Medical Hypotheses 122 (2019) 157–164

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

The role of endocrine disruptors in ocular surface diseases

Regina C.N. Pontelli[a], Marília C.O. Souza[b], Marina Z. Fantucci[a], Mônica de Andrade[a], Eduardo M. Rocha[a,*]

[a] Department of Ophthalmology, Otorhinolaryngology and Head & Neck Surgery, Ribeirao Preto Medical School, University of Sao Paulo University of São Paulo, Ribeirão Preto, Sao Paulo, Brazil
[b] Department of Clinical, Toxicological and Bromatological Analyzes, ASTox – Laboratory of Analytical and Systems Toxicology, Faculty of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, Brazil

ARTICLE INFO

Keywords:
Dry eye disease
Endocrine disruptors
Environmental contaminants
Ocular disease
Ocular surface

ABSTRACT

Endocrine disruptors are a group of compounds that occur in increasing amounts in the environment. These compounds change the hormone homeostasis of the target organs regulated by those hormones, mostly by binding to their receptors and affecting their signaling pathways. Among the hormones altered by endocrine disruptors are sex hormones, thyroid hormones, and insulin. Studies have documented abnormalities in the reproductive and metabolic systems of various animal species exposed to endocrine disruptors. Endocrine disruptors can play a significant role in ocular diseases once hormone deficiency or excess are involved in the mechanism of that disease. Cataracts, dry eye disease and retinal diseases, such as macular hole and diabetic retinopathy, are some of the frequent problems where hormones have been implicated. We found that some compounds function as endocrine disruptors in the metabolism of body organs and systems. The increasing frequency of dry eye and other ocular diseases indicates the need to better investigate the potential relationships beyond the isolated associations mentioned by patients and documented as rare case reports. The evidence from case-control studies and experimental assays can provide the information necessary to confirm the endocrine effects of these chemicals in the pathophysiology of dry eye disease. We hypothesize that endocrine disruptors may contribute to the increase of ocular diseases, such as dry eye disease, in recent years.

Introduction

Dry eye disease (DED) is a multifactorial disease of the ocular surface (OS) characterized by the loss of lacrimal film homeostasis and accompanied by ocular symptoms caused by factors such tear film instability, tear hyperosmolarity, inflammation and damage to the OS [1]. DED causes discomfort and visual disturbances and affects mainly adult women over 40 years old [2,3]. The TFOS DEWS Epidemiology Subcommittee Report reviewed the major international epidemiological studies and concluded that the prevalence of DED ranged from 5% to 30% in individuals over the age of fifty years old [4]. A study conducted in several Brazilian regions showed a prevalence of 12.8% [5]. DED may be associated with autoimmune diseases, such as Sjogren's syndrome (SS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and progressive systemic sclerosis (PSS) [6–10]. Hormonal dysfunctions are part of the pathophysiology in the development of disease, mainly androgen, estrogen and progesterone deficiencies [11–15]. Despite a growing number of articles showing the relationship between sex hormones and the pathophysiology of the DED, many points remain unclear, including how these sex hormones interact with environmental agents. The etiology of DED still requires more in-depth studies; however, there is a consensus that genetic, hormonal and external factors contribute to the disease [7,16–19]. The increased prevalence of DED in women has been associated with changes in estrogen and androgen levels in ocular tissues, where these hormones modulate the expression of several genes and the function and secretion of the lacrimal gland (LG), meibomian glands (MG) and other tissues [20,21]. Sexual hormone imbalance may lead to dysfunctions of the glands, including a reduction in acinar cell size and number, changes in DNA expression and an increased inflammatory status in glandular tissue [22–24]. Estrogenic and androgenic receptors are present in the LG, MG, cornea and other ocular tissues [25,26]; therefore, the disruption of sex hormone signaling may directly interfere with the normal function of these glands, contributing to DED [27,28]. In this scenario, a class of chemical compounds called endocrine disruptors (EDs) can be identified. These compounds are present in several daily life items, which once in

* Corresponding author at: Department of Ophthalmology, Otorhinolaryngology and Head & Neck Surgery, Ribeirao Preto Medical School, University of Sao Paulo, Av. Bandeirantes, 3900, CEP 14049–900 Sao Paulo, Brazil.
E-mail address: emrocha@fmrp.usp.br (E.M. Rocha).

https://doi.org/10.1016/j.mehy.2018.11.009
Received 20 August 2018; Accepted 20 November 2018

contact with living organisms, including humans, are able to deregulate the production of hormones affecting different tissues and organs and to induce reproductive, neurological and metabolic disorders that may take place in the mechanisms of DED [29–33]. These compounds are defined by the World Health Organization (WHO) as exogenous substances or a mixture of compounds that alter the endocrine system and consequently cause adverse health effects in target organs or its progeny [34]. EDs are substances of varied chemical structure that are ubiquitous and produced on a large scale worldwide. A large number of EDs have the ability to bind to estrogen, androgen and other hormone receptors and change the homeostasis of this target tissue and its interaction with other organs [35]. The hypothesis investigated in this review addresses the possibility that exposure to EDs contributes to the mechanisms of ocular diseases, such as DED. The aim of the present study was to identify the effects of EDs on ocular disease (OD) using a comparative analysis of scientific evidence.

Harmful environmental agents cause eye diseases

Previous studies were able to correlate the presence of symptoms and signs of DED with low humidity, high temperature, high levels of air pollution and other environmental factors [36–40]. Moreover, it is possible to conceive that more than working isolated, well-known and hidden factors combine, once in contact with the OS, may disrupt the clinical findings associated with DED. In this context, paraquat, a chemical compound used as an herbicide and well known as an environmental pollutant and a potential ED, is associated with chronic and acute damage of the OS, where the severity may depend on the amount of exposure [41–45]. The hypothesized and explored mechanisms to explain the harm of pollutants to the OS involve increased tear osmolarity due to evaporation and higher levels of particles in contact with the OS [39,46]. The changes in OS trigger inflammatory pathways activated by nociceptive receptors, known as transient receptors of potential vanilloid (TRPV), which are ionic channels that activate ion influx to OS cells [47,48]. These receptors, working as calcium channels, can increase the calcium influx to cells, initiating the signaling for innate inflammatory humoral and cellular responses [49,50]. As a consequence, the sensitivity is perpetuated and amplified to annex tissues, thereby disturbing the homeostatic events related to replacing tear basal secretion and maintaining tear film stability in normal cells [50,51]. Chemical compounds known to disrupt the peripheral nerves, such as benzalkonium chloride (BAK), are chronically in contact with the OS, thereby inducing neuropathic keratopathy, damaging the sensory nerves of the cornea, reducing Dtear secretion, increasing tear osmolarity and consequently inflammation and impairing epithelial cell replacement [52–54].

Estrogens formed in the gonads and adrenals are regulated by feedback mechanisms via hypothalamo-pituitary-gonadal or adrenal axes [55,56]. These hormones play significant roles in amplifying the nociceptive signals driven by the TRPV receptor family in peripheral and OS nerves [57–59]. Additionally, estrogen promotes a pro-inflammatory response in genetically conditioned autoimmunity in LG. Several OS inflammatory conditions are more prevalent in women, and the presence of estrogen is associated with this sexual imbalance [17]. The possibility that exogenous events and chemical compounds may interfere with estrogen secretion and action has been proposed and observed in previous studies in different conditions and organs [60,61].

The estrogenic or antiestrogenic activity of some EDs occurs across estrogen receptors (ERs) [62]. EDs affect the genes involved in proliferation and cellular differentiation, contributing to increased infertility, developmental anomalies and various types of cancer [63–67]. Moreover, these compounds may interfere with the synthesis of estrogens by inactivating the enzyme aromatase [68,69]. The possibility and detailed mechanism by which sex hormone homeostasis can be locally dysregulated in the OS or LG by EDs and impact tear function requires further investigation.

Endocrine disruptors

EDs have been defined by the US Environmental Protection Agency (EPA) as exogenous substances that interfere with the production, release, transport, metabolism, binding, action or elimination of natural body hormones, impacting homeostasis and growth and development processes [20]. Several definitions are presented in the medical literature [70,71]. According to the WHO), EDs are mostly man-made and can be found in many daily products, including plastic bottles, food cans, detergents, flame-retardants, toys, cosmetics and toiletries [72,73]. Moreover, these compounds may be included in this group as herbicides, pesticides, fungicides and pharmaceuticals. Some EDs are of natural origins and others are synthetic [72]. EDs with their respective categories and most common uses are detailed in the reviews of Kabir and coworkers [62] and Diamanti-Kandarakis and coworkers [71].

Human exposure to EDs occurs through ingesting food packaged in cans or plastics, drinking water, inhaling gases and dust particles and penetrating the skin. EDs are lipophilic compounds that can be transferred from the mother to the fetus through the placenta and to the child through the breast milk. Pregnant women and children are the most vulnerable populations to be affected by ED exposures [35,73]. An important source of exposure to EDs is water, which is due to human and animal excretion and the use of products such as herbicides and pesticides that reach water bodies and cannot be removed by traditional water treatment processes [74]. Downstream of the places where the sewage is dumped, male fish produce vitellogenin, a biomarker of estrogen exposure in males. This protein is generally found only in females, but male fish may exhibit the hepatic expression of induced vitellogenin when exposed to environments contaminated with estrogenic substances [75,76]. This fact occurs because conventional sewage treatments were not developed for the removal of these compounds [74,77]. Some sources of EDs are presented in Table 1.

Mechanisms of action

The compounds classified as EDs have different chemical configurations, and these structures are capable of simulating or altering the hormonal system of humans and other animals, thereby impairing the normal functioning of the immune, nervous and endocrine systems [78,79]. Two basic ED action mechanisms are known: the genomic pathway, which involves the transcription of target genes, and the nongenomic pathway, which transduces signals mediated by membrane-bound ERs or other receptors through cross talk and/or bypassing [70,80,81]. EDs can also act through epigenetic mechanisms or several signaling-independent mechanisms simultaneously [33,82,83].

Exposure to EDs leads to an increase in insulin release, leptin, tumor necrosis factor TNF-α and interleukin IL-1 β, accelerates oxidative stress and lipid peroxidation, stimulates lipid accumulation in adipocytes, interferes with insulin receptors and reduces glucose oxidation [84,85]. The major difficulty in studying the mechanism of these

Table 1
Environmental sources of Endocrine Disruptor (ED) contamination.

Sources	Endocrine disruptors
Agricultural outflow	Insecticides, Herbicides, Fungicides, Hormones Synthetics
Incineration	PCBs, Dioxins
Occupational	Herbicides, Fungicides
Industrial effluent	Alkylphenols, PAHs, Bisphenol, Phthalates
Surface /ground water	Insecticides, Herbicides, Synthetic hormones, PAHs, Bisphenol, Phthalates
Consumer products	Parabens, Bisphenol, Phthalates
Food packaging and diet	Herbicides, Bisphenol, Phthalates

Abbreviations: PCBs: polychlorinated biphenyls/PAHs: polycyclic aromatic hydrocarbons

Table 2
Endocrine disruptors may be related to reproductive, metabolic and neurological disorders.

Organ/System	Disorders	Endocrine disruptors
Male Reproductive	Testicular dysgenesis syndrome	BPA, DDT, DES
	Semen quality	BPA, DDT, DES, Phthalate
	Cryptorchidism/ hypospadias	BPA, DDT, DES, PCBs, Phthalate
	Prostate cancer	BPA, DES
Female Reproductive	Puberty	PCBs, Pesticides, Phthalate
	Fertility and fecundity	BPA, DES, PCBs, Pesticides
	Menstrual and ovarian function	BPA, DDT, DES, PCBs, Pesticides, Phthalate
	Endometriosis	Phthalate
	Breast cancer	BPA, Pesticides
Endocrine	Thyroid: Affect homeostasis	BPA, PCBs
	Obesity	BPA, Phthalate
	Diabetes	BPA, Dioxin
Neurological	Neurobehavioral development	BPA, Phthalate
Cardiovascular	Cardiovascular disease	BPA, Phthalate

Table adapted from Diamanti-Kandarakis et al. [71] and Rochester 2013 [87]. Abbreviations: BPA: Bisphenol/DDT: dichlorodiphenyltrichloroethane/PCBs: polychlorinated biphenyls/DES: diethylstilbestrol.

compounds is that there is no exposure to only one ED but rather exposure to a mixture of compounds with additive or synergistic effects. The effect is not linearly dose-dependent; the dose effect is similar to the letter U, with minimal doses capable of having identical effects as higher doses, which makes the understanding of the mechanism a challenge for researchers [71,86]. Several EDs behaves like xenoestrogens due to reproductive disorders, such as the reduction of sperm count and the induction of reproductive tract anomalies, breast cancer, asthma, type II diabetes, cardiovascular disorders, obesity, and thyroid disorders (Table 2) [70,87]. These compounds bind ERα and ERβ nuclear estrogen receptors and the G1 protein-coupled estrogen receptor (GPER), which is a membrane receptor, to initiate cell signaling. However, recent studies have revealed the presence of other nuclear receptors involved with EDs that share some common features, although there are differences in structure, signaling pathways, cell specificity, and functional outcomes [80]. These compounds could interfere with lacrimal film homeostasis because they are related to tissue hormonal, vascular and neurological dysregulation. All of these mechanisms are known to be associated with tear film homeostasis disruption [17,88].

EDs in the environment

As mentioned earlier, EDs are present in our daily lives, and we are exposed to these compounds by air, water and food. One of the most researched EDs is Bisphenol A (BPA), whose estrogenic effects were reported for the first time in 1936 [89]. BPA is a disruptor with known activity on estrogen receptors binding to estrogen receptors ERα and ERβ by influencing the transcription of estrogen-sensitive genes via altering the homeostasis of affected tissues [85,90]. Additionally, BPA acts via alternative routes, such as estrogen-related receptor-gamma (ERR-γ), aryl hydrocarbon receptor (AhR), or G-protein coupled membrane receptors [91,92]. BPA also acts as an antagonist of the thyroid hormone, has antiandrogenic activity and causes changes in DNA methylation (epigenetic effect) [93,94]. Epidemiological studies have related BPA exposure to diseases, such as cancer, diabetes, obesity, cardiac, reproductive, renal, respiratory, thyroid gland and autoimmune diseases [87]. Although BPA is widely researched and its exposure is associated with several pathologies, studies specifically relating exposure to BPA and eye diseases are not known.

Other significant EDs are present in many personal hygiene and cosmetic formulations, such as triclosan (TCS) and parabens. TCS is a compound with antimicrobial activity introduced into the environment in the 1970s by the health and beauty care industry to be used as an ingredient in disinfectants, soaps, detergents, toothpaste, mouthwashes, shampoos and plastic additives [95,96]. TCS has been considered an ED because of its demonstrated estrogenic and androgenic activity in animal studies [97]. In vitro studies have determined that TCS not only functions as an agonist of estrogen receptors but also alters the production of this hormone [98–100]. In cell culture, TCS activate a cation channel named TRPA1 (transient receptor potential ankyrin 1) [101]. The presence of TRPA1 in the cornea indicates that TCS and BPA may present synergic actions in the OS and take part in allergic diseases and other processes related to corneal wound healing [102,103].

Parabens are esters of parahydroxybenzoic acid (p-HBA) that, due to their chemical characteristics, show broad spectrum antibacterial activity, great stability in different pH and temperature environments and a low level of systemic toxicity [104]. Human exposure to parabens occurs via a transdermal route because they are rapidly absorbed through the skin during use or ingested through water and food [105,106]. The most significant effects, including immune system dysfunction and reproductive and behavioral disorders, occur due to the estrogenic effects of parabens [71]. Parabens and other EDs work through the activation of ERα, ERβ and ERRγ receptors [107–109]. Some parabens exhibit antiandrogenic activity, binding to androgen receptors and causing the inhibition of testosterone-induced transcription [110]. The imbalance between estrogenic and androgenic hormone action promoted by chronic exposure to parabens may be involved in the perpetuation of a pro-inflammatory status of LG and other OS glands and tear film quality loss, triggered by different causes. However, this hypothesis deserves a controlled experiment for confirmation.

Benzophenones (BP) are also used in cosmetics and hygiene preparations, especially in sunscreens. Through several in vitro and in vivo assays, the effects of BPs as EDs, acting on estrogenic, androgenic, progesterone and thyroid hormone receptors, were shown [111–113]. Benzophenone 3 (BP-3) is an essential compound of this class and is used worldwide as a UV filter in formulations for use on the skin and hair [114–117]. BP-3 has been reported as an ED with an affinity for ERα and ERβ receptors [118,119]. BP-3 also triggered antiestrogenic and antiandrogenic activities in various in vitro tests [117,118]. These antiandrogenic and antiestrogenic effects may participate in the pathophysiology and overall increased incidence of DED in the elderly population in the developed world in recent decades [4,87]. Herbicides, such as paraquat (PQ) and glyphosate, can also act as EDs. PQ is a quaternary nitrogen herbicide that can produce reactive oxygen species (ROS), which function in oxidative stress [120,121]. The continuous production of ROS and the ability to carry out the lipid peroxidation of cell membranes cause morphological changes in various organs, such as the kidneys, liver, brain and adrenal glands [122]. Exposure to PQ may cause damage to the OS in chronic or acute exposure, showing a clinical presentation similar to cicatricial pemphigoid, as reported in recent cases, or increase the potential for allergic conjunctivitis, as demonstrated in an experimental study [40,42,44,123,124]. Mice models of oxidative damage-induced retinal degeneration were induced with PQ injection into the vitreous cavity. The ROS produced by this herbicide caused progressive retinal damage [125].

Glyphosates are currently the most heavily applied herbicides in the world and are widely used in a great range of cultures. [126,127]. Studies suggest that even at doses considered safe for humans, glyphosates can induce damage to the liver and kidney and have carcinogenic and teratogenic effects, although its carcinogenic power is controversial [128,129]. Glyphosate, even at low concentrations, disrupts the aromatase enzyme in human cells in vitro and causes damage in the synthesis of estrogens, and formulations of glyphosate have been shown to disrupt aromatase activity in human liver cells [130–132]. In a study reported by De Liz Oliveira Cavalli and coworkers (2013),

Table 3
Animal and human studies with increased (estrogen treatment) or decreased estrogen levels (ovariectomy, estrogen absence, and anti-estrogen administration).

	Estrogen increased	Estrogen decreased
Lacrimal gland regression	Identified	Identified
Lacrimal gland histology	_	No effect
Glandular tissue	_	Downward
DNA and RNA levels	Upward	_
DNA degradation	Downward	_
Gene expression (numerous genes)	Altered	Altered
Total activity of β-adrenergic receptors	Upward	Downward
Total activities of cholinergic receptors & Naþ, Kþ-ATPase	Downward	Downward
Acid & alkaline phosphatase activities	Downward	Downward
Total protein content	No effect	Altered
Membrane-bound protein content	_	Altered
20 kDa protein content	Downward	Altered
Inflammation	Upward	
Tear output	Upward	Upward (Male only)
Dry eye improvement	Identified	
Dry eye development	Negative impact	Negative impact

Table adapted from: Sullivan et al., 2017 [6]

Wistar rats exposed to a low dose (0.036 g/L) of glyphosate showed induced oxidative stress [133]. The adrenal gland can also be affected by glyphosate inhibitory effects on the hypothalamic-pituitary axis, reducing the synthesis of corticosterone [134]. These hormone effects indicate the need for investigations of how the chronic exposure to glyphosate impacts OS and tear film homeostasis.

Eye diseases and hormones

Hormone deprivation, excess or malfunction can cause or contribute to the severity of ocular diseases (Table 3) [17]. The classic association between corticosteroids and glaucoma or cataracts and between statins and cataracts are the best-known examples of OD caused by excess hormones [135–138]. In Diabetes Mellitus type 2, insulin resistance is an example of hormone malfunction that may induce dysfunctions of the retina, lens, cornea and LG due to impairments of insulin intracellular signaling due to hyperglycemic chronic exposure and the dysfunction of supportive systems, such as the vascular, immune and nervous systems [139–142]. Among these problems are the early onset of cataracts, diabetic retinopathy and dry eye [143–145]. The deprivation of thyroid hormone (TH) and other hormones, such as growth hormone (GH), are associated with DED [14,17]. Sex hormones at normal levels are associated with OD predisposition, as several of diseases show sex bias prevalence, including the frequent DED and macular hole, which are both more frequent in women [17]. The assumption that sex hormones and no other sexual factors are driving this bias is based on the observation that in aging, when the sex hormones decline, the prevalence of the diseases equalizes [146,147]. In addition, in animal models that mimic DED, castration or cross hormone treatment equalizes markers of disease manifestation, including inflammatory cell infiltration [11,148,149].

Considering all these facts, it is reasonable to propose that environmental compounds in our daily life activities, as described above, may work as EDs and contribute to ocular problems related to DED and OS inflammation. These chemical compounds may act directly because ocular tissues have hormone receptors and EDs may bind to them. EDs can also function indirectly, affecting the lacrimal functional unit comprising the OS, LG, annex tissues and neural tissues and their links to the sensorial and autonomic central nervous system, which are ultimately supported by the neuroimmune endocrine network [150–152]. The increased prevalence of DED in women has been associated with changes in estrogen levels in ocular tissues, where this hormone modulates the expression of several genes and the function and secretion of LG, MG and other tissues [20,153]. The EDs can also affect the target tissues by changing the gene expression towards pro-inflammatory and other effects that may bring prejudice to the optimal function and homeostasis of the OS.

Endocrine disruptors can be harmful to the eyes

The chemical compounds discussed in this article represent a minority of the extensive universe of EDs present in the environment. The exposure leads to damage because the EDs interact with receptors of living beings due to structural similarities with hormones, which cause damage to the homeostasis of tissues and organs. A British physician developed the first synthetic estrogen, diethylstilbestrol, in 1938. This estrogenic compound was used by thousands of pregnant women between the ages of 40 and 7 to prevent abortion and decrease nausea but was abandoned because this drug mimicked natural estrogen, causing abnormalities in the reproductive tract of the offspring of mothers who used this medication [60]. In the 1960s, the book Silent Spring, considered a milestone, in the history of environmental pollution and the author Rachel Carson drew attention to the effects on the reproductive system of fishes exposed to pesticides, such as DDT (dichlorodiphenyltrichloroethane) [154].

The book also reports Canadian studies in which fish exposed to DDT have experienced blindness due to lens opacity. Studies of compounds that mimic hormones have increased, as shown by the number of articles published in PubMed with the word “endocrine disrupters” in the last five years (2013 to 2017), with 4163 articles in this database alone. Due to the advances of research that permeate several fields of knowledge, the study of the mechanism of action in vitro and in vivo, the effects on living organisms, the detection processes and the methods of removal from water bodies, was partially clarified.

Concerning exposure to EDs in humans and their possible harmful effects, studies have addressed a positive correlation between exposure and reproductive, metabolic, developmental, and thyroid function disorders, as seen in a recent review [87]. However, no studies have correlated exposure to EDs and DED. The fact that the inflammatory condition that causes dry eye results from an imbalance of the estrogen and androgen sex hormones and the high levels of pro-inflammatory cytokines, tumoral necrosis factor and interleukins suggests that there could be a relationship between the increasing exposure to environmental contaminants and the growing number of DED cases in recent years. Estrogen and androgen receptors are present in the LG and MG, and these hormones cause a pro-inflammatory state that alters the normal functioning of the entire OS system [19]. Oxidative stress has been implicated in the protective and pathogenic mechanisms of dry eye and OS disease [155–157] and that exposure to Eds, such as BPA, for example, acts as an inducer of oxidative stress in animals [158–160]. Several studies have demonstrated that sex hormones have a high influence on meibomian gland function by regulating gene expression and lipid production [19,160,161]. TCS is an ED that alters lipid production in tissues in addition to inducing oxidative stress, which could lead to functional damage in the MG exposed to TCS. In a study in which zebrafish were exposed to the BPA substitute Bisphenol S, the authors observed morphological abnormalities in the retinal tissue that seriously compromised the visual behavior of this species [162].

The answer to the question of whether exposure to EDs can be related to DED or other ocular diseases mediated by hormones is far from simple because there are numerous factors involved in the mechanism of action of EDs and numerous doubts regarding the etiology of DED. Initially, we must acknowledge that we not exposed to only one ED but to a set of these compounds, which makes it more difficult to understand how their effects occur in a given organism. Another relevant factor is that the exposure varies according to the lifestyle of each

subject [72]. The fact that EDs do not have a normal dose-response curve and act even in small doses amplifies this challenge. Experimental and in vitro tests usually only analyze one ED and rarely examine a set of EDs, and these compounds have synergism that may exacerbate their effects when associated [106]. Despite the growing number of studies related to the mechanism of the action of EDs, there are still many gaps to be elucidated. Research indicates that the period in which the individual is exposed at an intrauterine phase, for example, interferes with the type and intensity of the deleterious effects caused [163,164]. Classical effects have been detected and shown as those mentioned above. There is great difficulty in avoiding such exposure. The EDs are present in our daily lives in hygiene and beauty products and in the foods we consume and the water that we drink. Our own body is a source of EDs because we excrete hormones and metabolites of drugs that cannot be removed from the water because our water and sewage treatment systems are not designed for this purpose. The problem with ED removal occurs in many countries including developed countries. The whole world suffers from the presence of these compounds in the aquatic environment. It is evident that water has the power of self-purification, but every day, the population grows, increasing the consumption of industrialized products and the amount of chemicals used for animal and food production. In this context, water self-purification power is not enough and taking into account the ED bioaccumulation power, this fact becomes even more worrying.

Conclusion

The comparative analysis of the growing effects of many chemical products that act as EDs in the metabolism of body organs and systems, confronted with the increasing frequency of DED and OS diseases, indicates the need to better investigate the potential relationships beyond the isolated associations mentioned by patients and documented as rare case reports. The evidence from case-control studies and experimental assays can provide the information necessary to confirm the hypotheses concerning the endocrine effects of those chemicals on the pathophysiology of the DED and OS diseases.

Acknowledgements

The authors would like to acknowledge the following Brazilian public agencies for financial support: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (2014-23211-0), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (32355-2017-0), Coordenação de Pessoal de Nível Superior (CAPES) (Finance code 001) e Fundação de Apoio ao Ensino, Pesquisa e Assistência do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (FAEPA).

Financial support

CAPES, CNPq, FAPESP, FAEPA

Conflict of interest statement

The authors declare no conflict of interest.

References

[1] Wolffsohn JS, Arita R, Chalmers R, Djalilian A, Dogru M, Dumbleton K, et al. TFOS DEWS II diagnostic methodology report. Ocul Surf 2017;15(3):539–74.
[2] Schein OD, Hochberg MC, Munoz B, Tielsch JM, Bandeen-roche K, Provost T, et al. Dry eye and dry mouth in the elderly. Arch Intern Med 1999;159:1359–63.
[3] Muñoz B, West SK, Rubin GS, Schein OD, Quigley HA, Bressler SB, et al. Causes of blindness and visual impairment in a population of older Americans: the salisbury eye evaluation study. Arch Ophthalmol 2000;118(6):819–25.
[4] Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, et al. TFOS DEWS II epidemiology report. Ocul Surf 2017 Jul 1;15(3):334–65.
[5] de Castro JS, Selegatto IB, de Castro RS, Miranda ECM, de Vasconcelos JPC, de Carvalho KM, et al. Prevalence and Risk Factors of self-reported dry eye in Brazil using a short symptom questionnaire. Sci Rep 2018;8(1):2076.
[6] Brayer JB, Cha S, Nagashima H, Yasunari U, Lindberg A, Diggs S, et al. IL-4-dependent effector phase in autoimmune exocrinopathy as defined by the NOD.IL-4-gene knockout mouse model of Sjögren's syndrome. Scand J Immunol 2001;54(1–2):133–40.
[7] Kuo CF, Grainge MJ, Valdes AM, See LC, Luo SF, Yu KH, et al. Familial risk of Sjögren's syndrome and co-aggregation of autoimmune diseases in affected families: a nationwide population study. Arthritis Rheumatol 2015;67(7):1904–12.
[8] Fujita M, Igarashi T, Kurai T, Sakane M, Yoshino S, Takahashi H. Correlation between dry eye and rheumatoid arthritis activity. Am J Ophthalmol 2005;140(5):808–13.
[9] Manoussakis MN, Georgopoulou C, Zintzaras E, Spyropoulou M, Stavropoulou A, Skopouli FN, et al. Sjögren's syndrome associated with systemic lupus erythematosus: clinical and laboratory profiles and comparison with primary Sjögren's syndrome. Arthritis Rheum 2004;50(3):882–91.
[10] Tseng CC, Yen JH, Tsai WC, Ou TT, Wu CC, Sung WY, et al. Increased incidence of Sjogren's syndrome in systemic sclerosis: A nationwide population study. Autoimmunity 2015;48(7):438–44.
[11] Versura P, Campos EC. Menopause and dry eye. A possible relationship. Gynecol Endocrinol 2005;20(5):289–98.
[12] Sato EH, Sullivan DA. Comparative influence of steroid-hormones and immunosuppressive agents on autoimmune expression in lacrimal glands of a female mouse model of Sjogrens-syndrome. Invest Ophthalmol Vis Sci 1994;35(5):2632–42.
[13] Scuderi G, Contestabile MT, Gagliano C, Iacovello D, Scuderi L, Avitabile T. Effects of phytoestrogen supplementation in postmenopausal women with dry eye syndrome: a randomized clinical trial. Can J Ophthalmol 2012;47(6):489–92.
[14] Rocha EM, Mantelli F, Nominato LF, Bonini S. Hormones and dry eye syndrome: an update on what we do and don't know. Curr Opin Ophthalmol 2013;24(4):348–55.
[15] Sullivan DA, Sullivan BD, Ullman MD, Rocha EM, Krenzer KL, Cermak JM, et al. Androgen influence on the meibomian gland. Invest Ophthalmol Vis Sci 2018;41(12):3732–42.
[16] Wickham LA, Gao J, Toda I, Rocha EM, Ono M, Sullivan DA. Identification of androgen, estrogen and progesterone receptor mRNAs in the eye. Acta Ophthalmol Scand 2000;78(2):146–53.
[17] Sullivan DA, Rocha EM, Aragona P, Clayton JA, Ding J, Golebiowski B, et al. TFOS DEWS II sex, gender, and hormones report. Ocul Surf 2017;15(3):284–333.
[18] Schröder A, Abrar DB, Hampel U, Schicht M, Paulsen F, Garreis F. In vitro effects of sex hormones in human meibomian gland epithelial cells. Exp Eye Res 2016;151:190–202.
[19] Sullivan DA, Sullivan BD, Evans JE, Schirra F, Yamagami H, Liu M, et al. Androgen deficiency, Meibomian gland dysfunction, and evaporative dry eye. Ann N Y Acad Sci 2002;966:211–22.
[20] Richards SM, Liu M, Jensen RV, Schirra F, Yamagami H, Lombardi MJ, et al. Androgen regulation of gene expression in the mouse lacrimal gland. J Steroid Biochem Mol Biol 2005;96(5):401–13.
[21] Song X, Zhao P, Wang G, Zhao X. The effects of estrogen and androgen on tear secretion and matrix metalloproteinase-2 expression in lacrimal glands of ovariectomized rats. Investig Ophthalmol Vis Sci 2013;55(2):745–51.
[22] Sullivan DA. Tearful relationships? Sex, hormones, the lacrimal gland, and aqueous-deficient dry eye. Ocul Surf 2004;2(2):92–123.
[23] Konttinen YT, Fuellen G, Bing Y, Porola P, Stegaev V, Trokovic N, et al. Sex steroids in Sjögren's syndrome. J Autoimmun 2012;39(1–2):49–56.
[24] Azzarolo AM, Eihausen H, Schechter J. Estrogen prevention of lacrimal gland cell death and lymphocytic infiltration. Exp Eye Res 2003;77(3):347–54.
[25] Ploc I, Stárka L. Testosterone binding in the cytosol of bovine corneal epithelium. Exp Eye Res 1979;28(1):111–9.
[26] Lanthier A, Patwardhan VV. Sex steroids and 5-en-3β-hydroxysteroids in specific regions of the human brain and cranial nerves. J Steroid Biochem 1986;25(3):445–9.
[27] Suzuki T, Schirra F, Richards SM, Treister NS, Lombardi MJ, Rowley P, et al. Estrogen's and progesterone's impact on gene expression in the mouse lacrimal gland. Investig Ophthalmol Vis Sci 2006;47(1):158–68.
[28] Sullivan DA, Jensen RV, Suzuki T, Richards SM. Do sex steroids exert sex-specific and/or opposite effects on gene expression in lacrimal and meibomian glands? Mol Vis 2009;15(June):1553–72.
[29] Casals-Casas C, Desvergne B. Endocrine disruptors: from endocrine to metabolic disruption. Annu Rev Physiol 2011;73(1):135–62.
[30] Kinch CD, Ibhazehiebo K, Jeong J-H, Habibi HR, Kurrasch DM. Low-dose exposure to bisphenol A and replacement bisphenol S induces precocious hypothalamic neurogenesis in embryonic zebrafish. Proc Natl Acad Sci 2015;112(5):1475–80.
[31] Ma Y, Xia W, Wang DQ, Wan YJ, Xu B, Chen X, et al. Hepatic DNA methylation modifications in early development of rats resulting from perinatal BPA exposure contribute to insulin resistance in adulthood. Diabetologia 2013;56(9):2059–67.
[32] Santangeli S, Maradonna F, Gioacchini G, Cobellis G, Piccinetti CC, Dalla Valle L, et al. BPA-induced deregulation of epigenetic patterns: effects on female Zebrafish reproduction. Sci Rep 2016;6(February):1–11.
[33] Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR, Lee DH, et al. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. Endocr Rev 2012;33(3):378–455.
[34] World Health Organization, Damstra T, Barlow S, Bergman A, Kavlock R, Van der Kraak G. Chapter 1: Executive Summary. Int Progr Chem Safety Glob Assess Endocrine-disrupting Chem 2002:1–4.
[35] Bila DM, Dezotti M. Desreguladores endócrinos no meio ambiente: efeitos e conseqüências. Quim Nova 2007 Jun;30(3):651–66.

[36] Asonye CC, Bello ER. The blight of pollution keratoconjunctivitis among children in oil-producing industrial areas of Delta State, Nigeria. Ecotoxicol Environ Saf. 2004;59(2):244–8.
[37] Novaes P, Hilário do Nascimento Saldiva P, Matsuda M, Macchione M, Peres Rangel M, Kara-José N, et al. The effects of chronic exposure to traffic derived air pollution on the ocular surface. Environ Res 2010;110(4):372–4.
[38] Torricelli AAM, Novaes P, Matsuda M, Alves MR, Monteiro MLR. Efeitos adversos na superfície ocular relacionados à poluição ambiental. Arq Bras Oftalmol 2011;74(5):377–81.
[39] Berra M, Galperín G, Dawidowski L, Tau J, Márquez I, Berra A. Impact of wildfire smoke in Buenos Aires, Argentina, on ocular surface. Arq Bras Oftalmol 2015;78(2):110–4.
[40] Jung SJ, Mehta J, Tong L. Effects of environment pollution on the ocular surface. Ocul Surf 2018;16(2):198–205.
[41] Vlahos K, Goggin M, Coster D. Paraquat causes chronic ocular surface toxicity. Aust N Z J Ophthalmol 1993;21(3):187–90.
[42] Miyata M, Namba T, Li G, Aoki S, Abe M, Ishikawa S. Environmental chemicals and experimental allergic conjunctivictis. J Toxicol Sci 1996;21(1):57–9.
[43] McKeag D, Maini R, Taylor HR. The ocular surface toxicity of paraquat [1]. Br J Ophthalmol 2002;86(3):350–1.
[44] Milczarek R, Sokołowska E, Rybakowska I, Kaletha K, Klimek J. Paraquat inhibits progesterone synthesis in human placental mitochondria. Placenta 2016;43:41–6.
[45] Avery N, Lahood B, Covello A, Allbon D. Ocular exposure to paraquat resulting in keratopathy, pseudomembranous conjunctivitis and symblepharon. N Z Med J 2017;130(1456):83–5.
[46] Alves M, Novaes P, de Andrade Morraye M, Reinach PS, Rocha EM. Is dry eye an environmental disease? Arq Bras Oftalmol 2014;77(3):193–200.
[47] Are W. Transient receptor potential (TRP) cation channels. Br J Pharmacol 2009;158(2):S148–55.
[48] Zhang F, Yang H, Wang Z, Mergler S, Liu H, Kawakita T, Tachado DS, et al. Transient receptor potential in corneal epithelium through inflammatory cytokine release vanilloid 1 activation induces MAPK signalingo. J Cell Physiol 2007;213:730–9.
[49] Reinach P, Pokorny K. The corneal epithelium: clinical relevance of cytokine-mediated responses to maintenance of corneal health. Arq Bras Oftalmol 2008;71(6):80–6.
[50] Zheng Q, Ren Y, Reinach PS, Xiao B, Lu H, Zhu Y, et al. Reactive oxygen species 21 activated NLRP3 inflammasomes initiate inflammation in hyperosmolarity stressed human corneal epithelial cells and environment-induced dry eye patients. Exp Eye Res 2015;134:133–40.
[51] Gomes JAP, Azar DT, Baudouin C, Efron N, Hirayama M, Horwath-Winter J, et al. TFOS DEWS II iatrogenic report. Ocul Surf 2017;15(3):511–38.
[52] Li D-Q, Chen Z, Song XJ, Luo L, Pflugfelder SC. Stimulation of Matrix metalloproteinases by hyperosmolarity via a JNK pathway in human corneal epithelial cells. Investig Opthalmology Vis Sci 2004;45(12):4302.
[53] Hirata H, Rosenblatt MI. Hyperosmolar tears enhance cooling sensitivity of the corneal nerves in rats: Possible neural basis for cold-induced dry eye pain. Investig Ophthalmol Vis Sci 2014;55(9):5821–33.
[54] Marques DL, Alves M, Modulo CM, Da Silva LECM, Reinach P, Rocha EM. Lacrimal osmolaritu and ocular surface in experimental model of dry eye caused by toxicity. Rev Bras Oftalmol 2015;74(2):68–72.
[55] Handa RJ, Weiser MJ. Gonadal steroid hormones and the hypothalamo-pituitary-adrenal axis. Front Neuroendocrinol 2014;35(2):197–220.
[56] Weiser MJ, Handa RJ. Estrogen impairs glucocorticoid dependent negative feedback on the hypothalamic-pituitary-adrenal axis via estrogen receptor alpha within the hypothalamus. Neuroscience 2009;159(2):883–95.
[57] Payrits M, Sághy É, Cseko K, Pohóczky K, Bölcskei K, Ernszt D, et al. Estradiol sensitizes the transient receptor potential vanilloid 1 receptor in pain responses. Endocrinology 2017;158(10):3249–58.
[58] Kumar V, Sur VP, Guha R, Konar A, Hazra S. Estrogen modulates corneal nociception and maintains corneal homeostasis in rat eye. Cornea 2017;37(4):1.
[59] Bi RY, Meng Z, Zhang P, Wang XD, Ding Y, Gan YH. Estradiol upregulates voltage-gated sodium channel 1.7 in trigeminal ganglion contributing to hyperalgesia of inflamed TMJ. PLoS ONE 2017;12(6):1–19.
[60] Colborn T, Vom Saal FS, Soto AM. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. Environ Health Perspect 1993;101(5):378–84.
[61] Maqbool F, Mostafalou S, Bahadar H, Abdollahi M. Review of endocrine disorders associated with environmental toxicants and possible involved mechanisms. Life Sci 2016;145:265–73.
[62] Kabir ER, Rahman MS, Rahman I. A review on endocrine disruptors and their possible impacts on human health. Environ Toxicol Pharmacol 2015;40(1):241–58.
[63] Crain DA, Janssen SJ, Edwards TM, Heindel J, Ho S Mei, Hunt P, et al. Female reproductive disorders: the roles of endocrine-disrupting compounds and developmental timing. Fertil Steril 2008;90(4):911–40.
[64] Sifakis S, Androutsopoulos VP, Tsatsakis AM, Spandidos DA. Human exposure to endocrine disrupting chemicals: effects on the male and female reproductive systems. Environ Toxicol Pharmacol 2017;51:56–70.
[65] Byford JR, Shaw LE, Drew MGB, Pope GS, Sauer MJ, Darbre PD. Oestrogenic activity of parabens in MCF7 human breast cancer cells. J Steroid Biochem Mol Biol 2002;80:49–60.
[66] Main KM, Kiviranta H, Virtanen HE, Sundqvist E, Tuomisto JT, Tuomisto J, et al. Flame retardants in placenta and breast milk and cryptorchildism in newborn boys. Environ Health Perspect 2007;115(10):1519–26.
[67] Tsutsumi O. Assessment of human contamination of estrogenic endocrine-disrupting chemicals and their risk for human reproduction. J Steroid Biochem Mol Biol 2005;93(2–5):325–30.
[68] Adlercreutz H, Bannwart C, Wähälä K, Mäkelä T, Brunow G, Hase T, et al. Inhibition of human aromatase by mammalian lignans and isoflavonoid phytoestrogens. J Steroid Biochem Mol Biol 1993;44(2):147–53.
[69] Castro B, Sánchez P, Torres JM, Preda O, del Moral RG, Ortega E. Bisphenol a exposure during adulthood alters expression of aromatase and 5α-reductase isozymes in rat prostate. PLoS ONE 2013;8(2):1–7.
[70] Nohynek GJ, Borgert CJ, Dietrich D, Rozman KK. Endocrine disruption: fact or urban legend? Toxicol Lett 2013;223(3):295–305.
[71] Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, et al. Endocrine-disrupting chemicals: an endocrine society scientific statement. Endocr Rev 2009;30(4):293–342.
[72] Correia CC, Fontoura M. A influência da exposição ambiental a disruptores endócrinos no crescimento e desenvolvimento de crianças e adolescentes. Rev Port Endocrinol Diabetes e Metab 2015;10(2):1–7.
[73] Monneret C. What is an endocrine disruptor? Comptes Rendus – Biol 2017;340(9–10):403–5.
[74] Chen CY, Wen TY, Wang GS, Cheng HW, Lin YH, Lien GW. Determining estrogenic steroids in Taipei waters and removal in drinking water treatment using high-flow solid-phase extraction and liquid chromatography/tandem mass spectrometry. Sci Total Environ 2007;378(3):352–65.
[75] Folmar LC, Hemmer M, Hemmer R, Bowman C, Kroll K, Denslow ND. Comparative estrogenicity of estradiol, ethynyl estradiol and diethylstilbestrol in an in vivo, male sheepshead minnow (Cyprinodon variegatus), vitellogenin bioassay. Aquat Toxicol 2000;49(1–2):77–88.
[76] Gagné F, Blaise C, Salazar M, Salazar S, Hansen PDD, Gagne F, et al. Evaluation of estrogenic effects of municipal effluents to the freshwater mussel Elliptio complanata. Comp Biochem Physiol Part C Toxicol Pharmacol 2001;128(2):213–25.
[77] Liu ZHua, Kanjo Y, Mizutani S. Removal mechanisms for endocrine disrupting compounds (EDCs) in wastewater treatment – physical means, biodegradation, and chemical advanced oxidation: a review. Sci Total Environ 2009;407(2):731–48.
[78] Dodson RE, Nishioka M, Standley LJ, Perovich LJ, Brody JG, Rudel RA. Endocrine disruptors and asthma-associated chemicals in consumer products. Environ Health Perspect 2012;120(7):935–43.
[79] Lintelmann J, Katayama A, Kurihara N, Shore L, Wenzel A. Endocrine disruptors in the environment (IUPAC Technical Report). Pure Appl Chem 2003;75(5):631–81.
[80] Kiyama R, Wada-Kiyama Y. Estrogenic endocrine disruptors: molecular mechanisms of action. Environ Int 2015;83:11–40.
[81] Welshons WV, Thayer KA, Judy BM, Taylor JA, Curran EM, vom Saal FS. Large effects from small exposures. I. Mechanisms for endocrine-disrupting chemicals with estrogenic activity. Environ Health Perspect 2003;111(8):994–1006.
[82] De Coster S, Van Larebeke N. Endocrine-disrupting chemicals: associated disorders and mechanisms of action. J Environ Public Health. 2012;2012:52.
[83] Rajesh P, Balasubramanian K. Phthalate exposure in utero causes epigenetic changes and impairs insulin signalling. J Endocrinol 2014;223(1):47–66.
[84] Janesick A, Blumberg B. Endocrine disrupting chemicals and the developmental programming of adipogenesis and obesity. Birth Defects Res Part C – Embryo Today Rev 2011;93(1):34–50.
[85] Polyzos SA, Kountouras J, Deretzi G, Zavos C, Mantzoros CS. The emerging role of endocrine disruptors in pathogenesis of insulin resistance: a concept implicating nonalcoholic fatty liver disease. Curr Mol Med 2012;12(1):68–82.
[86] vom Saal FS, Akingbemi BT, Belcher SM, Birnbaum LS, Crain DA, Eriksen M, et al. Chapel Hill bisphenol A expert panel consensus statement: Integration of mechanisms, effects in animals and potential to impact human health at current levels of exposure. Reprod Toxicol 2007;24(2):131–8.
[87] Rochester JR. Bisphenol A and human health: A review of the literature. Reprod Toxicol 2013;42:132–55.
[88] Bron AJ, de Paiva CS, Chauhan SK, Bonini S, Gabison EE, Jain S, et al. TFOS DEWS II pathophysiology report. Ocul Surf. 2017;15(3):438–510.
[89] Flint S, Markle T, Thompson S, Wallace E. Bisphenol A exposure, effects, and policy: a wildlife perspective. J Environ Manage 2012;104:19–34.
[90] Vandenberg LN, Maffini MV, Sonnenschein C, Rubin BS, Soto AM. Bisphenol-a and the great divide: a review of controversies in the field of endocrine disruption. Endocr Rev 2009;30(1):75–95.
[91] Rubin BS. Bisphenol A: an endocrine disruptor with widespread exposure and multiple effects. J Steroid Biochem Mol Biol 2011;127(1–2):27–34.
[92] Krüger T, Long M, Bonefeld-Jørgensen EC. Plastic components affect the activation of the aryl hydrocarbon and the androgen receptor. Toxicology 2008;246(2–3):112–23.
[93] Kitamura S, Suzuki T, Sanoh S, Kohta R, Jinno N, Sugihara K, et al. Comparative study of the endocrine-disrupting activity of bisphenol A and 19 related compounds. Toxicol Sci 2005;84(2):249–59.
[94] Rosenmai AK, Dybdahl M, Pedersen M, van Vugt-Lussenburg BMA, Wedebye EB, Taxvig C, et al. Are structural analogues to bisphenol a safe alternatives? Toxicol Sci 2014;139(1):35–47.
[95] Fang JL, Stingley RL, Beland FA, Harrouk W, Lumpkins DL, Howard P. Occurrence, efficacy, metabolism, and toxicity of triclosan. J Environ Sci Heal - Part C Environ Carcinog Ecotoxicol Rev 2010;28(3):147–71.
[96] Dann AB, Hontela A. Triclosan: Environmental exposure, toxicity and mechanisms of action. J Appl Toxicol 2011;31(4):285–311.
[97] Matsumura N, Ishibashi H, Hirano M, Nagao Y, Watanabe N, Shiratsuchi H, et al. Effects of nonylphenol and triclosan on production of plasma vitellogenin and testosterone in male South African Clawed Frogs (Xenopus laevis). Biol Pharm Bull 2005;28(9):1748–51.
[98] Zorrilla LM, Gibson EK, Jeffay SC, Crofton KM, Setzer WR, Cooper RL, et al. The effects of triclosan on puberty and thyroid hormones in male wistar rats. Toxicol

Sci 2009;107(1):56–64.
[99] Ishibashi H, Matsumura N, Hirano M, Matsuoka M, Shiratsuchi H, Ishibashi Y, et al. Effects of triclosan on the early life stages and reproduction of medaka Oryzias latipes and induction of hepatic vitellogenin. Aquat Toxicol 2004;67(2):167–79.
[100] Stoker TE, Gibson EK, Zorrilla LM. Triclosan exposure modulates estrogen-dependent responses in the female wistar rat. Toxicol Sci 2010;117(1):45–53.
[101] Derouiche S, Mariot P, Warnier M, Vancauwenberghe E, Bidaux G, Gosset P, et al. Activation of TRPA1 channel by antibacterial agent triclosan induces vegf secretion in human prostate cancer stromal cells. Cancer Prev Res 2017;10(3):177–87.
[102] Acosta MC, Luna C, Quirce S, Belmonte C, Gallar J. Changes in sensory activity of ocular surface sensory nerves during allergic keratoconjunctivitis. Pain 2013;154(11):2353–62.
[103] Okada Y, Reinach P, Shirai K, Kitano-Izutani A, et al. Transient receptor potential channels and corneal stromal inflammation. Cornea 2015;34(11):S136–41.
[104] Soni MG, Carabin IG, Burdock GA. Safety assessment of esters of p-hydroxybenzoic acid (parabens). Food Chem Toxicol 2005;43(7):985–1015.
[105] Karpuzoglu E, Holladay SD, Gogal RM. Parabens: potential impact of low-affinity estrogen receptor binding chemicals on human health. J Toxicol Environ Heal – Part B Crit Rev. 2013;16(5):321–35.
[106] Błedzka D, Gromadzińska J, Wasowicz W. Parabens. From environmental studies to human health. Environ Int 2014;67:27–42.
[107] Darbre PD, Harvey PW. Paraben esters: review of recent studies of endocrine toxicity, absorption, esterase and human exposure, and discussion of potential human health risks. J Appl Toxicol 2008:561–78.
[108] Watanabe Y, Kojima H, Takeuchi S, Uramaru N, Ohta S, Kitamura S. Comparative study on transcriptional activity of 17 parabens mediated by estrogen receptor α and β and androgen receptor. Food Chem Toxicol 2013;57:227–34.
[109] Wang L, Wu Y, Zhang W, Kannan K. Characteristic profiles of urinary p -hydroxybenzoic acid and its esters (Parabens) in children and adults from the United States and China. Environ Sci Technol 2013;47(4):2069–76.
[110] Satoh K, Nonaka R, Ohyama K, Nagai F. Androgenic and antiandrogenic effects of alkylphenols and parabens assessed using the reporter gene assay with stably transfected CHO-K1 Cells (AR-EcoScreen System). J Heal Sci. 2005;51(5):557–68.
[111] Schlumpf M, Cotton B, Conscience M, Haller V, Steinmann B, Lichtensteiger W. In vitro and in vivo estrogenicity of UV screens. Environ Health Perspect 2001;109(3):239–44.
[112] Morohoshi K, Yamamoto H, Kamata R, Shiraishi F, Koda T, Morita M. Estrogenic activity of 37 components of commercial sunscreen lotions evaluated by in vitro assays. Toxicol Vitr 2005;19(4):457–69.
[113] Schmutzler C, Bacinski A, Gotthardt I, Huhne K, Ambrugger P, Klammer H, et al. The ultraviolet filter benzophenone 2 interferes with the thyroid hormone axis in rats and is a potent in vitro inhibitor of human recombinant thyroid peroxidase. Endocrinology 2007;148(6):2835–44.
[114] Fent K, Kunz PY, Gomez E. UV Filters in the Aquatic Environment Induce Hormonal Effects and Affect Fertility and Reproduction in Fish. Chim Int J Chem 2008;62(5):368–75.
[115] Heneweer M, Muusse M, Van Den Berg M, Sanderson JT. Additive estrogenic effects of mixtures of frequently used UV filters on pS2-gene transcription in MCF-7 cells. Toxicol Appl Pharmacol 2005;208(2):170–7.
[116] Kunz PY, Galicia HF, Fent K. Comparison of in vitro and in vivo estrogenic activity of UV filters in fish. Toxicol Sci 2006;90(2):349–61.
[117] Schreurs R, Lanser P, Seinen W, Van der Burg B. Estrogenic activity of UV filters determined by an in vitro reporter gene assay and an in vivo transgenic zebrafish assay. Arch Toxicol 2002;76(5–6):257–61.
[118] Molina-Molina JM, Escande A, Pillon A, Gomez E, Pakdel F, Cavaillès V, et al. Profiling of benzophenone derivatives using fish and human estrogen receptor-specific in vitro bioassays. Toxicol Appl Pharmacol 2008;232(3):384–95.
[119] Schreurs RHMM, Sonneveld E, Jansen JHJ, Seinen W, van der Burg B. Interaction of polycyclic musks and UV filters with the estrogen receptor (ER), androgen receptor (AR), and progesterone receptor (PR) in reporter gene bioassays. Toxicol Sci 2005;83(2):264–72.
[120] Suntres ZE. Role of antioxidants in paraquat toxicity. Toxicology 2002;180(1):65–77.
[121] Bus JS, Gibson JE. Paraquat: Model for oxidant-initiated toxicity. Environ Health Perspect 1984;55:37–46.
[122] Abdollahi M, Ranjbar A, Shadnia S, Nikfar S, Rezaie A. Pesticides and oxidative stress: a review. Med Sci Monit 2004;10(6):141–7.
[123] Joyce M. Ocular damage caused by Paraquat. Br J Ophthalmol 1969;53(10):688–90.
[124] Miyata M, Namba T, Li G, Aoki S, Abe M, Ishikawa S. Environmental chemicals and experimental allergic conjunctivitis. J Toxicol Sci 1996;21(1):57–9.
[125] Eriksson M, Taskinen M, Leppä S. Mitogen activated protein kinase-dependent activation of c-Jun and c-Fos is required for neuronal differentiation but not for growth and stress response in PC12 cells. J Cell Physiol 2006;207(1):12–22.
[126] Thongprakaisang S, Thiantanawat A, Rangkadilok N, Suriyo T, Satayavivad J. Glyphosate induces human breast cancer cells growth via estrogen receptors. Food Chem Toxicol 2013;59:129–36.
[127] Myers JP, Antoniou MN, Blumberg B, Carroll L, Colborn T, Everett LG, et al. Concerns over use of glyphosate-based herbicides and risks associated with exposures: a consensus statement. Environ Heal A Glob Access Sci Source 2016;15(1):1–13.
[128] Séralini GE, Clair E, Mesnage R, Gress S, Defarge N, Malatesta M, et al. Republished study: long-term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize. Environ Sci Eur 2014;26(1):1–17.
[129] Mesnage R, Arno M, Costanzo M, Malatesta M, Séralini GE, Antoniou MN. Transcriptome profile analysis reflects rat liver and kidney damage following chronic ultra-low dose Roundup exposure. Environ Heal A Glob Access Sci Source 2015;14(1):1–14.
[130] Richard S, Moslemi S, Sipahutar H, Benachour N, Seralini GE. Differential effects of glyphosate and roundup on human placental cells and aromatase. Environ Health Perspect 2005;113(6):716–20.
[131] Romano MA, Wisniewski P, Viau P, Romano RM, Campos DA, Bernardi MM, et al. Glyphosate impairs male offspring reproductive development by disrupting gonadotropin expression. Arch Toxicol 2012;86(4):663–73.
[132] Gasnier C, Dumont C, Benachour N, Clair E, Chagnon MC, Séralini GE. Glyphosate-based herbicides are toxic and endocrine disruptors in human cell lines. Toxicology 2009;262(3):184–91.
[133] De Liz Oliveira Cavalli VL, Cattani D, Heinz Rieg CE, Pierozan P, Zanatta L, Benedetti Parisotto E, et al. Roundup disrupts male reproductive functions by triggering calcium-mediated cell death in rat testis and Sertoli cells. Free Radic Biol Med 2013;65:335–46.
[134] Pandey A, Rudraiah M. Analysis of endocrine disruption effect of Roundup® in adrenal gland of male rats. Toxicol Rep 2015;2:1075–85.
[135] El Afrit M-A, Mazlout H, Trojet S, Larguech L, Megaieth K, Belhaj S, et al. Glaucome cortisonique: étude épidémiologique, clinique et thérapeutique. J Fr Ophtalmol 2007;49–52.
[136] Leuschen J, Mortensen EM, Frei CR, Mansi EA, Panday V, Mansi I. Association of statin use with cataracts a propensity score-matched analysis. JAMA Ophthalmol 2013;131(11):1427–34.
[137] Phulke S, Kaushik S, Kaur S, Pandav SS. Steroid-induced glaucoma: an avoidable irreversible blindness. J Curr glaucoma Pract. 2017;11(2):67–72.
[138] Renfro L, Snow JS. Ocular effects of topical and systemic steroids. Dermatol Clin 1992;10(3):505–12.
[139] Azar DT, Gipson IK. Repair of the corneal epithelial adhesion structures following keratectomy wounds in diabetic rabbits. Acta Ophthalmol 1989;67(192 S):72–9.
[140] Jeganathan VSE, Wang JJ, Wong TY. Ocular associations of diabetes other than diabetic retinopathy. Diabetes Care 2008;31(9):1905–12.
[141] Módulo CM, Jorge AG, Dias AC, Braz AM, Bertazolli-Filho R, Jordão AA, et al. Influence of insulin treatment on the lacrimal gland and ocular surface of diabetic rats. Endocrine 2009;36(1):161–8.
[142] Wang T-J, Wang I-J, Hu C-C, Lin H-C. Comorbidities of dry eye disease: a nationwide population-based study. Acta Ophthalmol 2012;90(7):663–8.
[143] Stevens VJ, Rouzer CA, Monnier VM, Cerami A. Diabetic cataract formation: potential role of glycosylation of lens crystallins. Proc Natl Acad Sci USA 1978;75(6):2918–22.
[144] Reeves BC. Evidence about evidence. Br J Ophthalmol 2005;89(3):253–4.
[145] Murat D. Tear secretion and tear function in insulin dependent diabetics. Br J Ophthalmol 2000;84(10):1210.
[146] Moss SE, Klein R, Klein BEK. Long-term incidence of dry eye in an older population. Optom Vis Sci 2008;85(8):668–74.
[147] Craig JP, Nelson JD, Azar DT, Belmonte C, Bron AJ, Chauhan SK, et al. The ocular surface tfos dews ii report executive summary. TFOS DEWS II Rep Exec Summ 2017;15(3):1–11.
[148] Sato HE, Ariga H, Sullivan DA. Impact of androgen therapy in Sjogren's syndrome: hormonal influence on lymphocyte populations and la expression in lacrimal glands of MRL/Mp-lpr/lpr Mice. Invest Ophthalmol 1992;33(8):2537–45.
[149] Rocha FJ, Sato EH, Sullivan BD, Sullivan DA. Comparative efficacy of androgen analogues in suppressing lacrimal gland inflammation in a mouse model (MRLilpr) of sjogren's syndrome.In: Sullivan DA (eds) Lacrimal Gland, Tear Film, and Dry Eye Syndromes. Advances in Experimental Medicine and Biology.vol 350. Springer, Boston, MA; 1994:697–700.
[150] Kelleher RS, Hann LE, Edwards JA, Sullivan DA. Endocrine, neural, and immune control of secretory component output by lacrimal gland acinar cells. J Immunol 1991;146(10):3405–12.
[151] Wilder RL. Neuroendocrine-immune system interactions and autoimmunity. Annu Rev Immunol 1995;13(1):307–38.
[152] Stern ME, Gao J, Siemasko KF, Beuerman RW, Pflugfelder SC. The role of the lacrimal functional unit in the pathophysiology of dry eye. Exp Eye Res 2004;78(3):409–16.
[153] Richards SM, Yamagami H, Schirra F, Suzuki T, Jensen RV, Sullivan DA. Sex-related effect on gene expression in the mouse meibomian gland. Curr Eye Res 2006;31(2):119–28.
[154] Bonzi RS. Meio século de Primavera silenciosa: um livro que mudou o mundo. Desenvolv e Meio Ambient 2013;28:207–15.
[155] Rocha EM, Alves M, Rios JD, Dartt DA. The aging lacrimal gland: changes in structure and function. Ocul Surf 2008;6(4):162–74.
[156] Cejkova J, Cejka C. The role of oxidative stress in corneal diseases and injuries. Histol Histopathol 2015;30(8):893–900.
[157] Shoham A, Hadziahmetovic M, Dunaief JL, Mydlarski MB, Schipper HM. Oxidative stress in diseases of the human cornea. Free Radic Biol Med 2008;45(8):1047–55.
[158] Kabuto H, Hasuike S, Minagawa N, Shishibori T. Effects of bisphenol A on the metabolisms of active oxygen species in mouse tissues. Environ Res 2003;93(1):31–5.
[159] Wu M, Xu H, Shen Y, Qiu W, Yang M. Oxidative stress in zebrafish embryos induced by short-term exposure to bisphenol A, nonylphenol, and their mixture. Environ Toxicol Chem 2011;30(10):2335–41.
[160] Schirra F, Suzuki T, Richards SM, Jensen RV, Liu M, Lombardi MJ, et al. Androgen control of gene expression in the mouse meibomian gland. Investig Opthalmology Vis Sci 2005;46(10):3666.
[161] Schirra F, Richards SM, Liu M, Suzuki T, Yamagami H, Sullivan DA. Androgen regulation of lipogenic pathways in the mouse meibomian gland. Exp Eye Res

2006;83(2):291–6.
[162] Liu W, Wang W, Ru S. Long-term exposure to bisphenol S damages the visual system and reduces the tracking capability of male zebrafish (Danio rerio). J Appl Toxicol 2017:248–58.
[163] Selevan SG, Kimmel CA, Mendola P. Identifying critical windows of exposure for children's health. Environ Health Perspect 2000;108(SUPPL. 3):451–5.
[164] Anderson LM, Diwan BA, Fear NT, Roman E. Critical windows of exposure for children's health: cancer in human epidemiological studies and neoplasms in experimental animal models lucy. Environ Heal 2000;108:573–94.