

# Bölüm 16

## ENDOKRİN BOZUCULAR

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### GİRİŞ

Sentetik kimyasallar, özellikle son yarım yüzyılda hayatımızın her dakikasında gereklilik duyduğumuz, kaçınılmaz ürünlerin başında yer almaktadırlar. Bu ürünlerin çoğu günlük hayat konforumuzu artırmak, toplumsal ihtiyaçları sağlamak (yangın söndürücüler, alev geciktiriciler vb.) ya da modern yaşamı kolaylaştırmak (besinlerdeki koruyucular, plastik maddeler) amacıyla birçok alanda kullanılmaktadır. Fetal yaşamdan başlayan bir etkilenme süreciyle beraber yaşam sonuna kadar yaş ve cinsiyet ayırt etmeksizin her şekilde karşımıza çıkmaktadırlar. Etki mekanizması, endokrin organlar ve dolayısıyla hormonlar üzerinden olduğundan bu maddeler endokrin bozucular olarak da adlandırılmaktadırlar<sup>1</sup>. Maddenin türüne bağlı olarak; gıda, içme suyu, hava, toprak, ev malzemeleri, tüketici malzemeleri, ilaçlar vb. yollar ile maruziyet yaşanabilmektedir. Çocuk yaş grubu özellikle plasental geçiş nedeniyle yeni doğan döneminden başlayıp, sonrasında beslenme sırasında kullanılan aparatlar ve bakım malzemeleriyle, ilerleyen aylarda kirlenmiş toz-toprak ile, oral fazın aktif döneminde nesnelere sık ağza götürme vb. nedenlerle endokrin bozuculara sıkça maruz kalmaktadır.

Endokrin bozucular; hipotalamohipofizer-gonad/tiroid/adrenal bez akslarını etkileyerek, endokrin sistem işleyişini sentez, sekresyon, transport, reaksiyonlar, aktivasyon dönemi, vücuttan atılma evresi, hedef organ etkileri vb. bir-

çok farklı basamakta bozabilen ekzojen madde veya madde karışımlarıdır<sup>2</sup>. Etkileri yıkıcı ve uzun süreli olup hayat konforunu bozacak seviyelere ulaşabilmektedir. Yıllar içerisinde yapılan çalışmalar; bu bileşiklerin nükleer reseptörler, steroid hormon reseptörleri, steroid olmayan hormon reseptörleri (norepinefrin, dopamin, serotonin) ve nörotransmitter reseptörleri üzerine yaptığı etkiler üzerine yoğunlaşmıştır<sup>3</sup>.

Fetal dönemden başlayan bu maruziyet gen metilasyonlarını tetikleyerek gerek çocukluk dönemi, gerekse de ileri yaşamda devam edecek olan bir genetik değişime ve soydan soya aktarılan bir patolojiye neden olmaktadır<sup>4</sup>. Yaşadığımız yüzyılın kaçınılmaz ürünleri olan bu bileşiklerin sınıflamasına ve organlar ve metabolizma üzerine etkilerini güncel bilgiler ışığında göz atalım.

### SINIFLAMA

**A) Doğal endokrin bozucular:** Östrojen reseptörlerine bağlanan ve onları uyaran doğal olarak oluşan non-steroidal bileşiklerdir. Gerek yarı ömürlerinin kısa olması gerekse de dokularda birikme özelliği olmaması ve vücuttan kolayca atılmaları nedeniyle yan etkileri önemli düzeyde olmayan grubu oluşturmaktadırlar<sup>5</sup>. Fitoöstrojenler olarak da adlandırılırlar. Vücutumuzda sentezlenen östrojene oranla daha zayıf etkili olup düşük dozlarda etkileri yok denecek kadar azdır. Günlük hayatımızda elma, kiraz, soya fasulyesi, maydanoz, havuç, patates, hububat vb. besinlerin içerisinde

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## KAYNAKÇA

1. Andreas Kortenkamp, O. M., Michael Faust, Richard Evans, Rebecca McKinlay, Frances Orton and Erika Rovivatz. (2011). State Of The Art Assessment Of Endocrine Disrupters Final Report
2. Diamanti-Kandarakis, E., Palioura, E., Kandarakis, S. A., & Koutsilieris, M. (2010). The impact of endocrine disruptors on endocrine targets. *Horm Metab Res*, 42(8), 543-552. doi: 10.1055/s-0030-1252034
3. Schug TT, Janesick A, Blumberg B, Heindel JJ: Endocrine disrupting chemicals and disease susceptibility. *J Steroid Biochem Mol Biol* 127: 204-215, 2011.
4. Meeker JD. Exposure to environmental endocrinedisrupting compounds and men's health. *Maturitas*. 2010 Jul;66(3):236-241.
5. Keith, L. H. (1998). Environmental Endocrine Disruptors. *Pure and Applied Chemistry*, 70(12), 2319-2326.
6. Çetinkaya, S. (2009). Endokrin Bozucular ve Ergenlik Üzerine Etkileri. *Dicle Tıp Dergisi*, 36(1), 59-66.
7. Crinnion WJ. Maternal levels of xenobiotics that affect fetal developmentandchildhoodhealth. *Altern Med Rev*. 2009;14:212-222
8. Barker, D. J. (2004). The developmental origins of adult disease. *J Am Coll Nutr*, 23(6 Suppl), 588S-595S.
9. Diamanti-Kandarakis, E., Bourguignon, J. P., Giudice, L. C., Hauser, R., Prins, G. S., Soto, A. M. ve diğerleri. (2009). Endocrine-disrupting chemicals: an Endocrine Society scientific statement. *Endocr Rev*, 30(4), 293-342. doi: 10.1210/er.2009-0002
10. Liu ZH, Kanjo Y, Mizutani S. A review of phytoestrogens: their occurrence and fate in the environment. *Water Res* 2010; 44: 567-577.
11. Sirotkin AV, Harrath AH. Phytoestrogens and their effects. *European Journal of Pharmacology* 2014;741:230-236
12. Ososki AL, Kennelly E J. Phytoestrogens: a review of the present state of research. *Phytotherapy Research* 2003;17:845-869.
13. Baran SM, Kocabağlı N. Yemlerdeki Östrojenik Etkili Maddeler ve Etkileri. *İstanbul Üniversitesi Veterinerlik Dergisi* 2000;26:141-148.
14. Wang CC, Prasain JK, Barnes S. Review of the methods used in the determination of phytoestrogens. *Journal of Chromatography B* 2002;777:3-28.
15. Özer Ö, Konuklugil B. Phytoestrogens and Their Effects On Menopause. *Ankara Ecz. Fak. Derg* 2007;36:199-222
16. Jonathan PE. Humulus Lupulus. *Alternative Medicine Review* 2003;8:190-192.
17. Gün Ç, Demirci N. Menopozda Bitkisel Tedavi Kullanımı. *Arşiv Kaynak Tarama Dergisi* 2015;24:520-530.
18. İnanç N, Tuna Ş. Fitoöstrojenler ve Sağlıkta Etkileri. *Erciyes Üniversitesi Veteriner Fakültesi Dergisi* 2005;2.
19. Cassidy A., Hanley B., Raventos R. Isoflavones, Lignans And Stilbens-Origins, Metabolism And Potential Importance To Human Health. *Journal Of The Science of Food And Agriculture* 80:1044-1062, (2000).
20. Büyüktuncer Z, Başaran AA. Fitoöstrojenler ve Sağlıkta Yaşamdaki Önemleri. *Hacettepe Üniversitesi, Eczacılık Fakültesi Dergisi* 2005;25:79-94.
21. Demlow BM., Duncan AM., Wangen KE., Et al. Soy Isoflavones Improve Plasma Lipids In Normocholesterolemic, Premenopausal Women. *Am J Clin Nutr* 71:1462-9, (2000).
22. Puska PP, Korpelainen V, Hoie LH, Et al. Soy In Hypercholesterolaemia: A DoubleBlind Plasebo-Controlled Trial. *Eur J Clin Nutr* 56:352-357, (2002).
23. Clarkson TB. Soy, Soy Phytoestrogens And Cardiovascular Disease. *J Nutr* 132:566- 596, (2002).
24. Gonzalez Canete N, Duran Aguero S (2014). Soya isoflavones and evidences on cardiovascular protection. *Nutr Hosp* 29: 1271-1282.
25. Wuttke W, Jarry H, Seidlova-Wuttke D (2007). Isoflavones--safe food additives or dangerous drugs? *Ageing Res Rev* 6: 150-188.
26. Rietjens IM, Sotoca AM, Vervoort J, Louisse J (2013). Mechanisms underlying the dualistic mode of action of major soy isoflavones in relation to cell proliferation and cancer risks. *Mol Nutr Food Res* 57: 100-113.
27. Andres S, Abraham K, Appel KE, Lampen A (2011). Risks and benefits of dietary isoflavones for cancer. *Crit Rev Toxicol* 41: 463-506
28. Ivonne M C M Rietjens, Karsten B. The potential health effects of dietary phytoestrogens. *Br J Pharmacol*. 2017 Jun; 174(11): 1263-1280.
29. M Fricke, U Lahl Risikobewertung von Perfluortensiden als Beitrag zur aktuellen Diskussion zum REACH-Dossier der EU Kommission. *Umweltwissenschaften und Schadstoff-Forschung*, 2005 - Springer
30. Umweltbundesamt (UBA): Perfluorierte Verbindungen: Falscher Alarm oder berechtigte Sorge Februar 2007, Dessau 2007.
31. Umweltbundesamt (UBA): Per- und Polyfluorierte Chemikalien. Einträge vermeiden-Umwelt schützen. Juli 2009, Dessau-Roßlau 2009.
32. Fasano WJ, Carpenter SC, Gannon SA, Snow TA, Stadler JC, Kennedy GL, Buck RC, Korzeniowski SH, Hinderliter PM, Kemper RA: Absorption, distribution, metabolism and elimination of 8-2 fluorotelomer alcohol in the rat. *Toxicol Sci* 2006, 91: 341-355.
33. Stahl T, Ackmann R, Georgii S, Wohlfarth R, Brunn H: Perfluorierte Tenside. Verwendung, Vorkommen und Aufnahme mit Trinkwasser und Nahrung. *Ernährung* 2007, 1: 27-35
34. Johnson JD, Gibson SJ, Ober RE: Cholestyramine-enhanced fecal elimination of carbon-14 in rats after administration of ammonium [14C] perfluorooctanoate or potassium [14C] perfluorooctansulfonate. *Fundam Appl Toxicol* 1984, 4: 972-976
35. Cui L, Liao CY, Zhou QF, Xia TM, Yun ZJ, Jiang GB: Excretion of PFOA and PFOS in male rats during a subchronic exposure. *Arch Environ Contam Toxicol* 2010, 58: 205-213
36. Woods MM, Lanphear BP, Braun JMet al. Gestational exposure to endocrine disrupting chemicals in relation to infant birth weight: a Bayesian analysis of the HOME Study. *Environ Health*. 2017 Oct 27;16(1):115.
37. Lenters V, Portengen L, Rignell-Hydbom A, Jonsson BAG, Lindh CH, Piersma AH, Toft F, Bonde JP, Heederik D, Rylander L, Vermeulen R. Prenatal phthalate, perfluoroalkyl acid, and organochlorine exposures and term birth weight in three birth cohorts: multi-pollutant

- models based on elastic net regression. *Environ Health Perspect.* 2016;124:365–372.
38. Johnson PI, Sutton P, Atchley DS, Koustas E, Lam J, Sen S, Robinson DA, Axelrad DA, Woodruff TJ. The navigation guide - evidence based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth. *Environ Health Perspect.* 2014;122:1028–1039.
  39. Maisonet M, Terrell ML, McGeehin MA, Christensen KY, Holmes A, Calafat AM, Marcus M. Maternal concentrations of polyfluoroalkyl compounds during pregnancy and fetal and postnatal growth in British girls. *Environ Health Perspect.* 2012;120(10):1432–1437.
  40. Fierler H. Stockholm Convention on POPs: Obligation and Implementation. In: Mehmetli E, Koumanova B, eds. *The Fate of Persistent Organic Pollutants in the Environment.* Dordrecht: Springer, 2008: 4.
  41. Li QQ, Loganath A, Chong YS, Tan J, Obbard JP. Persistent organic pollutants and adverse health effects in humans. *J Toxicol Environ Health A*, 2006; 69 (21): 1987-2005
  42. Lee DH, Lee IK, Jin SH, Steffes M, Jacobs DR. Association between serum concentrations of persistent organic pollutants and insulin resistance among nondiabetic adults: Results from the National Health and Nutrition Examination Survey 1999-2002. *Diabetes Care*, 2007; 30 (1): 622-628
  43. Shatalov V, Breivik K, Berg T, Dutchak S, Pacyna J. Persistent Organic Pollutants. In: Löfblad G, Tarrasón L, Torseth K, Dutchak S, eds. *EMEP Assessment Part I.* Oslo: Norwegian Meteorological Institute, 2005: 135-136.
  44. Chevri er J, Eskenazi B, Bradman A, Fenster L, Barr DB. Associations between prenatal exposure to polychlorinated biphenyls and neonatal thyroid-stimulating hormone levels in a Mexican-American population, Salinas Valley, California. *Environ Health Perspect.* 2007;115:1490–1496.
  45. Meerts IA, Assink Y, Ceni jn PH, Weijers BM, Bergman A, Koeman JH, Brouwer A. Placental transfer of a hydroxylated polychlorinated biphenyl and effects on fetal and maternal thyroid hormone homeostasis in the rat. *Toxicol Sci.* 2002;68:361–371.
  46. Mastalerz P. *The true story of DDT, PCB, and Dioxin.* Wroclaw: Wydawnictwo Chemiczne, 2005: 93-9.
  47. Longnecker MP, Klebanoff MA, Brock JW, Zhou H, Gray KA, Needham LL, Wilcox AJ. Maternal serum level of 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene and risk of cryptorchidism, hypospadias, and polythelia among male offspring. *Am J Epidemiol.* 2002;155:313–322.
  48. Bhatia R, Shiao R, Petreas M, Weintraub JM, Farhang L, Eskenazi B. Organochlorine pesticides and male genital anomalies in the child health and development studies. *Environ Health Perspect.* 2005;113:220–224.
  49. Zhang Y, Lin L, Cao Y, Chen B, Zheng L, Ge RS. Phthalate levels and low birth weight: a nested case-control study of Chinese newborns. *J Pediatr.* 2009;155:500–544.
  50. Cocco P, Brennan P, Ibba A, et al. Plasma polychlorobiphenyl and organochlorine pesticide level and risk of major lymphom subtypes. *Occup Environ Med*, 2008; 65: 132–40.
  51. Barber JL, Sweetman AJ, Van Wijk D, Jones KC. Hexachlorobenzene in the global environment: Emissions, levels, distribution, trends and processes. *Sci Total Environ*, 2005; 349 (1-3): 1-44.
  52. Agarwal SA. *Pesticide Pollution.* New Delhi: APH Publishing, 2009: 71-6.
  53. Committee on the Significance of International Transport of Air Pollutants. *Global sources of local pollution: an assessment of long-range transport of key air pollutants to and from the United States.* Washington DC: National Research Council, 2009: 113-4. 16.
  54. Secretariat of the Stockholm Convention. *Endosulfan. An Introduction to the Chemical Added to the Stockholm Convention by the Conference of the Parties at its Fifth Meeting.* Geneva: United Nations Environment Programme, 2011: 6-8.
  55. Rudel RA, et al. Food packaging and bisphenol A and bis(2-ethylhexyl) phthalate exposure: findings from a dietary intervention. *Environ Health Perspect.* 2011;119:914–920.
  56. Calafat AM. Contemporary Issues in Exposure Assessment Using Biomonitoring. *Current Epidemiology Reports.* 2016;3:145–153
  57. Meeker JD, Sathyanarayana S, Swan SH. Phthalates and other additives in plastics: human exposure and associated health outcomes. *Philos Trans R Soc Lond B Biol Sci.* 2009 Jul 27;364(1526):2097–2113.
  58. Meeker JD, Ferguson KK. Phthalates: Human Exposure and Related Health Effects. In: Schechter A, editor. *Dioxins and Health*, 3rd Edition. Hoboken, NJ: John Wiley & Sons; 2012.
  59. Ferguson KK, McElrath TF, Chen YH, Mukherjee B, Meeker JD. Urinary phthalate metabolites and biomarkers of oxidative stress in pregnant women: a repeated measures analysis. *Environ Health Perspect.* 2015;123:210–216. doi: 10.1289/ehp.1307996.
  60. LaRocca J, Binder AM, McElrath TF, Michels KB. First-Trimester Urine Concentrations of Phthalate Metabolites and Phenols and Placenta miRNA Expression in a Cohort of U.S. Women. *Environ Health Perspect.* 2015 doi: 10.1289/ehp.1408409.
  61. Wolff MS, Teitelbaum SL, Pinney SM, et al. Investigation of relationships between urinary biomarkers of phytoestrogens, phthalates, and phenols and pubertal stages in girls. *Environ Health Perspect.* 2010 Jul;118(7):1039–1046.
  62. Durmaz E, Ozmert EN, Erkekoglu P, et al. Plasma phthalate levels in pubertal gynecomastia. *Pediatrics.* 2010 Jan;125(1):e122–129.
  63. Miodovnik A, et al. Endocrine disruptors and childhood social impairment. *Neurotoxicology.* 2011;32:261–267. doi: 10.1016/j.neuro.2010.12.009.
  64. Factor-Litvak P, et al. Persistent Associations between Maternal Prenatal Exposure to Phthalates on Child IQ at Age 7 Years. *PLoS One.* 2014;9:e114003. doi: 10.1371/journal.pone.0114003.
  65. Braun JM, et al. Gestational exposure to endocrine-disrupting chemicals and reciprocal social, repetitive, and stereotypic behaviors in 4- and 5-year-old children: the HOME study. *Environ Health Perspect.* 2014;122:513–520. doi: 10.1289/ehp.1307261.

66. Huang HB, et al. Fetal and Childhood Exposure to Phthalate Diesters and Cognitive Function in Children Up to 12 Years of Age: Taiwanese Maternal and Infant Cohort Study. *PLoS One*. 2015;10:e0131910. doi: 10.1371/journal.pone.0131910.
67. Deierlein AL, et al. Longitudinal associations of phthalate exposures during childhood and body size measurements in young girls. *Epidemiology*.
68. Trasande L, Attina TM, Sathyanarayana S, Spanier AJ, Blustein J. Race/ethnicity-specific associations of urinary phthalates with childhood body mass in a nationally representative sample. *Environ Health Perspect*. 2013;121:501–506. doi: 10.1289/ehp.1205526
69. Woods MM, Lanphear BP, Braun JM, McCandless LC. Gestational exposure to endocrine disrupting chemicals in relation to infant birth weight: a Bayesian analysis of the HOME Study. *Environ Health*. 2017 Oct 27;16(1):115
70. Philippat C, Mortamais M, Chevrier C, Petit C, Calafat AM, Ye X, Silva MJ, Brambilla C, Pin I, Charles M-A, Cordier S, Slama R. Exposure to phthalates and phenols during pregnancy and offspring size at birth. *Environ Health Perspect*. 2012;120:464–470. doi: 10.1289/ehp.1103634.
71. Von Goetz N, Wormuth M, Scheringer M, Hungerbühler K. Bisphenol a: how the most relevant exposure sources contribute to total consumer exposure. *Risk Anal*. 2010;30:473–487
72. Ehrlich S, Calafat AM, Humblet O, Smith T, Hauser R. Handling of thermal receipts as a source of exposure to bisphenol A. *JAMA*. 2014;311:859–860. doi: 10.1001/jama.2013.283735
73. Thayer KA, et al. Pharmacokinetics of bisphenol A in humans following a single oral administration. *Environ Int*. 2015;83:107–115
74. Gentilcore D, Porreca I, Rizzo F, Ganbaatar E et al. Ambrosino C. Bisphenol A interferes with thyroid specific gene expression. *Toxicology*. 2013 Feb 8; 304():21-31
75. Ejaredar M, Lee Y, Roberts DJ et al. Bisphenol A exposure and children's behavior: A systematic review. *J Expo Sci Environ Epidemiol*. 2017 Mar;27(2):175-183.
76. Kondolot M, Ozmert EN, Asçı A et al. Plasma phthalate and bisphenol a levels and oxidant-antioxidant status in autistic children. *Environ Toxicol Pharmacol*. 2016 Apr;43:149-58.
77. Kardas F, Bayram AK, Demirci E et al. Increased Serum Phthalates (MEHP, DEHP) and Bisphenol A Concentrations in Children With Autism Spectrum Disorder: The Role of Endocrine Disruptors in Autism Etiopathogenesis. *J Child Neurol*. 2016 Apr;31(5):629-35.
78. Hoepner LA, Whyatt RM, Widen EM et al. Bisphenol A and Adiposity in an Inner-City Birth Cohort. *Environ Health Perspect*. 2016 Oct; 124(10):1644-1650
79. Joseph M, Braun J. Early Life Exposure to Endocrine Disrupting Chemicals and Childhood Obesity and Neurodevelopment. *Nat Rev Endocrinol*. 2017 Mar; 13(3): 161–173.
80. Berger K, Eskenazi B, Kogut K, Parra K, Lustig RH, Greenspan LC, et al. 2018. Association of prenatal urinary concentrations of phthalates and bisphenol A and pubertal timing in boys and girls. *Environ Health Perspect* 126(9):97004.
81. Rodricks JV, Swenberg JA, Borzelleca JF, Maronpot RR, Shipp AM. Triclosan: a critical review of the experimental data and development of margins of safety for consumer products. *Crit Rev Toxicol*. 2010 May; 40(5):422-84
82. Sandborgh-Englund G, Adolfsson-Erici M, Odham G, Ekstrand J. Pharmacokinetics of triclosan following oral ingestion in humans. *J Toxicol Environ Health A*. 2006 Oct; 69(20):1861-7
83. Koeppe ES, Ferguson KK, Colacino JA, Meeker JD. Relationship between urinary triclosan and paraben concentrations and serum thyroid measures in NHANES 2007-2008. *Sci Total Environ*. 2013 Feb 15; 445-446():299-305
84. Yee AL, Gilbert JA. MICROBIOME. Is triclosan harming your microbiome? *Science*. 2016 Jul 22; 353(6297):348-9.
85. Henrichs J, Ghassabian A, Peeters RP et al. Maternal hypothyroxinemia and effects on cognitive functioning in childhood: how and why? *Clin Endocrinol (Oxf)*. 2013 Aug; 79(2):152-62
86. Jensen RB, Juul A, Larsen T et al. Cognitive ability in adolescents born small for gestational age: Associations with fetal growth velocity, head circumference and postnatal growth. *Early Hum Dev*. 2015 Dec; 91(12):755-60.
87. Buser MC, Murray HE, Scinicariello F. Association of urinary phenols with increased body weight measures and obesity in children and adolescents. *J Pediatr*. 2014 Oct; 165(4):744-9138
88. Buckley JP, Herring AH, Wolff MS, Calafat AM et al. Prenatal exposure to environmental phenols and childhood fat mass in the Mount Sinai Children's Environmental Health Study. *Environ Int*. 2016 May; 91():350-6.
89. Boberg J, Taxvig C, Christiansen S, Hass U. 2010. Possible endocrine disrupting effects of parabens and their metabolites. *Reprod Toxicol* 30(2):301–312,
90. BUZEK J, ASK B: Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products. *OJ L* 342, 2009
91. Soni MG, Carabin IG, Burdock GA: Safety assessment of esters of p-hydroxybenzoic acid (parabens). *Food Chem Toxicol* 43: 985-1015, 2005.
92. L. Kolatorava , M. Duskov , J. Vitku , L. Starka. Prenatal Exposure to Bisphenols and Parabens and Impacts on Human Physiology . *Physiol. Res*. 66 (Suppl. 3): S305-S315, 2017.
93. Jiang Y, Zhao H, Xia W, Li Y, Liu H, Hao K, et al. 2019. Prenatal exposure to benzophenones, parabens and triclosan and neurocognitive development at 2 years. *Environ Int* 126:413–421.
94. Agier L, Basagaña X, Maitre L, Granum B, Bird PK, Casas M, et al. 2019. Early-life exposome and lung function in children in Europe: an analysis of data from the longitudinal, population-based HELIX cohort. *Lancet Planet Health* 3(2):e81–e92.
95. Harrison W, Goodman D. 2015. Epidemiologic trends in neonatal intensive care, 2007–2012. *JAMA Pediatr* 169(9):855–862, PMID: 26214387, 10.1001/jamapediatrics.2015.1305.
96. Iribarne-Durán LM, Artacho-Cordón F, Pena-Caballero et al. Presence of Bisphenol A and Parabens in a Neonatal Intensive Care Unit: An Exploratory Study of Potential Sources of Exposure. *Environ Health Perspect*. 2019 Nov;127(11):117004.

97. Oranges T, Dini V, Romanelli M. 2015. Skin physiology of the neonate and infant: clinical implications. *Adv Wound Care (New Rochelle)* 4(10):587-595, PMID: 26487977, 10.1089/wound.2015.0642.
98. Witorsch R.J. and Thomas J.A. (2010). Personal care products and endocrine disruption: a critical review of the literature. *Critical Reviews in Toxicology*, 40 (3), 1-30.
99. Scialli A.R. (2011). Reproductive effects of the parabens. *Reproductive Toxicology*, 32, 138-140.
100. Oishi S. (2001). Effect of butylparaben on the male reproductive system in rats. *Toxicology and Industrial Health*, 17, 31-39.
101. Oishi S. (2002). Effects of propylparaben on the male reproductive system. *Food and Chemical Toxicology*. 40, 1807-1813.
102. Hoberman A.M., Schreiv D.K., Leazer T., Daston G.P., Carthew P, Re T., Laretz L. and Mann P. (2008). Lack of effect of butylparaben and methylparaben on the reproductive system in male rats. *Birth Defects Research Part B: Developmental and Reproductive Toxicology*, 83 (2), 123-133.
103. Shaw J. and De Catanzaro D. (2009). Estrogenicity of parabens revisited: impact of parabens on early pregnancy and an uterotrophic assay in mice. *Reproductive Toxicology*, 28, 26-31.