SELENIO - SELENIUM

– Meli R, Monnolo A, Annunziata C, Pirozzi C, Ferrante MC

Oxidative Stress and BPA Toxicity: An Antioxidant Approach for Male and Female Dysfunction. *Antioxidants (Basel).* 2020; 9:405. doi: 10.3390/antiox9050405.

Bisphenol A (BPA) is a non-persistent anthropic and environmentally ubiquitous compound widely employed and detected in many consumer products and food items; thus, human exposure is prolonged. Over the last ten years, many studies have the underlying molecular mechanisms of BPA toxicity and revealed links among BPA-induced oxidative stress, male and female reproductive defects, and human disease. Because of its hormone-like feature, BPA shows tissue effects on specific hormone receptors in target cells, triggering noxious cellular responses associated with oxidative stress and inflammation. As a metabolic and endocrine disruptor, BPA impairs redox homeostasis via the increase of oxidative mediators and the reduction of antioxidant enzymes, causing mitochondrial dysfunction, alteration in cell signaling pathways, and induction of apoptosis. This review aims to examine the scenery of the current BPA literature on understanding how the induction of oxidative stress can be considered the "fil rouge" of BPA's toxic mechanisms of action with pleiotropic outcomes on reproduction. Here, we focus on the protective effects of five classes of antioxidants-vitamins and co-factors, natural products (herbals and phytochemicals), melatonin, selenium, and methyl donors (used alone or in combination)-that have been found useful to counteract BPA toxicity in male and female reproductive functions.

- Gurdemir G, Erkekoglu P, Balci A, Sur U, Ozkemahli G, Tutkun E, Yilmaz H, Asci A, Kocer-Gumusel B.

Oxidative Stress Parameters, Selenium Levels, DNA Damage, and Phthalate Levels in Plastic Workers. *J Environ Pathol Toxicol Oncol.* 2019;38:253-270.

Di(2-ethylhexyl)phthalate (DEHP) is the most widely used phthalate. DEHP is highly used in PVC floorings and PVC windows and carpeting. The objective of this study was to determine sex hormone levels, oxidative stress parameters, selenium levels, DNA damage, and phthalate levels in plastics workers (n = 24, age = 20-58 years) working in the production of rubber mechanical goods and exposed to DEHP in workplace. The control group (n = 29, age = 25-54, all male) was selected from age-matched healthy adults. Antioxidant parameters and DNA damage were determined by spectrophotometry. Selenium levels were determined by atomic absorption spectroscopy. Plasma hormone levels were measured by chemiluminescence microparticle immunoassay. Plasma phthalate levels were determined by high-pressure liquid chromatography. Plastic workers had lower serum testosterone and free T4 levels and higher follicle-stimulating hormone levels vs. controls. Liver enzyme activities were markedly higher in workers vs. controls. There were also increases in plasma glutathione peroxidase levels and marked decreases in plasma selenium and erythrocyte total glutathione levels in plastics workers ($P < 0.05$ vs. control). Plasma 8-hydroxy-2'-deoxyguanosine levels were 14-fold higher in plastics workers than in controls. Plasma DEHP and mono(2-ethylhexyl)phthalate were also markedly higher in workers vs. controls. The results of this study show that occupational exposure to DEHP may lead to disturbances in sex hormones, increased liver problems, higher oxidative stress and DNA damage levels, and lower trace element concentrations in workers. More comprehensive and mechanistic studies with higher numbers of subjects are needed to show the unwanted effects of occupational exposure to DEHP.

– Khalaf AA, Ahmed W, Moselhy WA, Abdel-Halim BR, Ibrahim MA.

Protective effects of selenium and nano-selenium on bisphenol-induced reproductive toxicity

in male rats. *Hum Exp Toxicol*. 2019 38:398-408.

Bisphenol A (BPA) is a widespread compound associated with the manufacture of many consumer products. The BPA-induced reproductive toxicity was reported to be mainly attributed to oxidative stress. However, the role of antioxidants usage to decrease the injurious effects of BPA, on male reproductive functions, remains to unveil. The present research is established to evaluate the role of selenium (Se) and its nano form (NSe) as protective agents to alleviate BPA-induced testicular toxicity. Ninety mature albino male rats were assigned into six equal groups: negative control; orally BPA 150 mg/kg; Se 3 mg/kg; NSe 2 mg/kg; both BPA 150 mg/kg and Se 3 mg/kg; and BPA 150 mg/kg + NSe 2 mg/kg. The experiment lasted for 70 consecutive days, and then serum was collected for estimation of prostatic acid phosphatase. Testicular tissues were subjected to measurement of antioxidant status, lipid peroxidation, DNA damage, and expression of some apoptotic genes. Our results reported that BPA-induced marked testicular damage evidenced by significant elevations in serum prostatic acid phosphatase activity, malondialdehyde levels, a decrease in testicular catalase activity and reduced glutathione level. Moreover, marked DNA internucleosomal fragmentation pattern as well as upregulation of cyclooxygenase-2 and estrogen receptor-2 NSe genes were detected. Coadministration of Se and NSe attenuated the reproductive toxicity induced by BPA via improvement of the antioxidant activity, genetic changes, and restoration of testicular tissue nearly as control one. These results indicated that both Se and NSe forms could be used as reproductive protective agents against the detrimental effect induced by BPA. However, the NSe surpassed the selenium in modulating the DNA laddering, and the studied gene expression levels, and offered a potent

- Rahman MM, Hossain KFB, Banik S, Sikder MT, Akter M, Bondad SEC, Rahaman MS, Hosokawa T, Saito T, Kurasaki M.

Selenium and zinc protections against metal-(loids)-induced toxicity and disease manifestations: A review. *Ecotoxicol Environ Saf.* 2019 168:146-163.

Metals are ubiquitous in the environment due to huge industrial applications in the form of different chemicals and from extensive mining activities. The frequent exposures to metals and metalloids are crucial for the human health. Trace metals are beneficial for health whereas non-essential metals are dangerous for the health and some are proven etiological factors for diseases including cancers and neurological disorders. The interactions of essential trace metals such as selenium (Se) and zinc (Zn) with non-essential metals viz. lead (Pb), cadmium (Cd), arsenic (As), and mercury (Hg) in biological system are very critical and complex. A huge number of studies report the protective role of Se and Zn against metal toxicity, both in animal and cellular levels, and also explain the numerous mechanisms involved. However, it has been considered that a tiny dyshomeostasis in the metals/trace metals status in biological system could induce severe deleterious effects that can manifest to numerous diseases. Thus, in this particular review, we have demonstrated the critical protection mechanism/s of Se and Zn against Cd, Pb, As and Hg toxicity in a one by one manner to clarify the up-to-date findings and perspectives. Furthermore, biomolecular consequences are comprehensively presented in light of particular cellular/biomolecular events which are somehow linked to a subsequent disease. The analyzed reports support significant protection potential of Se and Zn, either alone or in combination with other agents, against each of the abovementioned non-essential metals. However, Se and Zn are still not being used as detoxifying agents due to some unexplained reasons. We hypothesized that Se could be a potential candidate for detoxifying As and Hg regardless of their chemical speciations, but requires intensive clinical trials. However, particularly Zn-Hg interaction warrants more investigations both in animal and cellular level.

– Stojsavljević A, Rovčanin B, Krstić Đ, Jagodić J, Borković-Mitić S, Paunović I, Živaljević V, Mitić B, Gavrović-Jankulović M, Manojlović D

Cadmium as main endocrine disruptor in papillary thyroid carcinoma and the significance of Cd/Se ratio for thyroid tissue pathophysiology. *J Trace Elem Med Biol*. 2019 55: 190-195.

Background: The etiology of papillary thyroid carcinoma (PTC) is unknown and some literature data support the hypothesis that heavy metals, as endocrine disrupters, could play a major role in the pathogenesis of thyroid cancer. This study aimed to estimate the content of selected toxic and essential trace metals (Mn, Co, Ni, Cu, Zn, As, Se, Cd, Pb, Th, and U), as well as the selected ratio's (Cu/Zn and Cd/Se) in the malignant thyroid tissues according to sex, age, smoking habits, familial history of any thyroid disease, pathohistological (PH) types of PTC, tumor size, the existence of a thyroid capsular invasion, intrathyroid tumor dissemination, retrosternal thyroid growth, and TNM progress of PTC.
Methods: The study included 66 patients with PTC (women/men ratio = 46/20, mean age: 54 ± 14 years). A comparative analysis was made by collecting the healthy thyroid tissues (HTTs) of the same patients, making the total number of samples 132. All trace metals were quantified by inductively coupled plasma-mass spectrometry (ICP-MS).
Results: Metals that significantly separated papillary thyroid tissues (PTTs) from the HTTs were Cd, U and Se ($p < 0.05$). The obtained negative correlation between Cd and Se in the PTTs could explain extrusion of essential Se caused by increased content of Cd. Only Cd had an influence on the retrosternal thyroid growth, while the essential metals (Mn, Co, and Zn) had an influence on thyroid capsular invasion.
Conclusion: It was found that Cd act as the main endocrine disrupter, which could highlight its role in the etiology of PTC. Considering that the Cd/Se ratio significantly separated two studied groups and had an influence on the retrosternal thyroid growth, its altered content could contribute to the better understanding of the molecular basis for pathophysiological changes in the PTC.

– Aydemir D, Karabulut G, Şimşek G, Gok M, Barlas N, Ulusu NN.

Impact of the Di(2-Ethylhexyl) Phthalate Administration on Trace Element and Mineral Levels in Relation of Kidney and Liver Damage in Rats. *Biol Trace Elem Res*. 2018 186:474-488.

Di(2-ethylhexyl) phthalate (DEHP) is a widely used synthetic polymer in the industry. DEHP may induce reproductive and developmental toxicity, obesity, carcinogenesis and cause abnormal endocrine function in both human and wildlife. The aim of this study was to investigate trace element and mineral levels in relation of kidney and liver damage in DEHP-administered rats. Therefore, prepubertal male rats were dosed with 0, 100, 200, and 400 mg/kg/day of DEHP. At the end of the experiment, trace element and mineral levels, glucose-6-phosphate dehydrogenase (G6PD), 6-phosphogluconate dehydrogenase (6-PGD), glutathione reductase (GR) and glutathione S-transferase (GST) enzyme activities were evaluated in the serum, liver, and kidney samples of rats. Furthermore, serum clinical biochemistry parameters, organ/body weight ratios and histological changes were investigated to evaluate impact of DEHP more detailed. Our data indicated that sodium (Na), calcium (Ca), potassium (K), lithium (Li), rubidium (Rb) and cesium (Cs) levels significantly decreased, however iron (Fe) and selenium (Se) concentrations significantly increased in DEHP-administered groups compared to the control in the serum samples. On the other hand, upon DEHP administration, selenium concentration, G6PD and GR activities were significantly elevated, however 6-PGD activity significantly decreased compared to the control group in the kidney samples. Decreased G6PD activity was the only significant change between anti-oxidant enzyme activities in the liver samples. Upon DEHP administration, aberrant serum biochemical parameters have arisen and abnormal histological changes were observed in the kidney and liver tissue. In conclusion, DEHP may induce liver and kidney damage, also result abnormalities in the trace element and mineral levels.

- Zhang P, Guan X, Yang M, Zeng L, Liu C.

Roles and potential mechanisms of selenium in countering thyrotoxicity of DEHP. *Sci Total Environ*. 2018 619-620:732-739.

Di-(2-ethylhexyl) phthalate (DEHP) as a ubiquitous environmental contaminant could disturb thyroid hormone (TH) homeostasis. Selenium as an essential trace element has protective effects on thyroids. To verify roles of selenium in countering thyrotoxicity of DEHP and elucidate potential mechanisms, Sprague-Dawley rats and Nthy-ori 3-1 cells were treated with DEHP or/and selenomethionine (SeMet). Results showed that selenium supplementation elevated plasma free thyroxine (FT4) that was decreased by DEHP, and free triiodothyronine (FT3) and thyroid stimulating hormone (TSH) levels were also partially recovered. DEHP-caused histopathologic changes were ameliorated after selenium supplementation, as indicated by recovered thyroid follicular epithelial cell numbers and cavity diameters. DEHP disrupted the redox equilibrium, causing depletions of SOD, GPx1, GPx3, and TxnRd, and accumulations of MDA. Nevertheless, selenium supplementation effectively improved the redox status. DEHP affected biosynthesis, biotransformation, biotransport, and metabolism of THs, as well as thyrotropin releasing hormone receptor (TRHr) levels. Plasma selenium, thyroid peroxidase (TPO), deiodinase 1 (Dio1), and transthyretin (TTR) were downregulated, while Dio3, Ugt1a1, Sult1e1, CYP2b1, CYP3a1, and TRHr were upregulated by DEHP. However, selenium supplementation led to elevations of selenium, Dio1 and TTR, and reductions of Ugt1a1, Sult1e1, CYP2b1, and TRHr. TPO, Dio3, and CYP3a1 were not significantly affected by selenium supplementation. Taken together, selenium could ameliorate DEHP-caused TH dyshomeostasis via modulations of the redox status, Dio1, TTR, TRHr, and hepatic enzymes.

- Kondolot M, Ozmert EN, Ascı A, Erkekoglu P, Oztop DB, Gumus H, Kocer-Gumusel B, Yurdakok K.
Plasma phthalate and bisphenol a levels and oxidant-antioxidant status in autistic children. *Environ Toxicol Pharmacol*. 2016 43:149-58.

Phthalates and bisphenol A (BPA) are endocrine disruting chemicals (EDCs) that are suggested to exert neurotoxic effects. This study aimed to determine plasma phthalates and BPA levels along with oxidant/antioxidant status in autistic children [n=51; including 12 children were diagnosed with "Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS)]. Plasma levels of BPA, di (2-ethylhexyl)-phthalate (DEHP) and its main metabolite mono (2-ethylhexyl)-phthalate (MEHP); thiobarbituric acid reactive substance (TBARS) and carbonyl groups; erythrocyte glutathione peroxidase (GPx1), thioredoxin reductase (TrxR), catalase (CAT), superoxide dismutase (SOD) and glutathione reductase (GR) activities and glutathione (GSH) and selenium levels were measured. Plasma BPA levels of children with PDD-NOS were significantly higher than both classic autistic children and controls (n=50). Carbonyl, selenium concentrations and GPx1, SOD and GR activities were higher ($p<0.05$); CAT activity was markedly lower in study group. BPA exposure might be associated with PDD-NOS. Intracellular imbalance between oxidant and antioxidant status might facilitate its neurotoxicity.

– Vitku J, Heracek J, Sosvorova L, Hampl R, Chlupacova T, Hill M, Sobotka V, Bicikova M, Starka L.

Associations of bisphenol A and polychlorinated biphenyls with spermatogenesis and steroidogenesis in two biological fluids from men attending an infertility clinic. *Environ Int.* 2016 89-90:166-73.

Background: In the testis, steroid hormones play an important role in spermatogenesis, the production of semen, and the maintenance of secondary sex characteristics and libido. They may also play a role as a target for substances called endocrine disruptors (EDs). As yet, however, no complex study has been conducted evaluating the relationships between EDs and the steroid spectrum in the plasma and seminal plasma.
Objectives: To shed more light into mechanisms of EDs and the effects of bisphenol A (BPA) and polychlorinated biphenyls (PCBs) on human spermatogenesis and steroidogenesis.
Methods: We determined BPA and 11 steroids in the plasma and seminal plasma of 191 men with different degrees of fertility, using a newly developed liquid-chromatography mass spectrometry method. Concurrently, plasma levels of 6 congeners of PCBs, gonadotropins, selenium, zinc and homocysteine were measured. Partial correlations adjusted for age, BMI and abstinence time were performed to evaluate relationships between these analytes.
Results: Seminal BPA, but not plasma BPA, was negatively associated with sperm concentration (r=-0.198; p=0.009), sperm count (r=-0.178; p=0.018) and morphology (r=-0.160; p=0.044). Divergent and sometimes opposing associations of steroids and BPA were found in both body fluids. The sum of PCB congeners was negatively associated with testosterone, free testosterone, the free androgen index and dihydrotestosterone in plasma.
Conclusion: BPA may negatively contribute to the final state of sperm quality. Moreover, our data indicate that BPA influences human gonadal and adrenal steroidogenesis at various steps. Environmental levels of PCBs negatively correlated with androgen levels, but surprisingly without negative effects on sperm quality.

- Erkekoglu P, Zeybek ND, Giray BK, Rachidi W, Kızılgün M, Hininger-Favier I, Favier A, Asan E, Hincal F.

The effects of di(2-ethylhexyl)phthalate on rat liver in relation to selenium status. *Int J Exp Pathol*. 2014 95:64-77

This study was performed to determine the hepatotoxicity of di(2-ethylhexyl)phthalate (DEHP) in relation to selenium status. In 3-week-old Sprague-Dawley rats, selenium deficiency was induced by a ≤0.05 selenium mg/kg. A selenium supplementation group was given 1 mg selenium/kg diet for 5 weeks. Di(2-ethylhexyl)phthalate-treated groups received 1000 mg/kg dose by gavage during the last 10 days of the experiment. Histopathology, peroxisome proliferation, catalase (CAT) immunoreactivity and activity and apoptosis were assessed. Activities of antioxidant selenoenzymes [glutathione peroxidase 1 (GPx1), glutathione peroxidase 4 (GPx4), thioredoxin reductase (TrxR1)], superoxide dismutase (SOD), and glutathione S-transferase (GST); aminotransferase, total glutathione (tGSH), and lipid peroxidation (LP) levels were measured. Di(2-ethylhexyl)phthalate caused cellular disorganization while necrosis and inflammatory cell infiltration were observed in Se-deficient DEHP group (DEHP/SeD). Catalase activity and immunoreactivity were increased in all DEHP-treated groups. Glutathione peroxidase 1 and GPx4 activities decreased significantly in DEHP and DEHP/SeD groups, while GST activities decreased in all DEHP-exposed groups. Thioredoxin reductase activity increased in DEHP and DEHP/SeS, while total SOD activities increased in all DEHP-treated groups. Lipid peroxidation levels increased significantly in SeD (26%), DEHP (38%) and DEHP/SeD (71%) groups. Selenium supplementation partially ameliorated DEHP-induced hepatotoxicity; while in DEHP/SeD group, drastic changes in hepatic histopathology and oxidative stress parameters were observed.

- H, Li M, Wang B, Lai IK, Robertson LW, Ludewig G.

Dietary antioxidants (selenium and N-acetylcysteine) modulate paraoxonase 1 (PON1) in PCB 126-exposed rats. *Environ Sci Pollut Res Int*. 2014 21:6384-99.

Environmental pollutants polychlorinated biphenyls (PCBs), especially dioxin-like PCBs, cause oxidative stress and associated toxic effects, including cancer and possibly atherosclerosis. We previously reported that PCB 126, the most potent dioxin-like PCB congener, not only decreases antioxidants such as hepatic selenium (Se), Se-dependent glutathione peroxidase, and glutathione (GSH) but also increases levels of the antiatherosclerosis enzyme paraoxonase 1 (PON1) in liver and serum. To probe the interconnection of these three antioxidant systems, Se, GSH, and PON1, we examined the influence of varying levels of dietary Se and N-acetylcysteine (NAC), a scavenger of reactive oxygen species (ROS) and precursor for GSH synthesis, on PON1 in the absence and presence of PCB 126 exposure. Male Sprague-Dawley rats, fed diets with differing Se levels (0.02, 0.2, or 2 ppm) or NAC (1%), were treated with a single intraperitoneal injection of corn oil or various doses of PCB 126 and euthanized 2 weeks later. PCB 126 significantly increased liver PON1 mRNA, protein level and activity, and serum PON1 activity in all dietary groups but did not consistently increase thiobarbituric acid levels (thiobarbituric acid reactive substances, TBARS), an indicator of lipid oxidation and oxidative stress, in liver or serum. Inadequate (high or low) dietary Se decreased baseline and PCB 126-induced aryl hydrocarbon receptor (AhR) expression but further increased PCB 126-induced cytochrome P450 1A1 (CYP1A1) expression, the enzyme believed to be the cause for PCB 126-induced oxidative stress. In addition, a significant inverse relationship was observed not only between dietary Se levels and PON1 mRNA and PON1 activity but also with TBARS levels in the liver, suggesting significant antioxidant protection from dietary Se. NAC lowered serum baseline TBARS levels in controls and increased serum PON1 activity but lowered liver PON1 activities in animals treated with 1 μmol/kg PCB 126, suggesting antioxidant activity by NAC primarily in serum. These results also show an unexpected predominantly inverse relationship between Se or NAC and PON1 during control and PCB 126 exposure conditions. These interactions should be further explored in the development of dietary protection regimens.

- Tsujimoto S, Ishida T, Takeda T, Ishii Y, Onomura Y, Tsukimori K, Takechi S, Yamaguchi T, Uchi H, Suzuki SO, Yamamoto M, Himeno M, Furue M, Yamada H.
Selenium-binding protein 1: its physiological function, dependence on aryl hydrocarbon receptors, and role in wasting syndrome by 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Biochim Biophys Acta*. 2013 1830:3616-24.

Background: Selenium-binding protein 1 (Selenbp1) is suggested to play a role in tumor suppression, and may be involved in the toxicity produced by dioxin, an activator of aryl hydrocarbon receptors (AhR). However, the mechanism or likelihood is largely unknown because of the limited information available about the physiological role of Selenbp1.
Methods: To address this issue, we generated Selenbp1-null [Selenbp1 (-/-)] mice, and examined the toxic effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in this mouse model.
Results: Selenbp1 (-/-) mice exhibited only a few differences from wild-type mice in their apparent phenotypes. However, a DNA microarray experiment showed that many genes including Notch1 and Cdk1, which are known to be enhanced in ovarian carcinoma, are also increased in the ovaries of Selenbp1 (-/-) mice. Based on the different responses to TCDD between C57BL/6J and DBA/2J strains of mice, the expression of Selenbp1 is suggested to be under the control of AhR. However, wasting syndrome by TCDD occurred equally in Selenbp1 (-/-) and (+/+) mice.
Conclusions: The above pieces of evidence suggest that 1) Selenbp1 suppresses the expression of tumor-promoting genes although a reduction in Selenbp1 alone is not very serious as far as the animals are concerned; and 2) Selenbp1 induction by TCDD is neither a pre-requisite for toxicity nor a protective response for combating TCDD toxicity.
General significance: Selenbp1 (-/-) mice exhibit little difference in their apparent phenotype and

responsiveness to dioxin compared with the wild-type. This may be due to the compensation of Selenbp1 function by a closely-related protein, Selenbp