J. Fac. Pharm. Ankara / Ankara Ecz. Fak. Derg., 47(2): 408-419, 2023
Doi: 10.33483/jfpau.1217709

ORIGINAL ARTICLE / ÖZGÜN MAKALE

TOXIC EFFECTS OF AROCLOR 1254 ON RAT HEART AND THYROID AND MODIFYING ROLE OF SELENIUM STATUS

AROCLOR 1254'ÜN SIÇAN KALBİ VE TİROİT ÜZERİNDEKİ TOKSİK ETKİLERİ VE SELENYUM DÜZEYLERİNİN DEĞİŞTİRİCİ ROLÜ

Aylin BALCI ÖZYURT[1,2], Gizem ÖZKEMAHLI[2,3], Ünzile YAMAN[2,4], Ali AŞÇI[2,5], Murat KIZILGÜN[6], Pınar ERKEKOĞLU[2]*, Belma KOÇER-GÜMÜŞEL[7]*

[1]Bahçeşehir University, School of Pharmacy, Department of Toxicology, 34353, İstanbul, Turkey

[2]Hacettepe University, Faculty of Pharmacy, Department of Toxicology, 06100, Ankara, Turkey

[3]Erzincan Binali Yıldırım University, Faculty of Pharmacy, Department of Toxicology, 24100, Erzincan, Turkey

[4]İzmir Katip Çelebi University, Faculty of Pharmacy, Department of Toxicology, 35620, İzmir, Turkey

[5]Selçuk University, Faculty of Pharmacy, Department of Toxicology, 42130, Konya, Turkey

[6]University of Health Sciences, Gulhane Faculty of Medicine, Department of Clinical Biochemistry 06018, Ankara, Turkey

[7]Lokman Hekim University, Faculty of Pharmacy, Department of Toxicology, 06510, Ankara, Turkey

* **Corresponding Author / Sorumlu Yazar:** Belma Koçer-Gümüşel
e-mail / e-posta: belmagumusel@yahoo.com, **Phone / Tel.:** +905325009533
* **Corresponding Author / Sorumlu Yazar:** Pınar Erkekoğlu
e-mail / e-posta: erkekp@yahoo.com, **Phone / Tel.:** +905325151400

Submitted / Gönderilme : 12.12.2022
Accepted / Kabul : 28.01.2023
Published / Yayınlanma : 20.05.2023

ABSTRACT

Objective: *Polychlorinated biphenyls (PCBs) were very widely used in industrial products in past. These chemicals were banned in the 1970s due to their toxic effects. PCBs can still affect human health, as they are persistent in the environment. Aroclor 1254 (A1254) is a commercial PCB congener which was used in electrical transformers, fluorescent lighting fixtures and old appliances such as televisions or refrigerators. In this study, we aimed to evaluate the toxic effects of A1254 on heart and thyroid in male Sprague-Dawley rats. In addition, the modifying role of selenium status was also evaluated.*

Material and Method: *8-week-old male Sprague-Dawley (SD) rats were used in the experiment. The animals were separated randomly into 6 groups (n=6) as control; selenium supplemented (SeS); selenium deficient (SeD); A1254 exposed (A); selenium supplemented A1254 exposed (ASeS) and selenium deficient A1254 exposed (ASeD). A1254 was applied by gavage during the last 15 days of feeding period. Heart and thyroid weights and relative weights, plasma thyroid hormone levels, as well as thyroid and heart tissue oxidative/antioxidative parameters were evaluated.*

Result and Discussion: *Results showed that A1254 exposure and selenium deficiency caused oxidative stress on both heart and thyroid. Plasma fT3 and fT4 levels markedly changed in ASeD group. In conclusion, it can be stated that A1254 exposure can cause lead to oxidative/antioxidative imbalance in both thyroid and heart and can disrupt functioning of thyroid hormones. Selenium seems to have a modifying role in A1254 toxicity in both organs, the importance of which should be evaluated with further mechanistic experiments.*

Keywords: *Aroclor 1254, cardiotoxicity, oxidative stress, selenium, thyroid disorders*

ÖZ

Amaç: *Poliklorlu bifeniller (PCB'ler) geçmişte endüstriyel ürünlerde çok yaygın olarak kullanılmıştır. Bu kimyasallar, toksik etkileri nedeniyle 1970'lerde yasaklanmıştır. PCB'ler, çevrede kalıcı oldukları için insan sağlığını hala etkileyebilir. Aroclor 1254 (A1254), elektrik transformatörlerinde, fluoresan aydınlatma armatürlerinde ve televizyon veya buzdolabı gibi eski cihazlarda kullanılan ticari bir PCB türevidir. Bu çalışmada erkek Sprague-Dawley sıçanlarında A1254'ün kalp ve tiroid üzerindeki toksik etkilerinin değerlendirmesi amaçlanmıştır. Ayrıca selenyum durumunun düzenleyici rolü de değerlendirilmiştir.*

Gereç ve Yöntem: *Çalışmada 8 haftalık erkek Sprague-Dawley (SD) ratlar kullanılmıştır. Hayvanlar, kontrol grubu, selenyum suplemente grup (SeS); selenyum eksikliği olan grup (SeD); A1254 maruziyet grubu (A); selenyum suplemente A1254'e maruziyet grubu (ASeS) ve selenyum eksikliği olan A1254'e maruziyet (ASeD) olarak rastgele 6 gruba ayrıldı. A1254, beslenme sürecinin son 15 gününde uygulanmıştır. Kalp ve tiroid ağırlıkları ve bağıl ağırlıkları, plazma tiroid hormonu seviyeleri ve ayrıca tiroid ve kalp dokusu oksidatif/antioksidatif parametreleri değerlendirilmiştir.*

Sonuç ve Tartışma: *Sonuçlar, A1254 maruziyetinin ve selenyum eksikliğinin hem kalp hem de tiroit dokusunda oksidatif strese neden olduğunu göstermiştir. Plazma fT3 ve fT4 seviyeleri ASeD grubunda belirgin şekilde değişmştir. Sonuç olarak, A1254 maruziyetinin hem tiroit hem de kalpte oksidan/antioksidan dengesizliğe yol açabileceği ve tiroit hormonlarının işleyişini bozabileceği söylenebilir. Selenyum, her iki organda da A1254 toksisitesinde değiştirici bir role sahip olduğu görünmektedir ve bunun önemi daha ileri mekanistik deneylerle değerlendirilmelidir.*

Anahtar Kelimeler: *Aroklor 1254, kardiyotoksisite, oksidatif stress, selenyum, tiroit bozuklukları*

INTRODUCTION

Polychlorinated biphenyls (PCBs) belong to the class of "manmade halogenated aromatic hydrocarbon compounds" [1]. Since they are very stable substances in terms of chemical and physical structure, they are mainly used in the production of capacitors, transformers, hydraulic pumps, printing ink, paints, pesticides, and electrical insulation liquids [2].

Although most countries have banned the commercial production of PCBs since the 1970s, the compounds can still be detected in the environment [3]. Some researchers suggest that these compounds are still being used in the industry in developing countries while others suggest that their environmental persistence cause their presence in human and animal tissues and biological fluids. As PCBs are highly

lipophilic organic pollutants, they can accumulate and bioaccumulate in the food chain. Therefore, their body load increases due to increasing biological age in humans [4].

It has been determined by various studies that high levels of PCBs are found in water sources and soil samples in developing countries [5-7]. In various studies conducted in different countries, PCB concentrations in biological samples such as serum, breast milk, and adipose tissue indicates that human exposure exceeds the tolerable daily intake (TDI, 20 ng/kg body weight), which was determined by the World Health Organization (WHO) [8-11]. The threat posed by PCB accumulation in the environment leads to low-dose PCB toxicity as well as long-term human exposure. This phenomenon has received much attention among both environmental engineers and toxicologists as these compounds, which were banned years ago, are still a significant health threat today. PCB exposure may cause pathological effects, such as reproductive, neurological, endocrinologic, cardiovascular, and immunological disorders in both humans and animals [12-18].

Various studies have demonstrated that PCBs cause pathological changes in the thyroid gland and a decrease in serum thyroid hormone levels [19-23]. It has been observed that thyroid hormones increase in response to PCB exposure and this effect is sometimes followed by a decrease. Such effects usually depend on the type of PCB [24-25]. It is thought that the effects of PCBs on thyroid functions may be due to their structural similarity to thyroid hormones and their competing for binding to the same globulins in the blood [2,16,25,26].It is known that inflammation and oxidative stress in the thyroid gland may also play a role in thyroid hormone disorders and that PCBs may lead to inflammation and oxidative/antioxidative balance in multiple organs and systems [27,28].

Exposure to PCBs has been associated with different cardiac and circulatory pathologies such as heart failure, heart disease, atherosclerotic cardiovascular diseases and hypertension. Numerous epidemiological studies have found that exposure to PCBs, particularly dioxin-like (DL)-PCBs, is associated with an increased risk of cardiovascular disease [29-31].

Aroclor 1254 (A1254) was a highly used PCB congener. A1254 contains 54% chlorine by weight and contains 5 chlorines per biphenyl molecule [7,32]. Because Aroclors are composed of dozens of chlorinated PCB components, their biodegradation takes a very long time [33]. A1254 is known to have various toxic effects, including cardiac and thyroidal toxicities [34-37].

Selenium, an essential trace element, has important roles in many cellular processes in the human body, especially in the antioxidant and immune systems. Enzymes and proteins they have selenium as a component are called “selenoproteins”. Crucial proteins and antioxidant enzymes such as iodothyronine deiodinases, glutathione peroxidases, thioredoxin reductases, and selenoprotein P are all selenoproteins. Selenium supplementation is known to have a protective effect against the oxidative stress caused by physical, chemical and biological agents and selenium supplementation may be beneficial in chronic diseases at appropriate doses [38-41].

Our study aimed to evaluate the toxic effects of A1254 exposure on thyroid and heart in adult male Sprague-Dawley rats. The toxic effects of this PCB congener was determined by measuring oxidant/antioxidant parameters as well as plasma thyroid hormone levels. In addition, the modifying role of selenium status after A1254 exposure was evaluated.

MATERIAL AND METHOD

Chemicals and Kits

A1254 (purity 99%), alcohols, Tris, diethylenetriaminepentaacetic acid (DTPA), phenylmethanesulfonyl fluoride (PMSF), and BCA Protein Assay Kit were purchased from Sigma-Aldrich (St. Louis, MO). Total antioxidant capacity (TAOC), Malondialdehyde (MDA) and protein carbonyl assay kits were purchased from Cayman (Ann Arbor, MI). Rat thyroxine, T4 ELISA Kit was from Biomatik (Kitchener, Canada) and Rat Triiodothyronine (T3) ELISA Kit was from MyBioSource (Vancouver, Canada), respectively. All other chemicals were from Sigma-Aldrich.

Experimental Groups

3-week-old male Sprague-Dawley (SD) rats were obtained from the Laboratory of Experimental Animals at Hacettepe University. Six groups were randomly created (n=6 animals for each) and each

group was housed in polypropylene cages with stainless steel grid tops. The cages were kept in regulated humidity (at 50%), temperature (at 23°C), and 12-hour light/dark cycle. Every week body weights (bw) of the animals were measured. The feeding period lasted for five weeks and the animals had unlimited access to food and water. The experimental groups were as follows:
1-Control group was fed with normal rat diet (0.15 mg/kg Se) for 7 weeks.
2-Selenium supplemented (SeS) group was fed with selenium-supplemented diet (1 mg/kg Se) for 7 weeks.
3-Selenium deficient (SeD) group was fed with selenium-deficient diet (≤0.05 mg/kg Se) for 7 weeks.
4-Aroclor 1254 (A) group was fed with normal rat diet (0.15 mg/kg Se) for 7 weeks and received 10 mg/kg A1254 by gavage during the last 15 days of feeding period.
5-Selenium supplemented Aroclor 1254 (ASeS) group was fed with selenium-supplemented diet (1 mg/kg Se) for 7 weeks and received 10 mg/kg A1254 by gavage during the last 15 days of feeding period.
6-Selenium deficient Aroclor 1254(ASeD) group was fed with selenium-deficient diet (≤0.05 mg/kg Se) for 7 weeks and received 10 mg/kg A1254 by gavage during the last 15 days of feeding period.

Thyroid Hormone Levels

After decapitation, 5 ml blood samples were taken into heparinized tubes. Tubes were centrifuged at 3500 rpm for 10 min. Plasma samples were aliquoted and stored at -80^{o}C. fT3 levels were measured with a competitive ELISA kit and fT4 levels were determined by a quantitative sandwich ELISA kit.

Preparation of Tissue Homogenates

Teflon pestle homogenizer used for heart and thyroid homogenates 10% (w/v). Total homogenate in a volume of ice-cold buffer containing Tris (10 mM), diethylenetriaminepentaacetic acid (1 mM), and phenylmethanesulphonyl fluoride (1 mM; adjusted to pH 7.4). The supernatant's total antioxidant capacity (TAOC), malondialdehyde (MDA), and carbonyl concentrations were assessed after centrifugation at 1500 x*g*, 4 °C, for 10 min. The rest of the supernatants were recentrifugated at 9500 x*g*, 4°C for 20 min, and the antioxidant enzyme activities (SOD, CAT) were determined in the supernatant. All spectrophotometric measurements were performed using a spectrophotometer SpectraMax M2 (Molecular Devices, Sunnyvale, CA).

Determination of Antioxidant Enzyme Activities and Oxidative Stress Parameters

Catalase (CAT) activity was determined with the enzymatic decomposition of H_2O_2. One unit of CAT activity was defined as the amount of enzyme required to decompose 1 μmol H_2O_2 in one min was followed directly at 240 nm [42]. One unit of CAT activity was defined as the amount of enzyme required to decompose 1 μmol H_2O_2 in one min.

The total superoxide dismutase (total SOD) activity was determined by monitoring the auto-oxidation of pyrogallol at 420 nm [43]. One unit of total SOD activity was defined as the amount of enzyme required to inhibit the rate of pyrogallol auto-oxidation by 50%.

TAOC of experimental groups was evaluated with a commercial kit based on the ability of antioxidants in the sample to inhibit the oxidation of ABTS® (2,2'-Azino-di- [3-ethylben, followedulphonate]) to ABTS®•+ by metmyoglobin. The amount of ABTS®•+ produced can be monitored by reading the absorbance at 750 nm or 405 nm.

The carbonyl groups as the biomarker of protein oxidation were determined by a quantitative analysis of carbonyl groups is based on the formation of stable hydrazones after the derivatization of these groups with DNPH. Subsequently, the absorbance of the stable hydrazones formed is measured spectrophotometrically at 370 nm by "carbonyl assay kit".

MDA levels were measured as a biomarker of lipid peroxidation with a commercial kit. The basis of the Cayman kit used in the measurement is the reaction of malondialdehyde with thiobarbituric acid in acidic conditions and the color intensity of the pink compound formed is measured colorimetrically at 530 nm.

Total Protein Determination

Total protein measurement was performed using a commercial kit using the bicinchoninic acid (BCA) assay. This experiment is based on the spectrophotometric measurement of the absorbance of the purple complex formed by the reaction of BCA and Cu^{+2} ions and the Cu^{+1} ions formed as a result of the reaction of the protein in alkaline media, at 562 nm [44].

Statistical Analysis

The results were expressed as mean±standard deviation (SD). The differences among the groups were evaluated with Kruskal–Wallis one-way analysis of variance, followed by Mann–Whitney U test using a Statistical Package for Social Sciences Program (SPSS) version 17.0 (Chicago, IL). P values <0.05 were considered as statistically significant.

RESULT AND DISCUSSION

In our study, we determined the effects of A1254 exposure on heart and thyroid at different selenium status in rats. The results suggested that A1254 exposure may cause decrease in tissue weights, oxidative stress on organs, and hormonal disorders in rats. The results of this study can be discussed in five parts:

Heart Organ Weights

Heart weights in all study groups were lower than the control. In SeS and SeD groups, there were 8% and 18% decreases in heart weight while A group had 47% lower heart weight compared to control ($p<0.05$, all). ASeS group had 20% lower heart weight ($p>0.05$) while ASeD group has 21% decreased heart weight ($p<0.05$) vs. control (Figure 1A).

Relative heart weights in SeS (11%) and SeD (15%) groups were markedly lower than control while in A group there was 10% insignificant decrease vs. control group. Both ASeS (14%) and ASeD (11%) groups had significantly lower heart weights vs. control (Figure 1B).

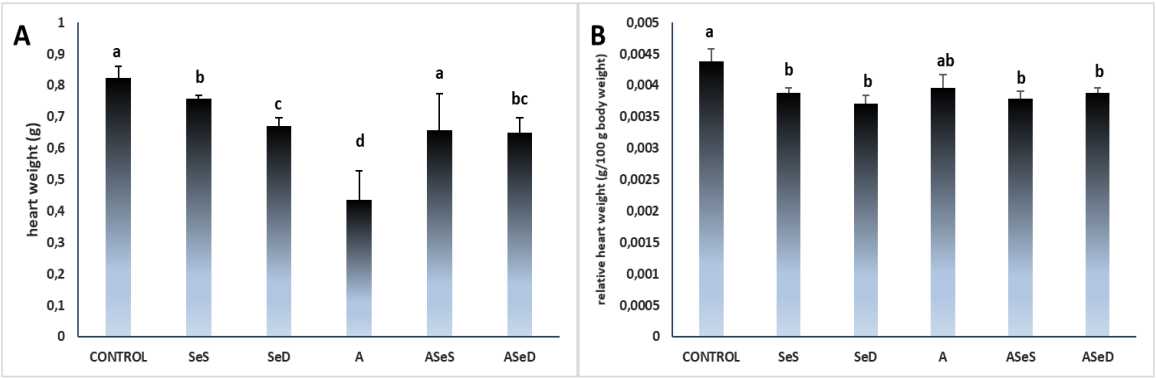

Figure 1. Heart and relative heart weights of groups.
A. Heart weights of groups; B. Relative heart weights of groups.
[a,b,c,d]Bars that do not share same letters (superscripts) are significantly different from each other ($p < .05$)

Wang et al. (2021) found that low dose (0.5 µg/kg and 50 µg/kg) PCB126 exposure caused an increase in relative heart weights. This increase is thought to be related to cardiac hypertrophy seen with low-dose exposure [45]. In our study, we can suggest that the inhibition of heart tissue development due to oxidative damage caused by high-dose A1254 exposure may be the underlying factor of lower heart and relative heart weights in A1254-exposed groups. Moreover, the decreases in heart and relative heart weights in selenium deficiency might be due to both increased cardiac oxidative stress and the lower antioxidant capacity of the heart tissue. In addition, other mechanisms yet to be identified might contribute to lower heart and relative heart weights in both selenium deficiency and/or A1254 exposure.

The contradiction between the results of our study and the study conducted by Wang et al. (2021) may be due to the difference in the PCB congeners.

Determination of Antioxidant Enzyme Activities and Oxidative Stress Parameters on Heart Tissue

Heart MDA levels in A group was higher than control (69%, $p<0.05$). There were no significant changes in MDA levels in other study groups (Fig 2A). Heart carbonyl levels in ASeD group was significantly higher than control (~2-fold). Carbonyl levels of SeD and A groups were higher vs. control group (46% and 27%, respectively; $p>0.05$, both) (Fig 2B). Heart TAOC levels in ASeD group was markedly lower than control (23%) (Fig 2C).

The results indicate that A1254 exposure leads to lipid peroxidation in heart. Heart carbonyl levels in the ASeD group were significantly higher than control (~2-fold). Although A1254 exposure alone does causes higher levels of protein oxidation and lower TAOC levels, the differences between A and control groups were not statistically significant for both of the measured parameters. These results suggest that selenium deficiency exacerbates the protein oxidation caused by A1254 exposure. All these results suggest that there is a deterioration in the oxidant/antioxidant balance in the heart tissue, particularly after A1254 exposure and selenium deficiency. The increase in CAT activity indicates the response of the organ to protect itself against the oxidative stress that occurs in the heart tissue with the application of A1254 in selenium deficiency. Several *in vivo* studies also suggest that different PCBs and PCB congeners lead to tissue damage, oxidative stress, disrupt the work of calcium and potassium channels and affect enzyme activities [46-50]. In studies conducted on humans, PCB exposure has been associated with important cardiac pathologies such as myocardial infarction, heart attack, coronary atherosclerosis and heart failure [31,51,52]. In addition, various studies show that selenium deficiency can have negative effects on cardiovascular health [40,53]. As selenium is the major component of glutathione peroxidases (GPxs), which are crucial antioxidant enzymes, the decrease in selenium levels mainly affects GPx activity. Lower GPx activity exacerbates endothelial dysfunction, a major contributing factor in the severity of chronic heart failure symptoms, in various conditions such as hyperhomocysteinemia. This suggests that homocysteine may be involved in the chronic heart failure associated endothelial dysfunction through a peroxide-dependent oxidative mechanism [54]. According to our results, it can be postulated that PCB toxicity may occur more predominantly in selenium deficiency and its consequences may be more pronounced.

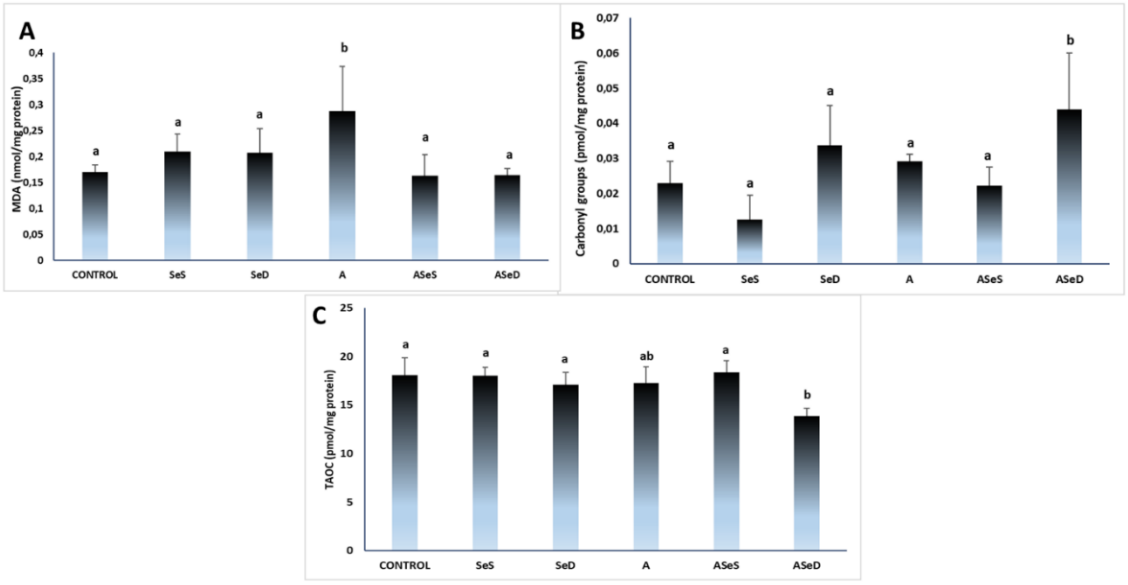

Figure 2. Heart oxidative stress parameters.
A. MDA levels in heart.; B. Carbonyl levels in heart; C. TAOC levels in heart.
[a,b,c,d]Bars that do not share same letters (superscripts) are significantly different from each other ($p < .05$)

CAT activity was significantly higher in ASeD group (33%) while there were no marked changes in SOD activities of the study groups vs. control.

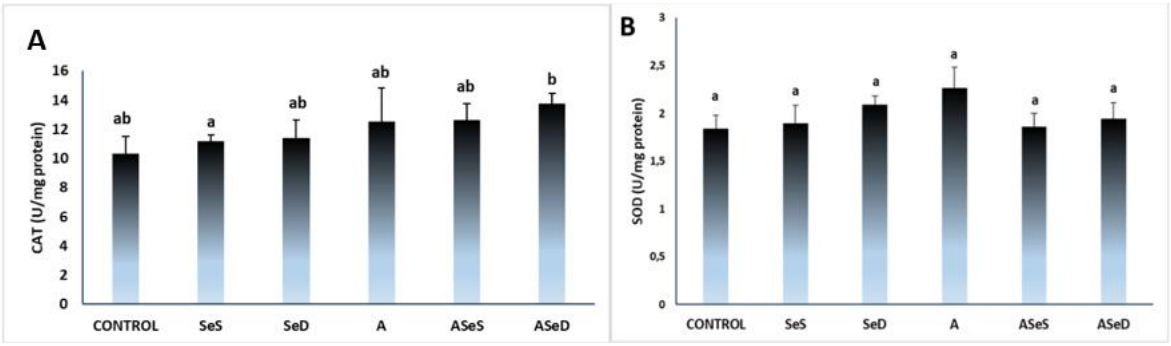

Figure 3. Heart antioxidant enzyme activities.
A. CAT activity of heart tissue; B. SOD levels of heart tissue
[a,b,c,d]Bars that do not share same letters (superscripts) are significantly different from each other ($p < .05$)

Thyroid Organ Weights

The thyroid weights in SeD (38%), A (39%), ASeS (55%) and ASeD (50%) groups were markedly lower than control (Fig. 4A). Relative thyroid weights were significantly lower in all study groups (21% in SeS, 34%in SeD, 30% in A, 52% in ASeS and 41% in ASeD groups vs. control) (Fig. 4B). These results indicate that Se deficiency and/or A1254 exposure cause more pronounced decreases in thyroid tissue weights and relative organ weights. As both A1254 alone and selenium deficiency alone lead to lower thyroid/relative thyroid weight, it is not suprising that the combination of A1254 exposure and selenium deficiency produces a more pronounced effect on thyroid/relative thyroid weights.

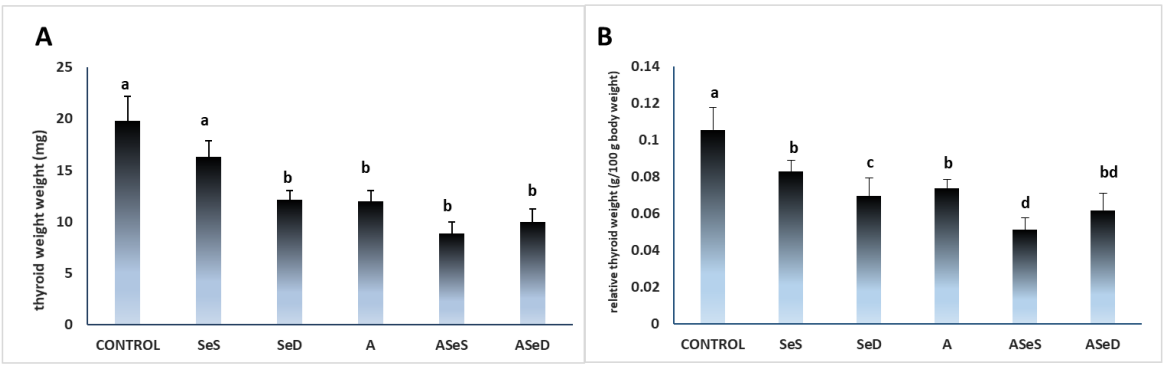

Figure 4. Thyroid and relative thyroid weights of groups.
A. Thyroid weights of groups; B. Relative thyroid weights of groups.
[a,b,c,d]Bars that do not share same letters (superscripts) are significantly different from each other ($p < .05$)

Thyroid Hormone Levels

fT4 levels in SeD group were significantly higher than control (64%). fT4 levels were markedly lower in A (51%), ASeS (22%) and ASeD (10%) groups vs. control group (Fig. 5A). fT3 levels were lower in A (37%) group vs. control (Fig. 5B). Numerous studies have shown that selenium is directly related to thyroid tissue and hormones as selenium is the integral component of iodothyronine deiodinases, which are a subfamily of deiodinase enzymes important in the activation and deactivation of thyroid hormones [38,55].

Limited number of *in vivo* and human studies indicate that exposures to A1254 and other PCBs can cause changes in thyroid hormone levels. Although the results of these studies varied depending on

the exposure period and dose, the data showed that rodents showed significant changes in thyroid hormone levels after PCB exposure. These alterations caused by A1254 in thyroid may be due to their structural similarity to thyroid hormones. In addition, as exposure to A1254 caused a significant decrease in serum fT3 levels, it can be concluded that A1254 also has an endocrine disrupting effect in the thyroid, most possible due to disruption of hormonal feedback flow and changes in enzyme levels that metabolize thyroid hormones. Moreover, thyroidal damage, oxidative stress and/or the interactions of A1254 with thyroid hormone receptors may lead to alterations in thyroid hormone levels [16, 27, 34, 56-63]. However, more mechanistic studies are needed to show the exact endocrine disrupting mechanisms of different PCB congeners in the thyroid.

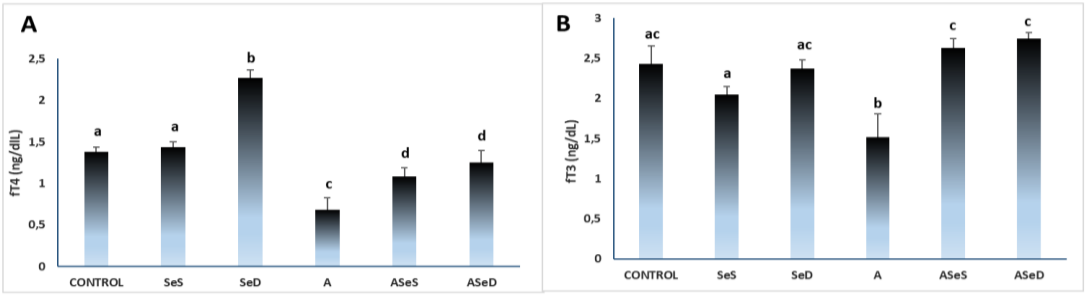

Figure 5. Plasma thyroid hormone levels
A. fT4 levels; B. fT3 levels
[a,b,c,d]Bars that do not share the same letters (superscripts) are significantly different from each other ($p < .05$)

Determination of Oxidative Stress Parameters on Thyroid Tissue

Thyroid MDA levels in SeD (58%), A (1.7-fold), ASeS (70%) and ASeD (2.5-fold) groups were markedly higher than control (Fig 6A). TAOC levels in SeD (36%), A (50%), ASeS (36%) and ASeD (33%) groups were significantly lower than control (Fig 6B). It has been determined that lipid peroxidation in thyroid was much more pronounced with the selenium deficiency with accompanying A1254 exposure. TAOC levels in SeD (36%), A (50%), ASeS (36%) and ASeD (33%) groups were significantly lower than control in thyroid. It has been observed that exposure to A1254 in the presence of selenium deficiency cause a more significant decrease in the antioxidant defense capacity of thyroid tissue. Several studies and comprehensive reviews suggested that selenium deficiency causes higher oxidative stress in thyroid in accordance with the results of the presence study [65-69].

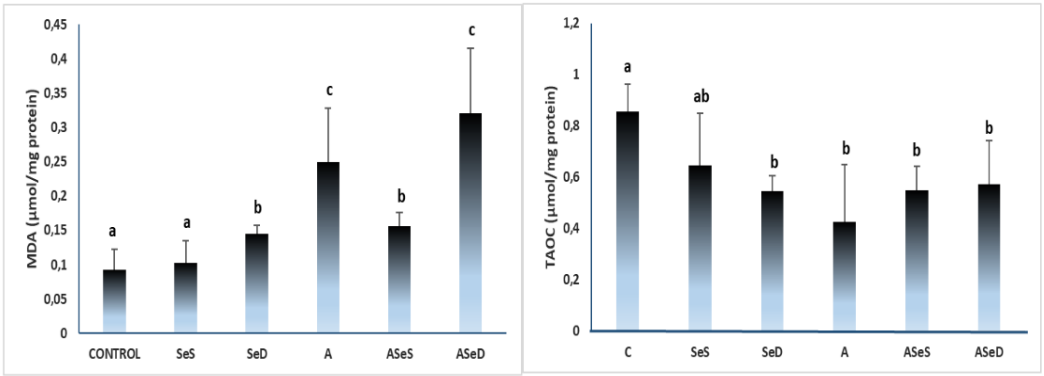

Figure 6. Thyroid oxidative stress parameters.
A. MDA levels of thyroid tissue; B. Carbonyl levels of thyroid tissue
[a,b,c,d]Bars that do not share same letters (superscripts) are significantly different from each other ($p < .05$)

In conclusion, it can be suggested that A1254 causes toxic effects in both heart and thyroid in rats. A1254 disrupts thyroid enzymes and causes oxidative/antioxidative imbalance in both thyroid and heart. Selenium, a crucial essential element, seems to have modifying role in the cardiac and thyroidal toxicity of A1254. The exact mechanism through which selenium is partially protective against toxicity of A1254 in heart and thyroid is not clear. However, as selenium is the integral component of many important antioxidants, selenium supplementation seems to augment the toxicity of A1254, at least partially. Mechanistic studies are needed to clarify the exact effects of selenium in PCB toxicity. moreover, as selenium is also an important element for the endothelial functioning through GPxs, the mechanism through which selenium shows a protective effect in heart against A1254 toxicity should be investigated in detail.

AUTHOR CONTRIBUTIONS

Concept: P.E., B.G.; Design: P.E., B.G.; Sources: A.B.Ö., G.Ö., Ü.Y., A.A., P.E., B.G.; Materials: A.B.Ö., G.Ö., Ü.Y., A.A., P.E., B.G.; Data Collection and/or Processing: A.B.Ö., Ü.Y., A.A., P.E.; Analysis and/or Interpretation: A.B.Ö., G.Ö., Ü.Y., A.A., M.K.; Literature Review: A.B.Ö., P.E.; Manuscript Writing: A.B.Ö., P.E.; Critical Review: P.E., B.G.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The study was approved by Hacettepe University Animal Ethics Committee (02.04.2012-2012/20-7) and animals were treated humanely.

REFERENCES

1. Shmarakov, I.O., Lee, Y.J., Jiang, H., Blaner, W.S. (2019). Constitutive androstane receptor mediates PCB-induced disruption of retinoid homeostasis. Toxicology and Applied Pharmacology, 381, 114731. [CrossRef]
2. Seyran, A., Erişir, M. (2008). Poli klorlu bifeniller ve sağlık üzerine etkileri. Fırat Üniversitesi Sağlık Bilimleri Veteriner Dergisi, 22(1), 33-40.
3. Vorkamp, K. (2016). An overlooked environmental issue? A review of the inadvertent formation of PCB-11 and other PCB congeners and their occurrence in consumer products and in the environment. Science of the Total Environment, 541, 1463-1476. [CrossRef]
4. Weber, R., Herold, C., Hollert, H., Kamphues, J., Blepp, M., Ballschmiter, K. (2018). Reviewing the relevance of dioxin and PCB sources for food from animal origin and the need for their inventory, control and management. In Environmental Sciences Europe, 30(1), 42.
5. Chakraborty, P., Prithiviraj, B., Selvaraj, S., Kumar, B. (2016). Polychlorinated biphenyls in settled dust from informal electronic waste recycling workshops and nearby highways in urban centers and suburban industrial roadsides of Chennai city, India: Levels, congener profiles and exposure assessment. Science of the Total Environment, 573, 1413-1421. [CrossRef]
6. Chakraborty, P., Khuman, S.N., Selvaraj, S., Sampath, S., Devi, N.L., Bang, J.J., Katsoyiannis, A. (2016). Polychlorinated biphenyls and organochlorine pesticides in River Brahmaputra from the outer Himalayan Range and River Hooghly emptying into the Bay of Bengal: Occurrence, sources and ecotoxicological risk assessment. Environmental Pollution, 219, 998-1006. [CrossRef]
7. Devi, N.L., Yadav, I.C., Chakraborty, P., Shihua, Q. (2018). Polychlorinated biphenyls in surface soil from North-East India: Implication for sources apportionment and health-risk assessment. Archives of Environmental Contamination and Toxicology, 75(3), 377-389. [CrossRef]
8. Alawi, M., Masaad, M., Al-Hussaini, M. (2018). Comparative study of persistent organic pollutant (POP) (chlorinated pesticides, PCBs, and dioxins/furans) concentrations in cancer-affected human organs with those of healthy organs. Environmental Monitoring and Assessment, 190(8), 470. [CrossRef]
9. Du, S., Rodenburg, L., Patterson, N., Chu, C., Riker, C.D., Yu, C.H., Fan, Z. (Tina). (2020). Concentration of polychlorinated biphenyls in serum from New Jersey biomonitoring study: 2016-2018. Chemosphere, 261, 127730. [CrossRef]

10. Raffetti, E., Speziani, F., Donato, F., Leonardi, L., Orizio, G., Scarcella, C., Apostoli, P., Magoni, M. (2017). Temporal trends of polychlorinated biphenyls serum levels in subjects living in a highly polluted area from 2003 to 2015: A follow-up study. International Journal of Hygiene and Environmental Health, 220(2), 461-467. [CrossRef]
11. He, F., Zuo, L., Ward, E., Arciero, P.J. (2017). Serum polychlorinated biphenyls increase and oxidative stress decreases with a protein-pacing caloric restriction diet in obese men and women. International Journal of Environmental Research and Public Health, 14(1), 59. [CrossRef]
12. Loch-Caruso, R. (2002). Uterine muscle as a potential target of polychlorinated biphenyls during pregnancy. International Journal of Hygiene and Environmental Health, 205, 121-130.
13. Brouwer, A., Longnecker, M.P., Birnbaum, L.S., Cogliano, J., Kostyniak, P., Moore, J., Schantz, S., Winneke, G. (1999). Characterization of potential endocrine-related health effects at low-dose levels of exposure to PCBs. Environmental Health Perspective, 107 Suppl 4(Suppl 4), 639-649. [CrossRef]
14. Sánchez-Alonso, J.A., López-Aparicio, P., Recio, M.N., Pérez-Albarsanz, M.A. (2003). Apoptosis-mediated neurotoxic potential of a planar (PCB 77) and a nonplanar (PCB 153) polychlorinated biphenyl congeners in neuronal cell cultures. Toxicology Letters, 144(3), 337-349. [CrossRef]
15. Tabb, M.M., Kholodovych, V., Grün, F., Zhou, C., Welsh, W.J., Blumberg, B. (2004). Highly chlorinated PCBs inhibit the human xenobiotic response mediated by the steroid and xenobiotic receptor (SXR). Environmental Health Perspectives, 112(2), 163-169. [CrossRef]
16. Schuur, A.G., Brouwer, A., Ke Bergman, A., Coughtrie, M.W.H., Visser, T.J. (1998). Inhibition of thyroid hormone sulfation by hydroxylated metabolites of polychlorinated biphenyls. In Chemico-Biological Interactions, 109, 293-297. [CrossRef]
17. Sergeev, A.V., Carpenter, D.O. (2011). Geospatial patterns of hospitalization rates for stroke with comorbid hypertension in relation to environmental sources of persistent organic pollutants: Results from a 12-year population-based study. Environmental Science and Pollution Research, 18(4), 576-585. [CrossRef]
18. Hertz-Picciotto, I., Park, H.Y., Dostal, M., Kocan, A., Trnovec, T., Sram, R. (2008). Prenatal exposures to persistent and non-persistent organic compounds and effects on immune system development. Basic and Clinical Pharmacology and Toxicology, 102(2), 146-154. [CrossRef]
19. Collins, W.T., Capen, C.C. (1980). Fine structural lesions and hormonal alterations in thyroid glands of perinatal rats exposed in utero and by the milk to polychlorinated biphenyls. The American Journal of Pathology, 99(1),125-142.
20. Gray, L.E. Jr, Ostby, J., Marshall, R., Andrews, J. (1993). Reproductive and thyroid effects of low-level polychlorinated biphenyl (Aroclor 1254) exposure. Fundamental and Applied Toxicology, 20(3), 288-294. [CrossRef]
21. Giera, S., Bansal, R., Ortiz-Toro, T.M., Taub, D.G., Zoeller, R.T. (2011). Individual Polychlorinated Biphenyl (PCB) Congeners Produce Tissue- and Gene-Specific Effects on Thyroid Hormone Signaling during Development. Endocrinology, 152(7), 2909-2919. [CrossRef]
22. Webb, C.M., McNabb, F.M.A. (2008). Polychlorinated biphenyl effects on avian hepatic enzyme induction and thyroid function. General and Comparative Endocrinology, 155(3), 650-657. [CrossRef]
23. Salay, E., Garabrant, D. (2009). Polychlorinated biphenyls and thyroid hormones in adults: A systematic review appraisal of epidemiological studies. Chemosphere, 74(11), 1413-1419. [CrossRef]
24. Hansen, L.G. (1998). Stepping backward to improve assessment of PCB congener toxicities. Environmental Health Perspective, 106 Suppl 1(Suppl 1), 171-189. [CrossRef]
25. Carpenter, D.O. (2006). Polychlorinated biphenyls (PCBs): routes of exposure and effects on human health. Reviews on Environmental Health, 21(1), 1-23.[CrossRef]
26. Kato, Y., Haraguchi, K., Shibahara, T., Masuda, Y., Kimura, R. (1998). Reduction of thyroid hormone levels by methylsulfonyl metabolites of polychlorinated biphenyl congeners in rats. Archives of Toxicology, 72, 541-544. [CrossRef]
27. Kochman, J., Jakubczyk, K., Bargiel, P., Janda-Milczarek, K. (2021). The influence of oxidative stress on thyroid diseases. Antioxidants, 10(9), 1442. [CrossRef]
28. Duntas, L.H., Stathatos, N. (2015). Toxic chemicals and thyroid function: hard facts and lateral thinking. In Reviews in Endocrine and Metabolic Disorders, 16(4), 311-318. [CrossRef]
29. Åkesson, A., Donat-Vargas, C., Berglund, M., Glynn, A., Wolk, A., Kippler, M. (2019). Dietary exposure to polychlorinated biphenyls and risk of heart failure - A population-based prospective cohort study. Environment International, 126, 1-6. [CrossRef]
30. Donat-Vargas, C., Moreno-Franco, B., Laclaustra, M., Sandoval-Insausti, H., Jarauta, E., Guallar-Castillon, P. (2020). Exposure to dietary polychlorinated biphenyls and dioxins, and its relationship with subclinical coronary atherosclerosis: The Aragon Workers' Health Study. Environment International, 136, 105433. [CrossRef]

31. Bergkvist, C., Berglund, M., Glynn, A., Julin, B., Wolk, A., Åkesson, A. (2016). Dietary exposure to polychlorinated biphenyls and risk of myocardial infarction in men - A population-based prospective cohort study. Environment International, 88, 9-14. [CrossRef]
32. Rao, P., Kodavanti, S., Kannan, N., Yamashita, N., Derr-Yellin, E.C., Ward, T.R., Burgin, D.E., Tilson, H.A., Birnbaum, L.S. (2001). Differential effects of two lots of Aroclor 1254: Congener-specific analysis and neurochemical end points. International Environmental Health Perspectives, 109(11), 1153-1161. [CrossRef]
33. Kaya, D., Imamoglu, I., Sanin, F.D., Payne, R.B., Sowers, K.R. (2017). Potential risk reduction of Aroclor 1254 by microbial dechlorination in anaerobic Grasse River sediment microcosms. Journal of Hazardous Materials, 321, 879-887. [CrossRef]
34. Crofton, K.M., Kodavanti, P.R.S., Derr-Yellin, E.C., Casey, A.C., Kehn, L.S. (2000). PCBs, thyroid hormones, and ototoxicity in rats: Cross-fostering experiments demonstrate the impact of postnatal lactation exposure. Toxicology Science, 57(1), 131-140. [CrossRef]
35. Lehigh Shirey, E.A., Jelaso Langerveld, A., Mihalko, D., Ide, C.F. (2006). Polychlorinated biphenyl exposure delays metamorphosis and alters thyroid hormone system gene expression in developing Xenopus laevis. Environmental Research, 102(2), 205-214. [CrossRef]
36. Li, M., Wang, X., Zhu, J., Zhu, S., Hu, X., Zhu, C., Guo, X., Yu, Z., Han, S. (2014). Toxic effects of polychlorinated biphenyls on cardiac development in zebrafish. Molecular Biology Reports, 41(12), 7973-7983. [CrossRef]
37. Borlak, J., Thum, T. (2002). PCBs alter gene expression of nuclear transcription factors and other heart-specific genes in cultures of primary cardiomyocytes: possible implications for cardiotoxicity. Xenobiotica, 32(12), 1173-1183. [CrossRef]
38. Gorini, F., Sabatino, L., Pingitore, A., Vassalle, C. (2021). Selenium: An element of life essential for thyroid function. Molecules, 26 (23), 7084. [CrossRef]
39. Al-Mubarak, A.A., van der Meer, P., Bomer, N. (2021). Selenium, selenoproteins, and heart failure: Current knowledge and future perspective. Current Heart Failure Reports, 18(3),122-131. [CrossRef]
40. Shimada, B.K., Alfulaij, N., Seale, L.A. (2021). The impact of selenium deficiency on cardiovascular function. International Journal of Molecular Sciences, 22(19), 10713. [CrossRef]
41. Kielczykowska, M., Kocot, J., Pazdzior, M., Musik, I. (2018). Selenium - A fascinating antioxidant of protective properties. International Advances in Clinical and Experimental Medicine, 27(2), 245-255.
42. Aebi, H., Wyss, S.R., Scherz, B., Skvarıl, F. (1974). Heterogeneity of erythrocyte catalase II: Isolation and characterization of normal and variant erythrocyte catalase and their subunits. European Journal of Biochemistry, 48(1), 137-145. [CrossRef]
43. Ramasarma, T., Rao, A.V.S., Devi, M.M., Omkumar, R.V., Bhagyashree, K.S., Bhat, S.V. (2015). New insights of superoxide dismutase inhibition of pyrogallol autoxidation. Molecular and Cellular Biochemistry, 400(1-2), 277-285. [CrossRef]
44. Walker, J.M. (1994). The bicinchoninic acid (BCA) assay for protein quantitation. Methods in Molecular Biology, 32, 5-8. [CrossRef]
45. Wang, C., Cui, R., Niu, C., Zhong, X., Zhu, Q., Ji, D., Li, X., Zhang, H., Liu, C., Zhou, L., Li, Y., Xu, G., Wei, Y. (2021). Low-dose PCB126 exposure disrupts cardiac metabolism and causes hypertrophy and fibrosis in mice. Environmental Pollution, 290, 118079. [CrossRef]
46. Teixidó, E., Barenys, M., Piqué, E., Llobet, J.M., Gómez-Catalán, J. (2019). Cardiovascular effects of PCB 126 (3,3',4,4',5-pentachlorobiphenyl) in zebrafish embryos and impact of co-exposure to redox modulating chemicals. International Journal of Molecular Sciences, 20(5), 1065. [CrossRef]
47. Brown, D.R., Clark, B.W., Garner, L.V.T., di Giulio, R.T. (2016). Embryonic cardiotoxicity of weak aryl hydrocarbon receptor agonists and CYP1A inhibitor fluoranthene in the Atlantic killifish (Fundulus heteroclitus). Comparative Biochemistry and Physiology Part - C: Toxicology and Pharmacology, 188, 45-51. [CrossRef]
48. Incardona, J.P., Scholz, N.L. (2016). The influence of heart developmental anatomy on cardiotoxicity-based adverse outcome pathways in fish. International Aquatic Toxicology, 177, 515-525. [CrossRef]
49. Brown, D.R., Clark, B.W., Garner, L.V.T., di Giulio, R.T. (2015). Zebrafish cardiotoxicity: the effects of CYP1A inhibition and AHR2 knockdown following exposure to weak aryl hydrocarbon receptor agonists. Environmental Science and Pollution Research, 22(11), 8329-8338. [CrossRef]
50. Deng, P., Wang, C., Wahlang, B., Sexton, T., Morris, A.J., Hennig, B. (2020). Co-exposure to PCB126 and PFOS increases biomarkers associated with cardiovascular disease risk and liver injury in mice. Toxicology and Applied Pharmacology, 409, 115301. [CrossRef]

51. Sallée, M., Dou, L., Cerini, C., Poitevin, S., Brunet, P., Burtey, S. (2014). The aryl hydrocarbon receptor-activating effect of uremic toxins from tryptophan metabolism: A new concept to understand cardiovascular complications of chronic kidney disease. International Toxins, 6(3), 934-949. [CrossRef]
52. Arsenescu, V., Arsenescu, R.I., King, V., Swanson, H., Cassis, L.A. (2008). Polychlorinated biphenyl-77 induces adipocyte differentiation and proinflammatory adipokines and promotes obesity and atherosclerosis. Environmental Health Perspective, 116(6), 761-768. [CrossRef]
53. Zhang, Z., Chang, C., Zhang, Y., Chai, Z., Li, J., Qiu, C. (2021). The association between serum selenium concentration and prognosis in patients with heart failure in a Chinese population. Scientific Reports, 11(1), 14533. [CrossRef]
54. de Lorgeril, M., Salen, P. (2006). Selenium and antioxidant defenses as major mediators in the development of chronic heart failure. Heart Failure Reviews,11(1),13-17. [CrossRef]
55. Burgin, D.E., Diliberto, J.J., Derr-Yellin, E.C., Kannan, N., Kodavanti, P.R.S., Birnbaum, L.S. (2001). Differential effects of two lots of Aroclor 1254 on enzyme induction, thyroid hormones, and oxidative stress. International Environmental Health Perspectives, 109(11), 1163-1168. [CrossRef]
56. Abdelsalam, E.E.E., Bandouchova, H., Heger, T., Kanova, M., Kobelkova, K., Nemcova, M., Piacek, V., Sedlackova, J., Seidlova, V., Vitula, F., Pikula, J. (2020). Polychlorinated biphenyl toxicity in the thyroid gland of wild ungulates: An in vitro model. Acta Veterinaria Brno, 89(2), 151-162. [CrossRef]
57. Fair, P.A., Peden-Adams, M.M., Mollenhauer, M.A.M., Bossart, G.D., Keil, D.E., White, N.D. (2021). Effects of an environmentally relevant PCB-mixture on immune function, clinical chemistry, and thyroid hormone levels in adult female B6C3F1 mice. Journal of Toxicology and Environmental Health-Part A: Current Issues, 84(7), 279-297. [CrossRef]
58. Klaassen, C.D., Hood, A.M. (2001). Effects of microsomal enzyme inducers on thyroid follicular cell proliferation and thyroid hormone metabolism. International Toxicologic Pathology, 29(1). [CrossRef]
59. Seldén, A.I., Lundholm, C., Johansson, N., Wingfors, H. (2008). Polychlorinated biphenyls (PCB), thyroid hormones and cytokines in construction workers removing old elastic sealants. International Archives of Occupational and Environmental Health, 82(1), 99-106. [CrossRef]
60. LeRoy, K.D., Thomas, P., Khan, I.A. (2006). Thyroid hormone status of Atlantic croaker exposed to Aroclor 1254 and selected PCB congeners. Comparative Biochemistry and Physiology - C Toxicology and Pharmacology, 144(3), 263-271. [CrossRef]
61. Coimbra, A.M., Reis-Henriques, M.A., Darras, V.M. (2005). Circulating thyroid hormone levels and iodothyronine deiodinase activities in Nile tilapia (Oreochromis niloticus) following dietary exposure to Endosulfan and Aroclor 1254. Comparative Biochemistry and Physiology - C Toxicology and Pharmacology, 141(1), 8-14. [CrossRef]
62. Coimbra, A.M., Reis-Henriques, M.A. (2007). Tilapia larvae aroclor 1254 exposure: Effects on gonads and circulating thyroid hormones during adulthood. Bulletin of Environmental Contamination and Toxicology, 79(5), 488-493. [CrossRef]
63. Takaguchi, K., Nishikawa, H., Mizukawa, H., Tanoue, R., Yokoyama, N., Ichii, O., Takiguchi, M., Nakayama, S.M.M., Ikenaka, Y., Kunisue, T., Ishizuka, M., Tanabe, S., Iwata, H., Nomiyama, K. (2019). Effects of PCB exposure on serum thyroid hormone levels in dogs and cats. Science of the Total Environment, 688, 1172-1183. [CrossRef]
64. Ibrahim, M.A.A., Elkaliny, H.H., Abd-Elsalam, M.M. (2021). Lycopene ameliorates the effect of Aroclor 1254 on morphology, proliferation, and angiogenesis of the thyroid gland in rat. Toxicology, 452, 152722. [CrossRef]
65. Köhrle, J. Selenium and the thyroid. (2013). Current Opinion in Endocrinology, Diabetes and Obesity, 20(5),441-448.
66. Winther, K.H., Rayman, M.P., Bonnema, S.J., Hegedüs, L. (2020). Selenium in thyroid disorders - essential knowledge for clinicians. In Nature Reviews Endocrinology, 16(3), 165-176. [CrossRef]
67. Erkekoglu, P., Giray, B.K., Kizilgun, M., Hininger-Favier, I., Rachidi, W., Roussel, A.M., Favier, A., Hincal, F. (2012). Thyroidal effects of di-(2-ethylhexyl) phthalate in rats of different selenium status. Journal of Environmental Pathology, Toxicology and Oncology, 31(2),143-153. [CrossRef]
68. da Silva, G.B., Yamauchi, M.A., Bagatini, M.D. (2022). Oxidative stress in Hashimoto's thyroiditis: possible adjuvant therapies to attenuate deleterious effects. Molecular and Cellular Biochemistry, 381 [CrossRef]
69. Hosnedlova, B., Kepinska, M., Skalickova, S., Fernandez, C., Ruttkay-Nedecky, B., Malevu, T.D., Sochor, J., Baron, M., Melcova, M., Zidkova, J., Kizek R. (2017). A summary of new findings on the biological effects of selenium in selected animal species-A critical review. International Journal of Molecular Sciences,18(10), 2209. [CrossRef]