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THE EFFECTS OF ENDOCRINE DISRUPTORS ON SOME VERTEBRATES

ABSTRACT

The studies about the histological effects of endocrine disruptor chemicals on vertebrates were presented and evaluated, and it was aimed to be summarized in such a way that it can generate resources for future studies. The available literatural information was arranged as review by revising in the direction of the researches in Kafkas University, Faculty of Arts and Sciences, Department of Biology Laboratories. Although the endocrine disruptor chemicals presence is tried to be limited at the ecosystem level, the extensive usage of this chemicals in various areas still continues. Many organisms are directly or indirectly exposed to the adverse effects of endocrine disruptor chemicals in this direction. In this review, histological changes occurring in vertebrates as a result of exposure to endocrine disruptor chemicals were investigated. It has been reported that different endocrine disruptor chemical types cause similar histopathological findings in vertebrates in the data obtained from investigations. In the context of the examined data, the effects of endocrine disruptors on some tissues seem to be more variable. Histopathology is a useful tool in endocrine disruptor studies and may provide information on the mechanism of endocrine disruptors that is sometimes unexpected.

Keywords: Endocrine Disruptors, Toxication, Histopathology, Vertebrates, Biology, Hormone

ENDOKRİN ENGELLEYİCİLERİN BAZI OMURGALILAR ÜZERİNDEKİ ETKİLERİ

ÖZ

Bu derlemede, endokrin bozucu kimyasalların omurgalılarda histolojik etkileri üzerine yapılan çalışmalar değerlendirilerek sunulup, gelecek çalışmalara kaynak sağlayacak şekilde özetlenmesi amaçlanmıştır. Elde edilebilen literatürel bilgiler, Kafkas Üniversitesi, Fen-Edebiyat Fakültesi, Biyoloji Bölümü Laboratuvarları'nda yapılan araştırmalar doğrultusunda gözden geçirilerek yeniden düzenlenmiştir. Endokrin bozucu kimyasalların varlığı ekosistem seviyesinde sınırlandırılmaya çalışılsa da, bu kimyasalların çeşitli alanlardaki yaygın kullanımı halen devam etmektedir. Birçok organizma doğrudan veya dolaylı olarak endokrin bozucu kimyasalların bu yöndeki olumsuz etkilerine maruz kalmaktadır. Bu derlemede, omurgalılarda endokrin bozucu kimyasallara maruz kalma sonucu ortaya çıkan histolojik değişiklikler araştırılmıştır. Araştırmalardan elde edilen verilerde, farklı endokrin bozucu kimyasal türlerin, omurgalılarda benzer histopatolojik bulgulara neden olduğu bildirilmiştir. İncelenen veriler bağlamında, bazı dokulardaki endokrin bozucuların etkileri daha değişken gibi gözükmektedir. Histopatoloji endokrin bozucu çalışmalarında faydalı bir araç olup, endokrin bozucuların mekanizması hakkında beklenmeyen bilgiler verebilir.

Anahtar Kelimeler: Endokrin Engelleyiciler, Toksikasyon, Histopatoloji, Biyoloji, Hormon

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1. INTRODUCTION

Endocrine disruptors are one of the external factors that have entered our life as a result of industrialization. Endocrine disruptors may interfere with endocrine process at several layers and may break the welfare status. A wide variety of chemicals can interact with the endocrine system, even at very low exposure levels. Alterations in development, changes in the reproductive system, decrease in fertility, changes in behavior in addition to changes in the brain, disorders of the immune system, and increase in the incidence of certain types of cancer such as endometriosis are major adverse effects of the endocrine disruptors caused in the organism. Some of prominent endocrine disruptors are industrial solvents (e.g. polychlorinated biphenyls and polybrominated biphenyls, phthalates, dioxin derivatives, and plastics), and pesticides (e.g. methoxychlor, chlorpyrifos, dichloro diphenyltrichloro ethane), and fungicides (e.g. vinclozolin) (Vos et al., 2000; Fox, 2001; Curtis and Skaar, 2002; Hale, 2012; Ertörer, 2013; Li et al., 2017).

The main concerns about endocrine disruptors are as follows:

- That endocrine disruptors may bring about negative health effects at even very low levels of exposure
- We are exposed to a wide variety of endocrine disruptors without being noticed and throughout our lives
- These chemicals are widely distributed around the environment and harm both humans and animals.

Below is a small list of common chemicals that are thought to interact with the endocrine system (Table 1; Hale, 2012).

Table 1. Potential endocrine disruptors (Hal, 2012)

Class	Chemical	Use
Pesticide	DDT	Insecticide (no longer allowed in US)
	2.4-D	Herbicide
	Atrazine	Herbicide
Plastics ingredients	Bisphenol-A	Hardener in plastics, building block for polycarbonate plastic
	Phthalates	Softener in plastics, solvent
Industrial chemical nonylphenol (Breakdown Product of Nonylphenol Ethoxylates)	Nonylphenol (Breakdown product of nonylphenol ethoxylates)	Detergents, paints, pesticides
Fire retardant	Polybrominated diphenyl	Fire retardant
	Ethers (PBDEs)	
Drug	Diethylstilbestrol (DES)	No longer used to prevent miscarriages
Contaminants	Dioxin	Byproduct PVC plastics, incineration byproduct, contaminant in certain chlorinated compounds
	Arsenic, Lead, Mercury	Widespread contaminants
	Polychlorinated biphenyls (PCBs)	Formerly used in transformer oils

There is increasing evidence that exposure to endocrine disruptors during development is dangerous. Early exposure to endocrine disruptor chemicals may cause cancer in later life (Birnbaum and Fenton, 2003). For example, animal and human investigations show that natural and synthetic estrogens can cause breast cancer in addition to vaginal cancers. Animal studies show that dioxin, an



environmental pollutant, can interact with the development of breast tissue and potentially bring about cancer (Ankley et al., 2001; Gray et al., 2002; Parrott and Wood, 2002; van der Oost et al., 2003; Vos et al., 2000; Hale, 2012). Another organ that is sensitive to endocrine disruptors, the thyroid glands and therefore the nervous system, begins to develop very early in pregnancy. Thyroid hormone production is regulated by a sensitive feedback system among the hypothalamus, pituitary, and thyroid gland. For normal brain development, brain cell growth and migration to affect the formation of connections between cells, and general functional development, thyroid hormone is indispensable. Reduced thyroid hormone, negatively affects all aspects of brain development. For proper development of hearing, normal thyroid function is also essential. A variety range of chemicals may be adversely interfere with thyroid hormone (Howdeshell, 2002), and there is an increased concern that early exposure to fetal and endocrine disruptors results in neurodevelopmental disorders (Zoeller, 2001; Schmutzler et al., 2007; Ahmed et al., 2008; Patrick, 2009; Jugan et al., 2010; Parent et al., 2011; Hale, 2012). By this review, it was aimed to summarize the available data and to constitute a source for further studies to be done by evaluating studies on the histopathological effects of bacteria, algae, fungus, plant and animal originated toxins on mammals which are contaminants of many materials worldwide and can cause both health effects and economic losses.

2. RESEARCH SIGNIFICANCE

Endocrine disruptors are exogenous chemicals, or mixture of chemicals, that can interfere with any aspect of hormone action. The developmental period at which endocrine disruptors exposures occur is a critical consideration in understanding their effects. In natural ecosystems, the various biological activities or the presence of endocrine disruptor chemicals in the nature of the organisms are important with regards to influencing the quality of life and health of the other organisms. In this context, the histopathological effects of the endocrine disruptor chemicals on some vertebrates as a strong indicator of the effects of endocrine disruptors have been assessed and interpreted by reviewing recent studies.

3. EXPERIMENTAL METHOD-PROCESS

The available literatural information was arranged as review by revising in the direction of the researches in Kafkas University, Faculty of Arts and Sciences, Department of Biology Laboratories.

4. RESULTS AND DISCUSSION

Histological changes can be used as sensitive tools to detect the direct toxic effects of various compounds and are considered good indicators of environmental stress (Schwaiger et al., 1997; Leino et al., 2005; Fontanetti et al., 2014). Histopathological studies play a supporting role by providing more information about possible mechanisms of action of pesticides on biomarkers at the cellular and molecular level and on non-target organisms (Miller-Morey and Dolah, 2004). Examination of gonadal histopathology is thought to be useful in understanding and assessing the effects of potential endocrine disrupting chemicals on fish and other organisms (Leino et al., 2005). In a research, the effects of bisphenol A (BPA) or 17 β -estradiol (E2) exposure on the liver and testis of *Cynoglossus semilaevis* were investigated. In particular, this research observed the pathological alterations in the liver (e.g., cellular swelling, hepatocyte adhesion, and vacuolation, etc.) and testis (e.g., cellular swelling,

sperm deformation, and flagellum bending, etc.). Results of the investigation revealed that exposure dose and response indicators are correlated with each other, and BPA or E2 exposure at different doses induces some degree of damage to *C. semilaevis* tissues on a histopathological level. Accordingly, this research provides a window for developing *C. semilaevis* as a model of marine fish in determining the effects of other kinds of pollutant exposure on the aquatic ecosystem and on humans (Figure 1-2; Li et al., 2017).

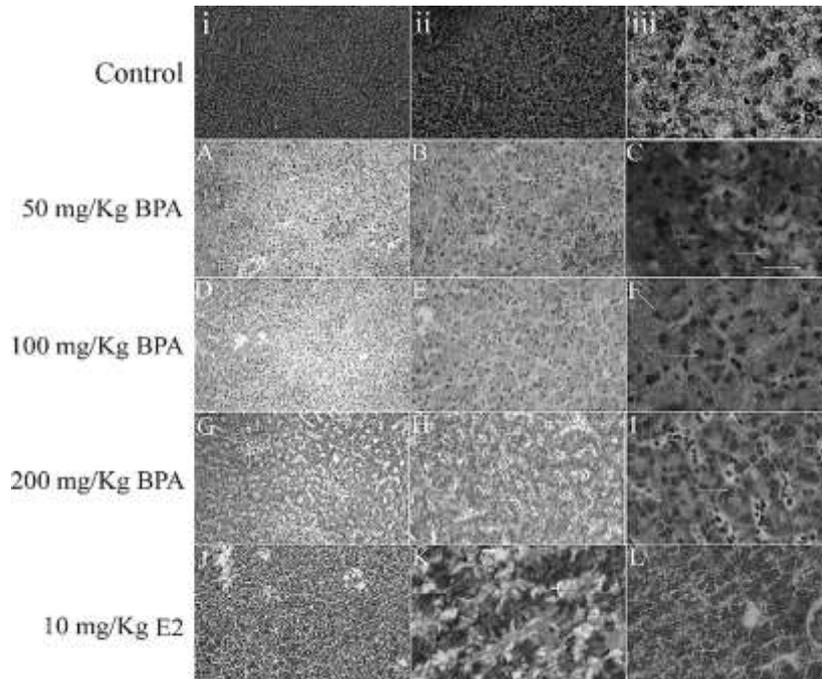


Figure 1. Normal liver of *C. semilaevis*: (i) hepatic plates with ordered arrangement, 200x; (ii) clear cell boundaries, 400x; (iii) vacuoles contained in some hepatocytes, 1000x. (A-L) Liver of *C. semilaevis* exposed to (A-C) 50 mg/kg BPA: (A) some hepatocytes with enlarged nucleus, 200x; (B) increased vacuoles in some hepatocytes, 400x; (C) vacuolation in separate hepatocytes, 1000x. (D-F) 100 mg/kg BPA: (D) enlarged blood sinusoids (BS), 200x; (E) swollen blood cells, 400x; (F) degenerated cytoplasm and deformed nuclei, 1000x. (G-I) 200 mg/kg BPA: (G) congested blood vessels, 200x; (H) swollen blood cells and enlarged blood sinusoids, 400x; (I) blurred cellular margins and irregular nuclei, 1000x. (J-L) 10 mg/kg E2: (J) necrosis of blood cells in blood vessels (arrow), 200x; (K) enlarged blood sinusoids (arrow) and vacuolar degeneration of hepatocytes (thick arrow), 400x; (L) adherent hepatocytes (arrow), 1000x (Li et al., 2017)

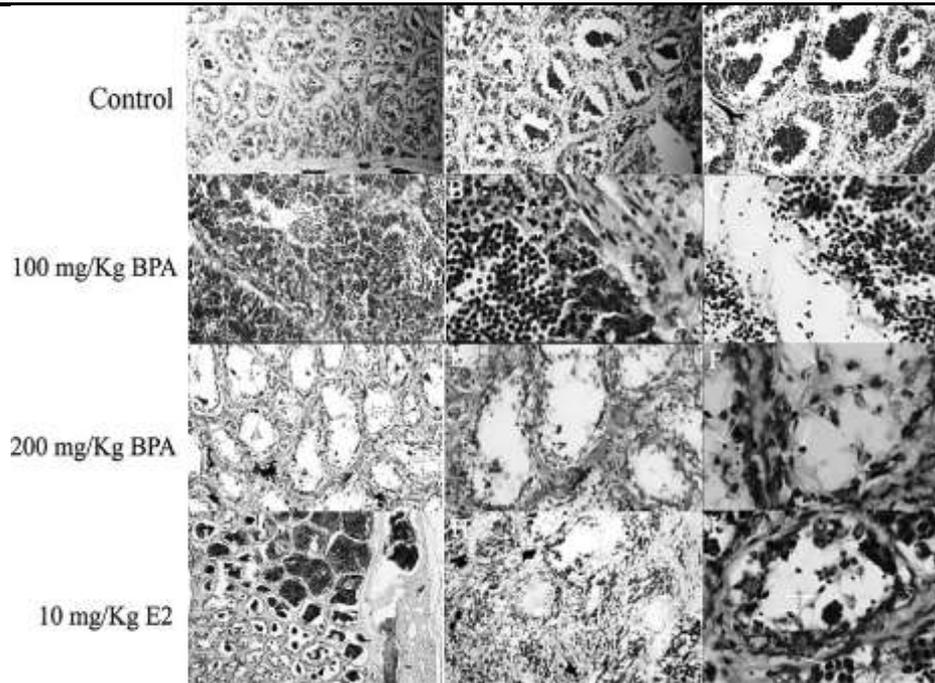


Figure 2. Normal testis of *C. semilaevis*: (i) seminiferous tubule with ordered arrangement, 100x; (ii) lobules and follicle in testis, 200x; (iii) spermatogonium (box), spermatocyte (arrow), and spermatid (thick arrow), 400x. (A-I) Testis of *C. semilaevis* exposed to (A-C) 100 mg/kg BPA: (A) oocytes (arrow), 400x; (B) dispersed nucleus (thick arrow) and swollen Sertoli cells (arrow), 1000x; (C) numerous sperms and fragmented tail (arrow), 1000x. (D-F) 200mg/kg BPA: (D) almost hollow lobule, 200x; (E) atrophy or degenerated Leydig cells, 400x; (F) dissolved cell membrane and deformed sperm, 1000x. (G-I) 10mg/kg E2: (G) dark colored, basophilic nuclei, 100x; (H) swollen cells and fragments, 400x; (I) enlarged nucleus and bending flagellum, 1000x (Li et al., 2017)

In the other research, adult male fish, *Cyprinus carpio carpio*, were exposed to three graded concentrations of BPA (10, 100 and 1000µg/L) for a period of 21 days, to evaluate the estrogenic effect of Bisphenol A (BPA). A single dose of 17-β estradiol (1ng/L) was used as positive control. The end points assessed at the end of the exposure period were condition factor, hepatosomatic index (HSI), gonadosomatic index (GSI), histopathological changes in the testis and lobular diameter. It was reported that BPA caused a significant decrease in gonadosomatic index (GSI) of the fish at the median concentration of 100µg/L. The major alterations observed in the gonad structure were a significant decrease ($p \leq 0.001$) in the lobular diameter ($65.1 \pm 12.2 \mu\text{m}$) compared with control ($211.7 \pm 36.60 \mu\text{m}$) and complete loss in lobular structure with degenerating spermatozoa in some carps. The histopathological effects also include delayed sperm maturation and impaired spermatogenesis. The findings clearly showed marked adverse histopathological effects of gonads of adult carps when exposed to BPA (Figure 3-4; Al-Sakran et al., 2016).

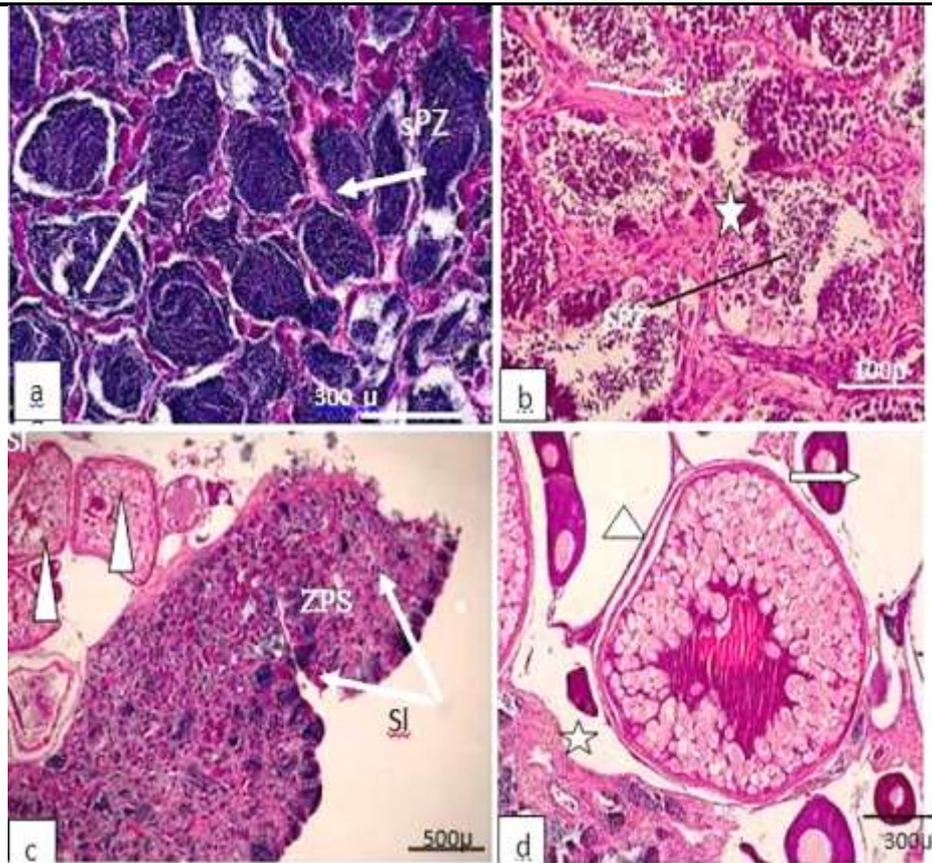


Figure 3. Photomicrographs of transverse sections of *C. carpio carpio* males from the control group and the group exposed to 10 µg/L of BPA. a) Testis (20x) of the control group with seminiferous lobules (Sl) filled with spermatozoa (SPZ). b) Testis (40x) of carp exposed to 10 µg/L of BPA. Notice atrophy of seminiferous tubules (Sl); a slight decrease in lobular diameter and increased perilobular connective tissue (star). c) Testis (20x) of carp exposed to 10 µg/L of BPA showing different stages of oocytes (arrowheads) in contact with the testis with seminiferous lobules (Sl). d) Higher magnification (100x) of the previous histological section focusing on the oocytes at different developmental stages. Notice Testis section (star), Vitellogenic stage of oocyte (arrowhead), Previtellogenic stage of oocyte (arrows) (Al-Sakran et al., 2016)

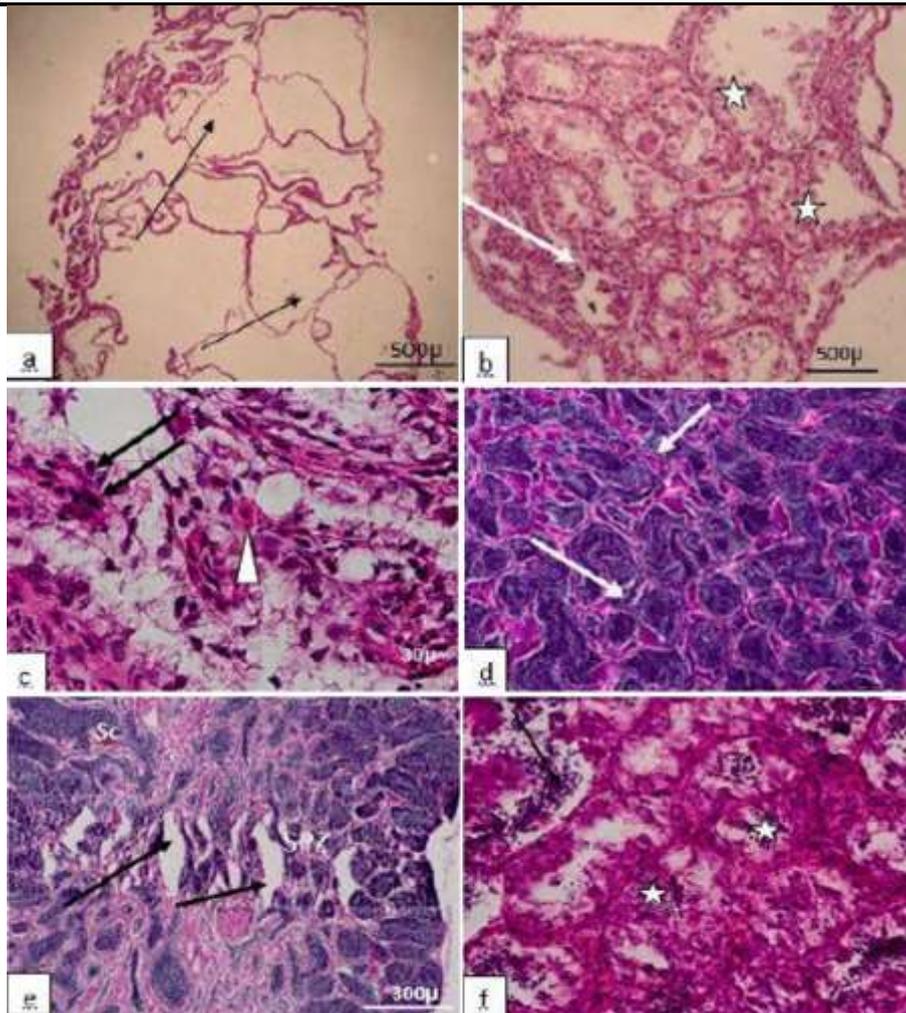


Figure 4. Photomicrographs of transverse sections of *C. carpio carpio* males from the groups exposed to 100µg/L, 1000µg/L of BPA and 1ng/L of E2. a) Testis (20x) of carp exposed to 100µg/L of BPA demonstrating acute testicular atrophy and vacuolated seminiferous lobules (arrows). b) Testis (40x) of another carp exposed to the same concentration, 100µg/L of BPA showing reduced lobular diameter, disintegration of the lobular structure (star), few residual spermatogonia (SPG) (arrows). c) Testis (100x) of carp exposed to 100µg/L of BPA showing pyknotic spermatogonia (arrows); presence of oogonia within the seminiferous lobules (arrowheads). d) Testis (20x) of carp exposed to 1000µg/L of BPA showing testicular organization; slightly reduced lobular diameter; spermatozoa (SPZ); spermatogenic cysts (SC). e) Testis (20x) of carp exposed to 1ng/L of E2 showing reduced lobular diameter; degeneration of seminiferous lobules (arrows). f) Higher magnification (40x) of the testis of carp exposed to the 1ng/L of E2 showing residual spermatogonia (arrows), distorted lobular structure (Sl) and degenerating germinal epithelium (star) (Al-Sakran et al., 2016)

In another research, in order to investigate the effects of Escravos crude oil on serum cholesterol, estradiol and progesterone in Chinchilla rabbits, a total of thirty female Chinchilla rabbits of age twelve to fourteen weeks and weighing 1.2 to 1.45kg were used. Crude oil was orally given at the dose of 15, 20, 25 and 30mg/kg body weight, corresponding to groups B, C, D and E, respectively for 28

days while group A was the Control. The results showed a significant increase in serum levels of estradiol, cholesterol and ovary weight ($p < 0.05$) while a significant decrease in serum level of progesterone ($p < 0.05$) was observed. The histological findings include: ovarian cysts, fibrosis, marked lymphocytic infiltrations and hydropic cells. Therefore, Escravos crude oil could be considered as a potential endocrine disruptor which can affect the tissue architecture and the endocrine functions of the ovary (Figure 5-9; Ogechukwu et al., 2014).

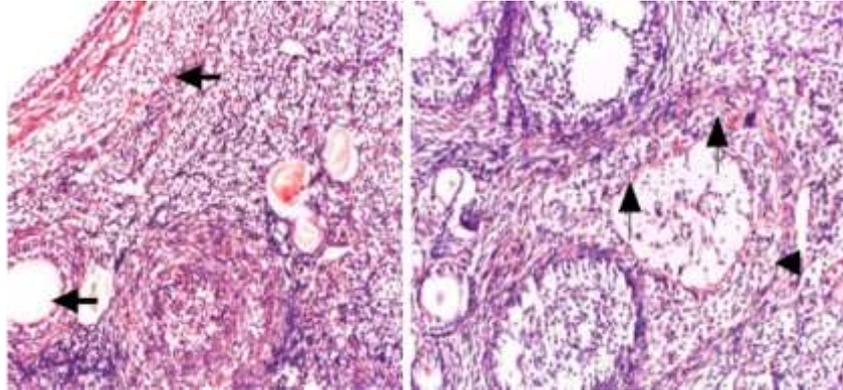


Figure 5. Group A (control): Ovarian section with a section of a developed (arrow at the top) and developing follicles (arrow head), HEx200 (Ogechukwu et al., 2014)

Figure 6. Group B (15mg/kg): Ovarian section with interlacing bundles of closely packed fibrocystic cell type with elongated spindle-shaped basophilic nuclei (arrows). The follicles are enlarged and cystic (arrow head), HEx200, Ogechukwu et al., 2014)

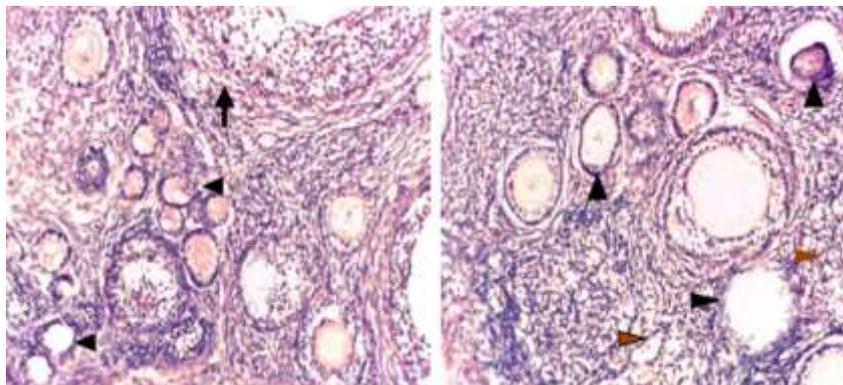


Figure 7. Group C (20mg/kg): Ovarian section with interlacing bundles of closely packed fibrocystic cell types with elongated spindle-shaped basophilic nuclei (arrow). Also observed are hydropic cells (brown arrow head) in some areas and multi-ovarian cysts (black arrow heads), HEx200 (Ogechukwu et al., 2014)

Figure 8. Group D (25mg/kg): Ovarian section with fibrocystic cell type and cystic spaces. Also observed are hydropic cells (brown arrow heads), HEx200, Ogechukwu et al., 2014)

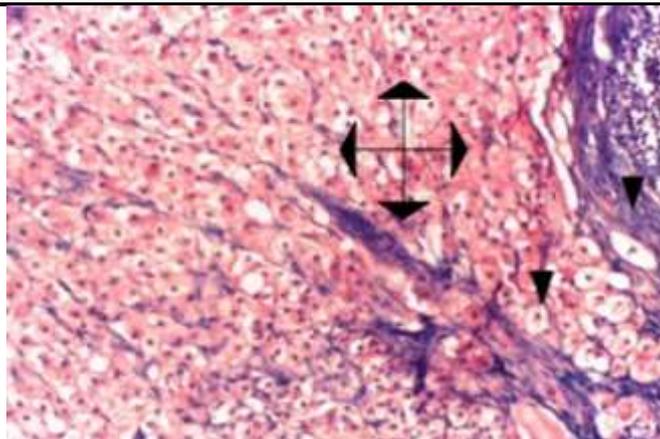


Figure 9. Group E (30mg/kg): Ovarian section with multi-hydronic cells (four black arrows) and fibrosis (black arrow heads), HEx200 (Ogechukwu et al., 2014)

5. CONCLUSIONS AND RECOMMENDATIONS

- Based on examined information, it has been determined that endocrine disrupter chemicals chosen can cause toxicity at different degrees depending on the amount of toxicity of the endocrine disrupter chemical the vertebrates are exposed to.
- And also toxicity increases in parallel with the amount of endocrine disrupter chemicals that is exposed and the exposure period.
- Additionally, it was reported that the effects may vary depending on the type of endocrine disrupter chemical.
- As a result, the research results evaluated are similar to each other.

NOTICE

This work is presented at 05-08 September 2017, 2nd International Science Symposium (ISS2017) in Tbilisi-Georgia.

REFERENCES

- Ahmed, O.M., El-Gareib, A.W., El-bakry, A.M., Abd El-Tawab, S.M, and Ahmed, R.G., (2008). Thyroid Hormones States and Brain Development Interactions. *International Journal of Developmental Neuroscience*, 26(2):147-209. doi: 10.1016/j.ijdevneu.2007.09.011.
- Al-Sakran, A.A.M., Virk, P., Elobeid, M., Hamed, S.S., Siddiqui, M.I., Omer, S., and Mirghani, N.M., (2016). Histopathological Effects on Testis of Adult Male Carp, *Cyprinus carpio carpio*, Following Exposure to Graded Concentrations of Water-Borne Bisphenol A. *Tropical Journal of Pharmaceutical Research*, 15(1):73-80. doi: 10.4314/tjpr.v15i1.10.
- Ankley, G.T., Jensen, K.M., Kahl, M.D., Korte, J.J., and Makynen, E.A., (2001). Description and Evaluation of a Short-term Reproduction Test with the Fathead Minnow (*Pimephales promelas*). *Environ. Toxicol. Chem.* 20, 1276-1290.
- Birnbaum, L.S. and Fenton, S.E., (2003). Cancer and Developmental Exposure to Endocrine Disruptors". *Environmental Health Perspectives*. 111(4), 389-396.
- Curtis, C. and Skaar, T., (2002). Ubiquitous and Dangerous. *Our Planet*, 24-26.



- Ertörer, (2013). Endokrin Engelleyiciler ve Reprodüktif Sistem Üzerindeki Etkileri (Endocrine Disruptors and Their Effects on Reproductive System). İç Hastalıkları Dergisi, 20, 113-119.
- Fontanetti, C.S., Cristofolletti, C.A., Pinheiro, T.G., Souza, T.S., and Pedro-Ester, J., (2014). Microscopy: Science, Technology, Applications and Education. In Microscopy as a Tool in Toxicological Evaluations A. Méndez-Vilas, J. Díaz (Eds.). p. 1001-1007. Formatex Research Center: Zurbaran, Spain.
- Fox, G.A., (2001). Effects of Endocrine Disrupting Chemicals on Wildlife in Canada: past, present, future. Water Qual. Res. J. Can. 36, 233-251.
- Gray Jr., L.E., Ostby, J., Wilson, V., Lambright, C., Bobseine, K., Hartig, P., Hotchkiss, A., Wolf, C., Furr, J., Price, M., Parks, L., Cooper, R.L., Stoker, T.E., Laws, S.C., Degitz, S.J., Jensen, K.M., Kahl, M.D., Korte, J.J., Makynen, E.A., Tietge, J.E., and Ankley, G.T., (2002). Xenoendocrine Disruptors-Tiered Screening and Testing: Filling Key Data Gaps. Toxicology 181-182, 371-382.
- Hale, R.C., (2012). A Small Dose of Endocrine Disruptors or an Introduction to the Health Effects of Endocrine Disruptors. Chapter: 17. In: A Small Dose Toxicology. Second edit. Maria M. Williams (Ed.). p:178-185. Healthy World Press; ISBN: 978-0-9833378-3-6.
- Howdeshell, K.L., (2002). A Model of the Development of the Brain as a Construct of the Thyroid System. Environmental Health Perspectives Supplements, 110(3). (Accessed date June 15, 2009).
- Jugan, M.L., Levi, Y., and Blondeau, J.P., (2010). Endocrine Disruptors and Thyroid Hormone Physiology. Biochemical Pharmacology, 79(7):939-947. doi: 10.1016/j.bcp.2009.11.006.
- Leino, R.L., Jensen, K.M., and Ankley, G.T., (2005). Gonadal Histology and Characteristic Histopathology Associated with Endocrine Disruption in the Adult Fathead Minnow (*Pimephales promelas*). Environmental Toxicology and Pharmacology, 19, 85-98. doi:10.1016/j.etap.2004.05.010.
- Li, F., Yao, L., Sun, W., Jiang, Y., Li, Z., and Zhai, Y., (2017). Histopathological Liver and Testis Alterations in Male Halfsmooth Tongue Sole (*Cynoglossus semilaevis*) Exposed to Endocrine Disruptors. Journal of Coastal Research, 1-6. doi: 10.2112/JCOASTRES-D-15-00244.1. ISSN:0749-0208.
- Miller-Morey, J.S. and Dolah, F.M.V., (2004). Differential Responses of Stress Proteins, Antioxidant Enzymes, and Photosynthetic Efficiency to Physiological Stresses in the Florida red tide Dinoflagellate, *Karenia brevis*. Comp. Biochem. Physiol. Part C: Toxicol. Pharmacol. 138:493-505.
- Ogechukwu, O.J., Ajuluchukwu, N.A., Ifedioranma, O.S., and Onyemelukwe Anulika Obianuju, O.A., (2014). Histopathological and Hormonal Disrupting Effects of Escravos Crude Oil on the Ovary of Chinchilla Rabbits. Journal of Toxicology and Environmental Health Sciences, 6(2):31-37., doi: 10.5897/JTEHS2013.0298.
- Parent, A.S., Naveau, E., Gerard, A., Bourguignon, J.P., Gary, L., and Westbrook, G.L., (2011). Early Developmental Actions of Endocrine Disruptors on the Hypothalamus, Hippocampus and Cerebral Cortex. J Toxicol Environ Health B Crit Rev. 2011; 14(5-7):328-345. doi:10.1080/10937404.2011.578556.



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- Parrott, J.L. and Wood, C.S., (2002). Fathead Minnow Lifecycle Tests for Detection of Endocrine-Disrupting Substances in Effluents. *Water Qual. Res. J. Can.* 37, 651-667.
 - Patrick, L.N.D., (2009). Thyroid Disruption: Mechanisms and Clinical Implications in Human Health. *Alternative Medicine Review*, 14(4), 326-346.
 - Schmutzler, C., Gotthardt, I., Hofmann, P.J., Radovic, B., Kovacs, G., Stemmler, L., Nobis, I., Bacinski, A., Mentrup, B. Ambrugger, P., Grüters, A., Malendowicz, L.K., Christoffel, J., Hubertus Jarry, H., Seidlovà-Wuttke, D., Wuttke, W., and Josef Köhrle, J., (2007). Endocrine Disruptors and the Thyroid Gland—A Combined *in Vitro* and *in Vivo* Analysis of Potential New Biomarkers. *Environmental Health Perspectives*, 115(Suppl. 1), 77-83.
 - Schwaiger, J., Wanke, R., Adam, S., Pawert, M., Honnen, W., and Triebkorn, R., (1997). The use of Histopathological Indicators to Evaluate Contaminant-Related Stress in Fish. *J. Aqua. Ecosyst. Stress Recovery*, 6, 75-86.
 - van der Oost, R., Beyer, J., and Vermeulen, N.P.E., (2003). Fish Bioaccumulation and Biomarkers in Environmental Risk Assessment: a Review. *Environ. Toxicol. Pharmacol.* 13, 57-149.
 - Vos, J.G., Dybing, E., Greim, H.A., Ladefoged, O., Lambre, C., Tarazona, J.V., Brandt, I., and Vethaak, A.D., (2000). Health Effects of Endocrinedisrupting Chemicals on Wildlife, with Special Reference to The European Situation. *Crit. Rev. Toxicol.* 30, 71-133.
 - Zoeller, R.T., (2001). Polychlorinated Biphenyls as Disruptors of Thyroid Hormone Action. Robertson and Hansen (Eds). The University Press of Kentucky. ISBN 0-8131-2226-0.