Human contact with phthalates during early life stages leads to weight gain and obesity

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Abstract: When human is exposed to endocrine-disrupting chemicals (EDCs) such as phthalates, for example, di(2-ethylhexyl) phthalate(DEHP) and diisononyl phthalate (DINP) in early life may contribute to overweight and obesity. EDCs are also called obesogens. Obesogen can promote adipogenesis and cause weight gain. Phthalates are man-made chemicals used in polyvinyl (PVC) products such as wires, cables, floorings, wall coverings, medical devices and cosmetics. The vulnerability of humans to EDCs has resulted in adverse health consequences, including decreased sperm motility, infertility in men, coronary heart disease, high blood pressure, atherosclerosis, and obesity. This paper will educate people all over the world about the danger associated with contact with phthalates. It will also help to make people limit exposure to materials made of phthalates.

Keywords: Environmental Management; Environment & Health; Health & Society

1. Introduction

Obesity is a disease that globally human beings are confronted with. The disease has reached a frightening proportion and is now common in developing countries such as Egypt, Ghana, Ethiopia, Kenya and Tanzania (Amugsi, 2018), whereas in the past obesity was thought to be a disease of the rich countries such as US (Levine, 2011), Italy, UK (El Sayeed et al., 2012), Spain and Poland (Berhofer et al., 2008). An obese person may suffer in addition to one or more of the following diseases; type 2 diabetes.
mellitus, hyperlipidemia, cardiovascular disease, liver and gall bladder diseases, stroke, hypertension and certain types of cancer (Williams et al., 2015). Obesogens are a group of chemicals that disrupt the endocrine system of the body. They stimulate the endocrine system and increase the amount of hormone produced. A subset of obesogen chemicals called Phthalates can be said to act as engineer to building fat cells in the body. This can raise the number of size of fat cells in the body. This may lead to a weight gain of the body. About 40% of all consumer products used by human beings have phthalates as one of the components (Halden, 2010). Phthalates are employed in the industry to effect softness, flexibility, and elongation in plasticizers such as polyvinyl chloride (PVC) (Halden, 2010). With time phthalates leach out from the material in which they are present. Therefore, they are present in indoor air or dust and thus present in the human environment.

2. Chemical structure of phthalates and uses
Phthalates are diesters of phthalic acid (1, 2-benzenedicarboxylic acid) and are produced in large quantities and used in the manufacture of plastics (Guo et al., 2011). Phthalates differ by molecular weight and physicochemical properties and this variation depends on the length of the hydrocarbon chain (R) and the degree of branching. Hence, they are either high molecular weight (HMW) \([n = 8–13 \text{ carbon}]\) or low molecular weight (LMW) \([n = 3–7 \text{ carbon}]\) with general structural formula \(C_nH_{2n+1}\) for the R group (alkyl) \([\text{where } n = \text{ no. of carbon}]\) (Figure 1).

Examples of common HMW phthalates include diisononyl phthalate (DINP), diisodecyl phthalate (DIDP) and di(2-ethylhexyl) phthalate (DEHP), whereas some examples of LMW phthalates are dimethyl phthalate (DMP), diethyl phthalate (DEP) and dibutyl phthalate (DBP) (Duty et al., 2003; Guo et al., 2011).

While the HMW phthalates are used in the production of goods such as wires, cables, floorings, wall coverings, and self-adhesive films, the LMW phthalates are used to make goods such as personal care products (e.g., perfumes, lotions and cosmetics), varnish, coatings and inks (Duty et al., 2003; Guo et al., 2011).

Given that di(2-ethylhexyl) phthalate is the most common member of the phthalate and mostly used in the industry for the manufacture of goods for humans (P. C. Huang et al., 2008), it has become relevant to outline its synthesis. As such the uses and synthesis of phthalates have been reviewed.

3. Uses and synthesis of di(2-ethylhexyl) phthalate (DEHP)
Di(2-ethylhexyl) phthalate (DEPH) is the most common member of the group of organic compounds called phthalate. It is also called diocyl phthalate. DEHP is colourless sticky and lipotropic liquid. It is estimated that 2 million tons of DEHP are manufactured annually in the world (Shelby, 2006). It is used as a softener in many industrial products; such as medical devices, packed food, and beverages; soft plastic products building and furniture materials, cosmetics and personal care products (Dobrzyńska, 2016; Earls et al., 2003; Koniecki et al., 2011). As a result of the enormous

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**Figure 1. General chemical structure of phthalates.**
uses of DEHP by humans, it is found in air, water, and soil (Roslev et al., 1998). Subsequently, it is everywhere in the environment where human finds himself/herself.

DEPH is produced by the esterification of phthalic anhydride (PAN) with 2-ethylhexanol (2EH) in the presence of methane sulphonic acid (MSA) and para-toluene acid (p-TSA) catalyst (Figure 2).

In the reaction, PAN is first converted to mono-2-ethylhexyl phthalate (MOP), which then reacts further to produce di(2-ethylhexyl) phthalate, DEPH, also known as dioctyl phthalate (DOP) as shown in Figure 2.

4. Metabolism of phthalates in human

Human exposure to phthalates is through ingestion of foods contaminated with phthalates, inhalation of phthalate polluted air or dust and dermal absorption (Scientific Committee on Health and Environmental Risks (SCHER), 2008). In the body, phthalates are metabolized in two enzymatic steps: a phase I hydrolysis followed by phase II conjugation (Calafat et al., 2005; Rusyn et al., 2006). During phase I, lipases and esterases in the intestines and the parenchyma catalyse the hydrolysis of phthalates into biologically active monoester phthalates (Calafat et al., 2005; H. M. Koch et al., 2005) (Figure 2). Phase II, however, is a conjugation reaction where 5-diphosphoglucuronyl transferase conjugates the monoester phthalates to become a biologically inactive glucuronide where the generated phthalate metabolites are then excreted in urine and faeces (Calafat et al., 2005; H. M. Koch et al., 2005) (Figure 2). Usually, LMW phthalates are excreted after phase I hydrolysis whereas HMW phthalates are excreted after phase II metabolism.

Figure 2. Synthesis of di(2-ethylhexyl) phthalate (DEHP).
5. Metabolism of Di-2-ethylhexyl phthalate (DEHP)
As described in section 1.3, the metabolism of di-(2-ethylhexyl) phthalate (DEHP) in human follows the same reaction and can be seen in Figure 4. In the process, DEHP is metabolized to mono-(2-ethylhexyl) phthalate; MEHP, in a phase 1 biotransformation which may undergo oxidation reaction to give mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEHHP, mono-(2-ethyl-5-oxohexyl) phthalate; MEOHP, and mono-(2-ethyl-5-carboxypentyl) phthalate; ME CPP or may undergo phase II biotransformation to produce glucuronide conjugate.

Though the above metabolism processes occur in human, for children, a study showed that the ratios of the oxidized DHPH metabolites; such as mono-(2-ethyl-5-hydroxyhexyl) phthalate.
(SOH-MEHP), mono-(2-ethyl-5-oxoxygenyl) phthalate (5oxo-MEHP), mono-(2-ethyl-5-carboxypen- 
yl) phthalate (5cx-MEPP), and mono-[2-(carboxymethyl)hexyl] phthalate (2cxMMHP) to mono-
(2-ethylhexyl) phthalate (MEHP) increased with decrease in age (Becker et al., 2004). An indication that more secondary metabolites are formed during the metabolic process.

6. Effects of exposure to phthalates
Studies have shown that increased levels of phthalate metabolites caused a decrease in the andro-
genetic distance in male newborns but not in female newborns (Swan et al., 2005, 2015). Other studies also showed that high phthalate metabolites were responsible for low sperm concentration (Murature et al., 1987), decreased sperm motility, impaired sperm growth and infertility in men (Axelsson et al., 2015; Rozati et al., 2002). In yet another study, high levels of phthalate metabolites were linked with many chronic diseases including coronary heart disease (Olsen et al., 2012), high blood pressure (Werner et al., 2015), atherosclerosis (Lind & Lind, 2011) and preterm birth (Ferguson et al., 2014). A recent study showed that pregnant women who frequently come into contact with phthalate chemi-
cals can give birth to baby boys who show traits of Autism (Healthline, 2020).

7. Obesity diagnosis
The World Health Organisation (WHO) defines obesity using body mass index (BMI = w/h²) to diagnose obesity in people where w is weight and h height of a person. A person with BMI between 30.00 and 34.99 is class 1 obese, between 35.00 and 39.99 class 2 obese and above 40 class 3 obese (World Health Organization (WHO), 2000). Whereas in adolescents and children, a nomogram is used to ascertain if one is obese or otherwise. BMI equal to or greater than the age- and gender-specific 95th percentile is considered obese (Centre for Disease Control and Prevention, 2014). A person who is obese gathers overabundance fat in the body; that is in the muscle, bone, fat, and water (Ogden et al., 2006). People who are obese may suffer from the following diseases: Coronary heart disease, Gallbladder disease, type 2 diabetes, mortality, high blood pressure (hypertension), high- or low-density lipoprotein (LDL) cholesterol or low high-density lipoprotein (HDL) cholesterol and high levels of triglycerides (Dyslipidemia), stroke, osteoarthritis and some cancers which includes endometrial, breast, colon, kidney, gallbladder and liver cancer (Jensen, 2013; Williams et al., 2015).

8. Studies done on phthalate metabolites and obesity
A Slovakian study of five phthalate metabolites, mono-(2-ethylhexyl) phthalate (MEHP), mono-(2-
ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxoxygenyl) phthalate (MEOHP), mono-
butyl phthalate (MnBP) and mono-isobutyl phthalate (MiBP) in urine was conducted. This study involved 129 adult participants, of which 45 were community service workers, 35 were plastic industry workers and 49 were from the general population. Anthropometric measures included the waist-to-height ratio (WHR), body mass index (BMI), waist-to-hip ratio (WHR), hip circumference (HC) and waist circumference (WC) were collected. In addition, urine sample was collected, though not the first-morning specimen, to determine phthalate metabolite concentration. Interestingly, this study showed an inverse relationship between MEHP and BMI, WHR, HC, WHTR and WC. In comparison, the workers in the plastic industry had higher concentrations of phthalate metabolites (Petrovičová et al., 2016). An indication of industrial exposure.

One more study in the USA involving 977 adult women was carried out, phthalate metabolites in urine were monitored, along with anthropometric measures including weight and height were collected. The study revealed that monobenzyl phthalate (MBzP) and mono-n-butyl phthalate (MBP) have a remarkable association with modestly faster gain in weight, while monoethyl phthalate (MEP) and MEHP were not monotonically associated with bodyweight change (Song et al., 2014).

Another study was done in China around the same period involving 259 participants aged between 8 and 15 determined phthalate metabolites such as MEHP and MEP in the urine. The anthropometric measures collected in this study were WC and BMI. The result indicated that MEP and MEHP had a positive association with BMI and WC (Wang et al., 2013).
A recent study by Vafeiadi et al. (2018) in Greece determined monoethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), monobenzyl phthalate (MBzP), mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono(2-ethyl-5-oxohexyl) phthalate (MEOHP) metabolites in 500 mother-child pairs. Spot urine samples were collected from 260 mothers of age 16 or above and 500 children at age 4. Anthropometric measures such as weight, height, waist circumference, skinfold thickness, blood pressure and lipids of children at ages 4 and 6, respectively, were collected. Other anthropometric measures collected at age 4 were leptin, adiponectin and C-reactive protein. The study found that childhood exposure to phthalate metabolites had an association with lower BMI z-scores with boys and higher BMI z-scores with girls. At age 4 the metabolites had a negative association with systolic and diastolic blood pressure of children. At the same age, MEP had an association with lower systolic BP z-scores of children. While the same research found an association between the metabolites MnBP and MBzP and lower BPz-scores of children. The study reported moreover, that prenatal phthalate exposure was not always associated with child adiposity and cardiometabolic measures (Vafeiadi et al., 2018).

A study in the USA involved 707 children whose mothers had phthalate concentrations in spot urine sample during pregnancy. Weight and height of children were the anthropometric measures collected at ages 4, 5, 5.5, 6, and 7–9. The metabolites, monoethyl phthalate (MEP), monon-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), mono(3-carboxypropyl) phthalate (MCPP), monobenzyl phthalate (MBzP), mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP) were analysed from spot urine samples of children. They reported that phthalate metabolite MCPP concentrations of prenatal mothers had a positive association with children between ages 4 and 7. Moreover, diethyl phthalate (DEHP) and its metabolites had an association with lower body mass index (BMI) of girls but not in boys (Buckley et al., 2016).

Also, in a research in south Korea, 128 pregnant women were selected and their blood and urine samples collected, while at birth, their newborns first urine and umbilical cord blood samples were collected. Anthropometric measures collected from the newborns were leptin levels, total cholesterol and triglyceride (TG) in cord serum and weight, length, head circumference and ponderal index (PI) all at birth. Two metabolites of diethyl phthalate (DEHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) and mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP) were determined from the urine sample. The study determined Body Mass Index (BMI) z-scores of newborns after 3 months. They found that exposure to DEHP has faster and positive association with body mass increase. DEHP has decreased and increases association with ponderal index and triglyceride, respectively, at birth (Kim et al., 2016).

In a review article by Filardi, et al. 2020, they made an observation that Bisphenol A (BPA) and Phthalates are endocrine-disrupting chemicals (EDCs) that can be found everywhere in the environment. They are therefore present in food, water, and air and can affect foetal growth leading to an excess of body fat in childhood. BPA and Phthalates have everlasting adverse health effects on humans. The reviewers found that the effect of exposure to many EDCs on the body is enhanced and suggested a study into the relations between distinct EDCs and their effect on the body (Filardi; et al., 2020).

9. Applicability of the study
Globally, obesity is a health problem and it is reported that between 1980 and 2008 obesity situations and trends have doubled (World Health Organization (WHO), 2014). Ghana is considered as one of the 73 countries in the world where overweight or obesity has doubled since 1980. During this time, the obesity rate has risen from less than 2% of the population to 13.6% (World Health Organization (WHO), 2000). Phthalates adversely affect reproductive organ, and as a result, the European Commission has forbidden the use of DEHP, di-n-butyl phthalate (DBP), butylbenzyl
phthalate (BBP), diisononyl phthalate (DINP), diisodecyl phthalate (DIDP) and di(n-octyl) phthalate (DNOP) in the manufacture of toys for children under 3 years and childcare articles (European Council Parliament, 2005). Consequently, to reverse the trend of rising cases of obesity in Ghana and the world at large, it is important to review EDCs such as phthalates. Since they are used for the production of most industrial products, leading to environmental exposure to humans, where there is a high chance of been absorbed into the body and distort the work of natural hormones such as estrogen and progesterone, making the body put on more weight leading to obesity (Franks et al., 2000; Legro et al., 2006; Sinha & Kuruba, 2007). It is our view that this paper will make human minimise or reduce hours of contact with phthalates made consumer products.

10. Conclusion
From the findings, it will be advisable to curtail or limit human contact with EDCs, especially in adolescents who are more susceptible to these substances. There is the need to do educational programmes at the maternity clinics so that parents will be educated about the repercussion of children being vulnerable to these EDCs. It is hoped that this paper will be accessed by many people worldwide so as to educate humans about the kind of finished EDCs industrial products used in our daily life which causes weight gain and consequent obesity. However, obesity is not only a result of the subjectation of humans to EDCs. A lifestyle such as overeating and absence of exercise could lead to an upsurge in obesity cases, consequently resulting from a rise in the caloric intake in the body causing weight gain.

Acknowledgements
The authors acknowledge the constructive suggestions of Prof Nathaniel Owusu Boadi, Department of Chemistry, College of Science, KwameNkrumah University of Science and Technology, of the manuscript which led to the improved quality of this paper. We also recognize and acknowledge the paramount role played by Dr Michael Baah Mensah in manuscript writing.

Funding
The authors received no direct funding for this research.

Competing Interests
The authors declare no competing interests.

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Citation information
Cite this article as: Human contact with phthalates during early life stages leads to weight gain and obesity, Joseph Apau, Wilfred Sefah & Eric Adua, Cogent Chemistry (2020), 6: 1815273.

References
Amugsi, D. (2018). Research shows shocking rise in obesity levels in urban Africa over past 25 years. Epidemiology Research. https://theconversation.com.
Accessed on January 6, 2019
Axelsson, J., Rylander, L., Rignell-Hydbom, A., Jönsson, B. A., Lindh, C. H., & Giwercman, A. (2015). Phthalate exposure and reproductive parameters in young men from the general Swedish population. Environment International, 85, 54–60. https://doi.org/10.1016/j.envint.2015.07.005
Becker, K., Seiwert, M., Angerer, J., Seifert, B., & Ullrich, D. (2006). DEHP metabolites in urine of children and DEHP in the house dust. International Journal of Hygiene and Environmental Health, 207(5), 409-417
Berhofer, A., Pischon, T., Reinhold, T., Aposian, C. M., Sharma, A. M., & Willich, S. N. (2008). Obesity prevalence from a European perspective: a systematic review. BMC Public Health, 8, 20. doi: 10.1186/1471-2458-8-200
Buckley, J. P., Engel, S. M., Braun, J. M., Whyyatt, R. M., Daniels, J. L., Mendez, M. A., Richardson, D. B., Xu, Y., Calafat, A. M., Wolff, M. S., Lanphear, B. P., Herring, A. H., & Rundle, A. G. (2016). Prenatal Phthalate Exposures and Body Mass Index Among 4- to 7-Year-old Children: A Pooled Analysis. Epidemiology, 27(3), 449-458. https://doi.org/10.1097/EDE.0000000000000436
Calafat, A. M., Ye, X., Silva, M. J., Kuklenyik, Z., & Needham, L. L. (2005). Human exposure assessment to environmental chemicals using biomonitoring. International Journal of Andrology, 29(1), 166–171. https://doi.org/10.1111/j.1365-2609.2005.00570.x
Centre for Disease Control and Prevention. (2014). Accessed August 30, 2016, from https://www.cdc.gov/niosh/topics/exposome/default.html
Dobrzyńska, M. M. (2016). Phthalates - widespread occurrence and the effect on male gametes. Part 1. General characteristics, sources and human exposure. Roczniki Państwowego Zakładu Higieny, 67(2), 97–103.
Duty, S. M., Singh, N. P., Silva, M. J., Barr, D. B., Brock, J. W., Ryan, L., Herrick, R. F., Christiani, D. C., & Hauser, R. (2003). The relationship between environmental exposures to phthalates and DNA damage in human sperm using the neutral comet assay. Environnemental Health Perspectives, 111(9), 1164. https://doi.org/10.1289/ehp.5756
Ears, A., Axford, I. P., & Braybrook, J. H. (2003). Gas chromatography-mass spectrometry determination of the migration of phthalate plasticisers from
polyvinyl chloride toys and childcare articles. Journal of Chromatography A, 983(1–2), 237–246. https://doi.org/10.1016/S0021-9673(02)01736-3
El Sayeed, A. M., Scarborough, P., & Galea, S. (2012). Uneven Distribution: a systematic review of the health literature about socio economic inequalities in adult obesity in the UK. BMC Public Health, 12(1), 18. https://doi.org/10.1186/1471-2458-12-18
European Council Parliament (2005). Accessed August 7, 2018, from http://eur-lex.europa.eu
Ferguson, K. K., McElrath, T. F., Ko, Y.-A., Mukherjee, B., & Meeker, J. D. (2016). Variability in urinary phthalate metabolite levels across pregnancy and sensitive windows of exposure for the risk of preterm birth. Environment International, 70, 118–124. https://doi.org/10.1016/j.envint.2014.05.016
Filardi, T., Paninoffle, F., Lenz, A., & Morano, S. (2020). Bisphenol A and Phthalates in Diet: An Emerging Link with Pregnancy Complications. Nutrients, 12(2), 525. https://doi.org/10.3390/nu12020525
Franks, S., Mason, H., & Willis, D. (2000). Follicular dynamics in the polycystic ovary syndrome. Molecular and Cellular Endocrinology, 163(1–2), 49–54. https://doi.org/10.1016/S0303-7207(99)00229-7
Guo, Y., Alomairah, H., Cho, H.-S., Mih, T. B., Mohd, M. A., Nakata, H., & Kannan, K. (2011). Occurrence of phthalate metabolites in human urine from several Asian countries. Environmental Science & Technology, 45(7), 3138–3144. https://doi.org/10.1021/es103879m
Holden, R. U. (2010). Plastics and health risks. Annual Review of Public Health, 31(1), 179–194. https://doi.org/10.1146/annurev.publhealth.012809.103714
Healthline. (2020). Accessed on March 19, 2020.
Huang, P. C., Tien, C. J., Sun, Y. M., Hsieh, C. Y., & Lee, C. C. (2008). Occurrence of phthalates in sediment and biota: Relationship to aquatic factors and the biota-sediment accumulation factor. Chemosphere, 73(4), 539–544. https://doi.org/10.1016/j.chemosphere.2008.06.019
Jensen, D. M. (2013). Guidelines for the Management of overweight and obesity in Adults. Lancet, 255–260.
Kim, J. H., Park, H., Lee, J., Cho, G., Choi, S., Choi, G., Kim, S. Y., Eun, S.-H., Suh, E., Kim, S. K., Kim, H.-J., Kim, G.-H., Lee, J. J., Kim, Y. D., Eom, S., Kim, S., Moon, H.-B., Park, J., Choi, K., Kim, S., & Kim, S. (2016). Association of diethyhexyl phthalate with obesity-related markers and body mass change from birth to 3 months of age. Journal of Epidemiology and Community Health, 70(5), 466–472. https://doi.org/10.1136/jech-2015-206315
Koch, H. M., Bolt, H. M., Preuss, R., & Angerer, J. (2005). New metabolites of di-(2-ethylhexyl) phthalate (DEHP) in human urine and serum after single oral doses of deuterium-labelled DEHP. Archives of Toxicology, 79(7), 367–376. https://doi.org/10.1007/s00204-005-0629-4
Koniecki, D., Wong, R., Moody, R. P., & Zhu, J. (2011). Phthalates in cosmetic and personal care products: Concentrations and possible dermal exposure. Environmental Research, 111(3), 329–336. https://doi.org/10.1016/j.envres.2011.01.013
Legro, R. S., Aziz, R., & Giudice, L. (2000). A twenty-first century research agenda for polycystic ovary syn-

ode. Best Practice & Research Clinical Endocrinology & Metabolism, 2(2), 331–336. https://doi.org/10.1016/j.

j.beem.2006.03.001
Levine, J. A. (2011). Poverty and obesity in the US. Diabetes. BMJ, 60(11), 2567–2568.
Lind, P. M., & Lind, L. (2011). Circulating levels of bisphenol A and phthalates are related to carotid atherosclerosis in the elderly. Atherosclerosis, Epub, 218(1), 207–213. https://doi.org/10.1016/j.atherosclerosis.2011.05.001
Muratore, D. A., Tang, S., Steinhardt, G., & Dougherty, R. C. (1997). Phthalate esters and semen quality para-

terics. Biological Mass Spectrometry, 14(8), 473–477. https://doi.org/10.1021/bms.0200140815
Ogden, C. L., Carroll, M. D., Curtin, L. R., McDowell, M. A., Tabak, C. J., & Flegal, K. M. (2006). Prevalence of overweight and obesity in the United States, 1999-2004. Jama, 295(13), 1549–1555. https://doi.org/10.1001/jama.295.13.1549
Olsen, L., Lind, L., & Lind, P. M. (2012). Associations between circulating levels of bisphenol A and phthalate metabolites and coronary risk in the elderly. Ecotoxicology and Environmental Safety, 80, 179–183. https://doi.org/10.1016/j.ecoenv.2012.02.023
Petrovićová, I., Kolena, B., Šidlovská, M., Plika, T., Wimmerová, S., & Trnovcová, T. (2016). Occupational exposure to phthalates in relation to gender, consumer practices and body composition. Environmental Science and Pollution Research, 23(23), 24125–24134. https://doi.org/10.1007/s11356-016-7394-6
Roslavle, P., D’Arcy, J. B., & Henriksen, K. (1998). Degradation of phthalate and Di-(2-Ethylhexyl) phthalate by indigenous and inoculated microorganisms in sludge-amended soil. Applied and Environmental Microbiology, 64(12), 4711–4719. https://doi.org/10.1128/AEM.64.12.4711-4719.1998
Rozati, R., Reddy, P., Reddanna, P., & Mujtaba, R. (2002). Role of environmental estrogens in the deterioration of male factor fertility. Fertility and Sterility, 78(6), 1187–1194. https://doi.org/10.1016/S0005-0282(02)04389-3
Rusyni, I., Peters, J. M., & Cunningham, M. L. (2006). Modes of action and species-specific effects of di-(2-ethyl-

hexyl) phthalate in the liver. Critical Reviews in Toxicology, 36(5), 459–479. https://doi.org/10.1080/10408440600779065
Scientific Committee on Health and Environmental Risks (SCHER). (2008). Opinion on phthalates in School Supplies. European Commission, Directorate General for Health and Consumers.
Shelby, M. D. (2006). NTP-CEHR monograph on the potential human reproductive and developmental effects of di-(2-ethylhexyl) phthalate (DEHP). NTP-CEHR Monograph, (18).
Sinha, P., & Kuruba, N. (2007). Premature ovarian failure. Journal of Obstetrics and Gynaecology, 27(1), 16–19. https://doi.org/10.1111/j.1443-6100.2007.00665.x
Song, Y., Hauser, R., Hu, F., Franke, A., Liu, S., & Sun, Q. (2014). Urinary concentrations of bisphenol A and phthalate metabolites and weight change: A prospective investigation in US women. International Journal of Obesity, 38(12), 1532–1537. https://doi.org/10.1038/ijo.2014.63
Swan, S., Main, K., Liu, F., Stewart, S., Kruse, R., Calafat, A., Sullivan, J. B., Tornand, C. L., Sullivan, S., Teague, J. L., & Mao, S. (2005). Study for future families research team: Anogenital distance—a marker of fetal androgen action—is decreased in male infants follow-

ing phthalate exposure during pregnancy. Environmental Health Perspectives, 113(8), 1056–1061. https://doi.org/10.1289/ehp.8100
Swan, S., Sathyanarayana, S., Barrett, E., Janssen, S., Liu, F., Nguyen, R., Stasenko, M., Liu, F., Scher, E., Stasenko, M., Ayyash, E., Schirmer, M., Forrell, J., Thielt, M. P., Roskin, L., Gray, L., D. H., Georgesen, H. L., Rody, B. J., Terrell, C. A., Kaur, K., Alcedo, G., & Redmon, J. B. (2015). First trimest-

er phthalate exposure and anogenital distance in
newborns. Human Reproduction, 30(4), 963–972. https://doi.org/10.1093/humrep/deu363
Vafeiadi, M., Myridakis, A., Roumeliotaki, T., Margetaki, K., Chalkiadaki, G., Dermizaki, E., Venihaki, M., Sarri, K., Vassilaki, M., Leventakou, V., Stephanou, E. G., Kojevnikov, M., & Chatzi, L. (2018). Association of early life exposure to phthalates with obesity and cardio-metabolic traits in childhood: Sex specific associations. Frontiers in Public Health, 6, 327. https://doi.org/10.3389/fpubh.2018.00327
Wang, H., Zhou, Y., Tang, C., He, Y., Wu, J., Chen, Y., & Jiang, Q. (2011). Urinary phthalate metabolites are associated with body mass index and waist circumference in Chinese school children. PloS One, 8(2), e56800. https://doi.org/10.1371/journal.pone.0056800
Werner, E. F., Braun, J. M., Yolton, K., Khoury, J. C., & Lanphear, B. P. (2015). The association between maternal urinary phthalate concentrations and blood pressure in pregnancy: The HOME Study. Environmental Health, 14(1), 75. https://doi.org/10.1186/s12940-015-0062-3
Williams, E. P., Mesidor, M., Winters, K., Dubbert, P. M., & Wyatt, S. B. (2015). Overweight and obesity: Prevalence, consequences, and causes of a growing public health problem. Current Obesity Reports, 4(3), 363–370. https://doi.org/10.1007/s13679-015-0169-4
World Health Organization (WHO). (2000). Technical report series geneva.
World Health Organization (WHO). (2014) Obesity situation and trends. www.who.int