as exogenous chemical compounds. The effects of MXC and HPTE on CYP2C9, CYP2C19, CYP2D6 and CYP3A4 in human microsomes, and on CYP2C11, CYP2C6, CYP2D2 and CYP3A1 activity in homologous rat hepatic microsomes have been investigated. It was found that exposure to MXC and HPTE lead to inhibition of human CYP2C9 and CYP2C19, and rat CYP2C11 and CYP2C6. No effects were observed in human CYP3A4 and rat CYP2C6 activity. HPTE marginally inhibited human CYP2D6 and rat CYP2D2 activity. [36].

Tsuchiya et al. [37] studied a sample of 138 diagnosed

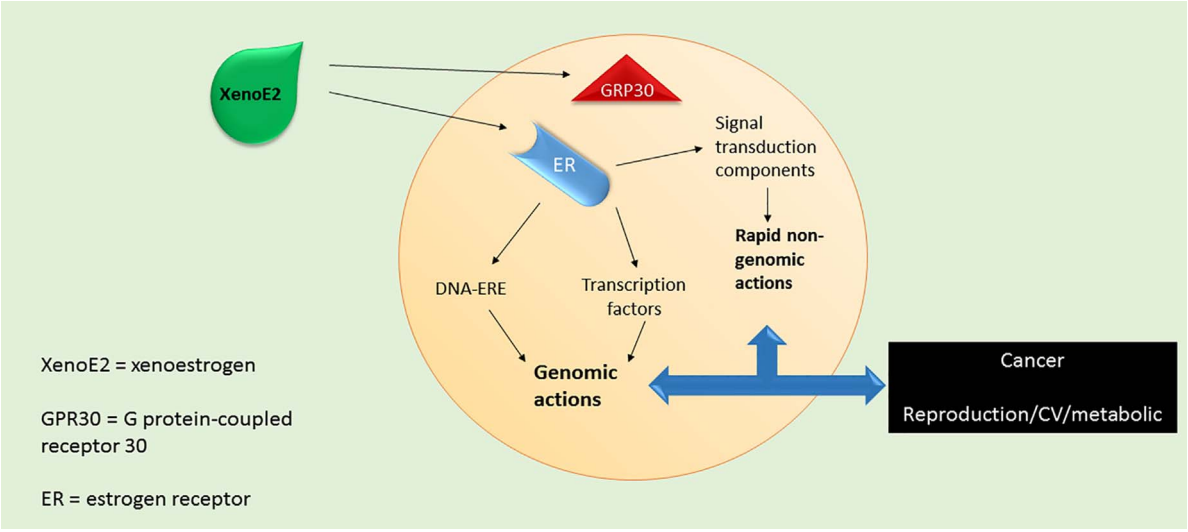

Fig. 1. The effects of xenoestrogen-behaving OCs in cellular function. Genotoxic and xenoestrogenic OCs action in relation with CYP polymorphisms and cancer (modified from Wallace [79]).

endometriosis related infertile women. Plasma PCBs levels were measured and genotypes of the CYP1A1 Ile462Val (rs1048943) and CYP1B1 Leu432Val (rs1056836) polymorphisms were determined. At high serum dioxin concentrations, individuals carrying the CYP1A1 rs1048943 polymorphism had a reduced risk of developing advanced endometriosis. Moreover, a strong correlation was found between PCB serum levels and the risk of advanced endometriosis in the presence of the CYP1B1 rs1056836 polymorphism. The authors concluded that these polymorphisms can affect the risk of advanced endometriosis following increased exposure to OCs [37].

In a semen-qualities study (motility, concentration and morphology), clinical history, demographic information and semen samples from 336 patients were collected. PCB plasma levels were obtained and the CYP1A1 Msp*I* genotype was determined by restriction fragment length polymorphism (RFLP). A relationship between OC plasma concentration, semen functionality and CYP1A1 Msp*I* (rs4646903) polymorphism could be demonstrated [38]. CYP1A1 participates in detoxification and bio activation of polycyclic aromatic hydrocarbons, such as PCPs. These reactions generate reactive oxygen species (ROS), which potentially damage DNA [39]. The presence of a CYP1A1 Msp*I* (rs4646903) polymorphism associated with OCs exposure may affect spermatogenesis by modifying the metabolism of androgens. It was concluded that increased DDE-DDT (Dichlorodiphenyldichloroethylene-DDT) exposure affects semen motility, concentration and morphology, especially under the existence of CYP1A1 Msp*I* (rs4646903) polymorphism [38].

Possible connection between polymorphisms in CYP1A1, CYP1B1 and CYP17 and the development of benign prostatic hyperplasia (BPH), secondary to chronic OC exposure, has also been investigated [27]. Benign prostatic hyperplasia is a disorder which is common in elderly men. In its pathology are included both genetic and environmental factors. In a study including 100 newly diagnosed BPH subjects, CYP1A1, CYP1B1 and CYP17 polymorphisms were studied and p,p′-DDE and endosulfan-α blood levels were determined. OCs levels were found to be significantly higher amongst BPH patients and CYP17 polymorphism was significantly associated with patients developing BPH, indicating that all three CYP polymorphisms may be important risk factors for BPH development. CYP17 is expressed in large amounts in the prostatic gland while playing an important role in steroid metabolism. The authors concluded that CYP17 polymorphisms may induce changes in the metabolism of steroid hormones, increasing the risk for benign hyperplasia [40].

Badawi et al. [35] evaluated the endocrine disrupting activity of TCDD (tetrachlorodibenzodioxin) and dieldrin on female Sprague-Dawley rats. Correlation of the OCs studied with the expression of CYP1A1, CYP1A2 and CYP1B1 was examined. The findings confirmed the hypothesis, that, exposure to OCs may be related to CYP1 family genes induction, modifying subsequently 17β-estradiol metabolism. Similarly, Kimura et al. [41] reported a 27-fold increase of hepatic CYP1A1 mRNA, induced by TCDD and a 12-fold renal CYP1A1 mRNA increase. Nevertheless, these mRNA elevations were accompanied by a relatively lower than expected protein production. Therefore, OCs may incite transcription of various genes pertaining to estrogen metabolism, such as CYP1B1. Production of 4-catechol estrogen would thus be increased. This can then be converted into quinones via oxidation, which react with DNA. This event could initiate mutations, some of them possibly being oncogenic. Several studies have indicated that 4-catechol estrogens are related to an increased risk of breast cancer in humans and cause kidney cancer in hamsters [42–46]. OCs may be related to alterations in gene expression, that in turn may affect estrogen biotransformation. These modifications may promote redeeming mechanisms (e.g. continuous up-regulation in estrogen metabolism and production of catechol estrogens). Oxidation of these may lead to the production of DNA-reactive catechol estrogen quinones, eventually leading to neoplasia [35].

Polymorphisms in CYP1A1, CYP1B1 [33], CYP2D6 and CYP19 have been linked to increased breast cancer risk. PCBs strongly increase CYP1A1 enzyme levels. Women with the CYP1A1*2C polymorphism (rs1048943) present an increased risk of breast cancer when exposed to PCBs [47].

Similarly, Li et al. [48] performed a population-based case-control study, where the breast cancer risk was evaluated, in association to PCB levels and the CYP1A1 polymorphisms M1 (CYP1A1*2A), M2 (CYP1A1*2C), M3 (CYP1A1*3) and M4 (CYP1A1*4). It emerged that M2 and PCB plasma levels strongly correlated with risk in white women, whereas M3 and PCB plasma levels correlated with risk in African American women [48]. Moreover, an increased risk, as depicted by odds ratio analysis, of breast cancer has been shown in post-menopausal women, whose PCB plasma concentrations were above average, and whose CYP1A1 polymorphism (CYP1A1*2C) was present, possibly due to increased DNA destruction [49].

With respect to CYP1B1 polymorphisms, Saintot et al. [50] examined the relationship between polymorphisms of CYP1B1 and OCs, in breast cancer patients. OCs are known to incite the expression of CYP1B1 and to bind with AhR (aryl hydrocarbon receptor). CYP1B1 partakes in the hydroxylation of estrogens into catechol estrogens,

which could generate DNA mutations [51]. The homozygous or heterozygous presence of the aminoacid Valin in the CYP1B1 protein chain (CYP1B1*3-8) leads to CYP1B1 induction triggering, elevated production of toxic catechol estrogens. CYP1B1.3-8 enzyme, catalyzes more efficiently the 4-hydroxylation of estrogens, in comparison with the homozygous Leucin CYP1B1 [52,53]. CYP1B1*3-8 is also responsible for the induction of PCBs hydroxylation, which act as pseudoestrogens or as ROS to DNA destruction [49,54].

Human data on breast cancer are in accordance with the above mentioned findings. Coumoul et al. [55] performed a study on the breast tumor cell line MCF-7 and reported that the regulation of genes encoding enzymes metabolizing estrogens may hold significance in OC toxicity. In another study, it was found that an elevated breast cancer risk, as depicted by odds ratio analysis, existed for women having the Val CYP1B1 allele and being chronically exposed to OCs [50]. OCs exert their action probably through the AhR, that is a ligand-incited transcription factor, and this pathway increases CYP expression [56,57].

Mustafa et al. [58] studied the association between several OCs, such as hexachlorocyclohexane (HCH), γ-HCH, Dichlorodiphenyldichloroethylene (p′p′-DDE), DDT etc, and polymorphisms in glutathione S-transferase mu 1 (GSTMI), glutathione *S*-transferase theta 1 (GSTTI), and certain cytochrome P450 genes (CYP1A1 alleles), in relation to idiopathic preterm delivery in 156 women not occupationally exposed to OCs. In the PTD women, levels of HCH, γ-HCH and p′p′-DDE were significantly increased in maternal blood, while in the cord blood significantly high levels of p,p′-dichlorodiphenyltrichloroethane and p′p′-DDE were found. When the GSTM1 genotype was absent, increasing levels of β-HCH in maternal blood resulted in an estimated reduction in POG of 1.84 weeks. At the same time in the CYP1A1*2C genotype a significant reduction of 1.11 weeks in POG was observed at elevated dieldrin cord blood levels [58].

AhR is a transcription factor, found in cytoplasmic matrix. It is bound to co-chaperones, forming a protein complex, and is physiologically inactive. Its' activating ligands, including PCDDs (polychlorinated dibenzodioxins), PCDFs (polychlorinated dibenzofurans) and PCBs (polychlorinated biphenyls), enable the regulation of enzymes of xenobiotic metabolism (cytochrome P450) (Fig. 2). A relationship exists between the AhR signaling pathway and CYP1A1 incitement following OC exposure, as metabolizing enzymes get activated by AhR ligands. A toxic result may occur subsequently to AhR activation, involving the generation of metabolites and alterations of cellular function.

Scientists determined this interaction between polymorphisms in the AhR signaling pathway and OCs, as a factor impinging on the male reproductive system. Certain OCs act by forwardly activating the AhR pathway, while others affect this procedure via indirect inhibition. The AhR pathway induces not only the transcription of genes responsible for metabolism and detoxification, but also partakes in the induction of estrogen and androgen receptor transcription. Polymorphisms in the human AhR have been linked to poor semen quality and general reproductive abnormalities. The AhR P185 polymorphism has been proved to affect activation of CYP1A2 in vivo, an event that leads to a lower suppressive effect on AhR signaling [59].

In a similar context, TCDD is thought to be the most potent activator of the AhR, a ligand activated transcription factor involved in the regulation of biological responses to planar aromatic hydrocarbons. Activation of this receptor is a contingent way of CYP1A1, CYP1A2 and CYP1B1 induction, and enhancement of metabolism [60]. In detail, the expression of CYP1A1, CYP1A2 and CYP1B1 is dependent on AhR function. When the cytoplasmic complex that contains AhR binds with a ligand, AhR enters the nucleus and constructs an active heterodimer with the nuclear protein ARNT. The AhR-ARNT (AhR-aryl hydrocarbon receptor nuclear translocator) complex binds to xenobiotic responsive elements, which reside in the promoters and enhancers of target-genes and incites their transcription. Polyaromatic hydrocarbons and halogenated aromatic hydrocarbons may act as ligands of AhR. The most potent activator of AhR is TCDD, which belongs to dioxin compounds. The epithelium of mammary glands expresses significant levels of AhR and ER, and the MCF-7 carcinoma cell line expresses both receptors. It was found that CYP1A1 and CYP1B1, which are expressed in this cell line, were induced by TCDD. Activities of both CYPs were elevated, leading to increased estradiol metabolism, transfusing the anti-estrogenic properties to TCDD. Herein, it was evident that certain xenobiotics can alter the CYP1A1/CYP1B1 relative activity, which possibly is responsible for their toxic actions [55]. Similar effects of TCDD have been reported in a number of studies [56,57,61,62].

The relationship between hepatic lesions and gene variations in metabolic enzymes has been studied with regards to workers exposed to

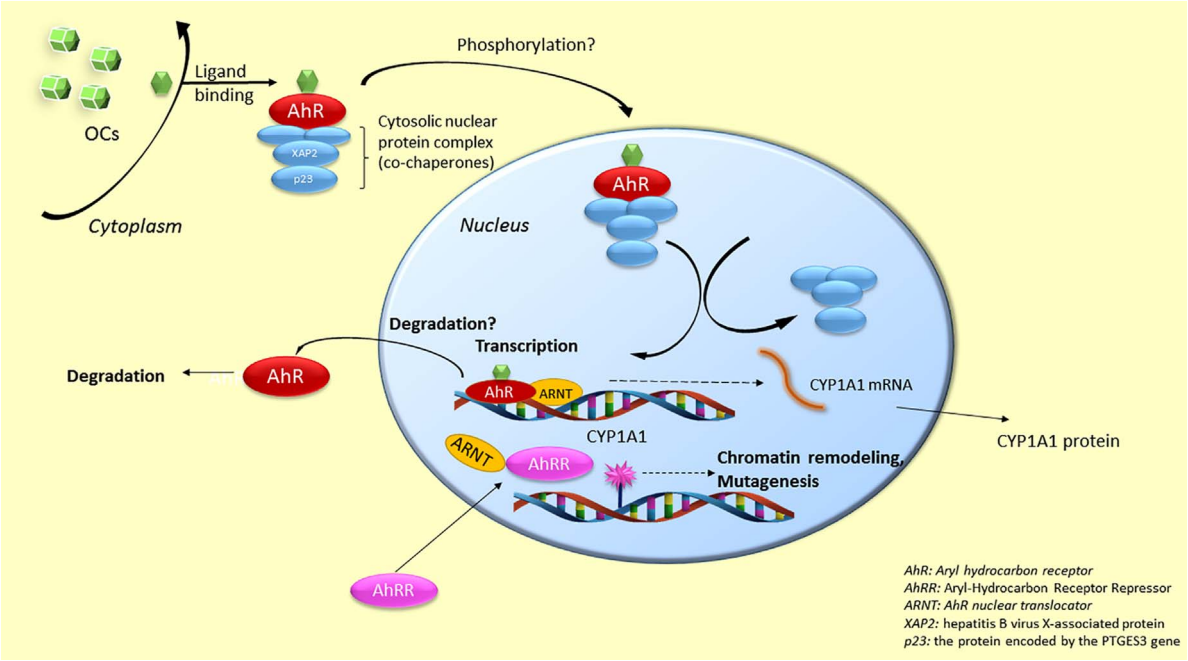

Fig. 2. OCs mediated activation of AhR and regulation of CYP (modified from Murray et al. [81]).

vinyl chloride monomer (VCM). It was observed that incidences of neurasthenia and hepatic aberrations are increased when the exposure occurs cumulatively. VCM is metabolized by CYP2E1. Genetic variations in CYP2E1 are possibly a reason for liver impairment observed following VCM exposure. It was concluded that workers exposed to high concentrations of VCM, who additionally carried the CYP2E1 polymorphism (rs3813867), had an increased risk of developing hepatic damage [63].

When mutagenic dichlorobiphenyls were administered to a Chinese hamster V79-derived cell line which expresses CYP2E1, micronuclei were strongly induced and other congeners were weakly positive. These effects were diminished or intensified in the presence of a CYP2E1 inhibitor or inducer respectively. A strong connection has been, therefore, proven between CYP2E1 and inherited genetic changes, induced by PCBs, in mammalian cells [64].

In a 2007 study, a connection between cytochrome P450 functionality in *Cyprinuscarpio* fish and lake water polluted with OC by-products (OBPs) produced by two disinfectants (NaClO and ClO_2) was supported. A concurrent incitement and inhibition of various CYP450 isoenzymes was found, exerting synergetic or competitive actions. Important elevation of ROS levels was detected following 10 days of OBPs exposure, due to CYP variations. The OBPs were able to disturb fish microsomal metabolism, both enhancing and inhibiting metabolic phase I enzymes. Phenoxyacetic acid (PAA), a newly used disinfectant that does not produce OBPs, did not succeed in directly inducing DNA damage, but it clearly up-regulates CYP-dependent metabolism. If one were to extrapolate those findings to humans, long-term exposure to OBP producing disinfectants at low doses could pose a potential carcinogenic risk. That risk may be a result of increased activation of pro-mutagens/pro-carcinogens, an event that could lead to exhaustion of enzymatic mechanisms, including DNA repair and ROS production. Overall this study suggests that prolonged exposure to OBPs produces deleterious toxic mixtures which in turn intervene in CYP-mediated metabolism pathways and provoke oxidative stress [65].

OCs exposure induces ROS production and CYP2D6 polymorphisms and also increases endoG and DNA fragmentation, therefore promoting diseases in organs where CYP2D6 and other alleles are noticeable. This effect appears to be diverse in terms of gender and development phase or age [66].

Moreover, OCs exposure and especially its ability to induce CYP polymorphisms, has been intensively associated with increased morbidity for Parkinson's [67] and Alzheimer's [68] diseases. Singh NK et al. studied the influence of genetic and environmental factors interactions in the pathogenesis of Parkinson's disease and shows that CYP2D6*4 mt allelic variants are associated with an increased risk for the disease developing, especially under the exposure to OCPs [69]. In the case of Alzheimer's disease, even if the CYP2D6*4 polymorphism itself is not a risk factor for the disease, the interaction of OCs with this polymorphism could increase the risk compared with those without polymorphism [68].

In addition, CYP polymorphisms, mediated by long term OCs exposure, activate protein dynamics via allosteric regulation of mitochondria's electron transport [70] and related metabolic pathways [71]. Knowledge of polymorphisms in the genome will enable the development of predictive models of therapeutic efficacy [72]. The framework of all known phenotype and disease gene associations, could be indicative of the common genetic origin of many diseases [73,74]. Colorectal [75], pancreatic [76], hepatic [77], thyroid [78], breast cancer [79–81], renal cancer and sarcoma are involved in the correlation between OCs exposure and carcinogenicity [82].

2. Conclusion

There is now increasing scientific evidence showing an interaction between OCs and CYP polymorphisms. Exposure to OCs could be a serious risk factor for various pathological conditions, including cancer and infertility. The proposed mechanism of pathogenesis is induction of CYP metabolism, mediated most likely by the AhR pathway. CYP polymorphisms have been closely related with an elevated risk of cancer development and progression. It is now believed that an altered CYP genotype leads to altered metabolism of endogenous and exogenous compounds, some of which might have their genotoxic and carcinogenic properties activated or enhanced by first pass metabolism. Moreover, a change in CYP metabolism may lead to hormonal dysregulation, which has in its turn been associated both with cancer and infertility. However, more research is still needed to elucidate the mechanisms underlying CYP polymorphisms observed following OC exposure. This will hopefully lead to better, individualized therapeutic strategies for patients suffering from adverse effects of prolonged exposure to environmental pollutants.

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