Phthalates, esters of 1,2-dicarboxylic acid - phthalic acid, are synthetic industrial chemical compounds which were introduced in 1920. Ever since 1933 and the synthesis of di (2-ethylhexyl) phthalates (DEHP), the phthalates have been the most common chemical compounds with the possibility to disrupt the endocrine system [1]. The effect of phthalates depends on dosage, duration of action and stage of the development of the individual, thus having more negative consequences of exposure to phthalates.

Interest in chemical matters that disrupt the endocrine system work - endocrine disrupting chemicals (EDCs) has been increased over the last several years. EDCs may affect the synthesis, secretion, mechanism of action, metabolism and elimination of hormones in humans and animals, with harmful health consequences.

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Introduction

Phthalates are synthetic industrial compounds capable of disrupting endocrine system. Effects of phthalates depend on dosage, duration of action and stage of development of the individual, thus making the fetus, newborn, and children at puberty the most vulnerable groups. Metabolism of Phthalates: Metabolism of these compounds consists of at least two steps: hydrolysis and conjugation. They are mainly excreted in urine, with a low percent being excreted through feces. Exposure to Phthalates: Exposure to the effects of phthalates begins in the intrauterine stage since the phthalates pass through the placental barrier. Phthalates may be found in plastic products, toys, medical equipment, industrial materials, food, and clothes.

Determination of Phthalate Levels in Humans. Urine is the best sample for evaluating phthalate levels in humans because of rapid phthalate metabolism and high concentrations of metabolites in the urine. Fetal Testicular Dysgenesis Syndrome: Fetal testicular dysgenesis syndrome involves disorders of male genital tract such as shortened anogenital distance, hypospadia, cryptorchidism, malformations of seminal vesicles, prostate, epididymis and it results from the harmful effects of phthalates. Other Effects of Phthalates on Health. Negative effects of phthalates on female health are mostly reflected in anovulation, premature puberty, changes in duration of pregnancy. There is a possible effect on neurocognitive development, occurrence of allergies, asthma, testicular carcinoma, hepatic and renal damages, insulin resistance and obesity, thyroid dysfunction.

Conclusion. Further studies are needed to establish the safe phthalate concentration in certain products and to determine more negative consequences of exposure to phthalate.

Key words: Phthalic Acids; Fetus; Endocrine Disruptors; Plastics; Gonadal Dysgenesis; Insulin Resistance

Sažetak


Ključne reči: Ftalna kiselina; Fetus; Endokrin disrupcija; Plastika; Gonadna disogeneza; Insulininska rezistenctja

Summary

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Bajkin I, et al. Phthalates and fetal health

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Metabolism of Phthalates

After they enter the body, phthalates are subjected to hydrolysis and conjugation [4]. Monoester phthalates are created by hydrolysis. In vivo and in vitro studies proved monoester phthalates to be biologically more active than their diesters [5,6]. Short chain phthalates are excreted in the urine as monoester phthalates, and the long chain phthalates are subjected to further metabolism in terms of hydroxylation and oxidation after which they are excreted in urine and feces [7, 8]. Their biological half-life is short, more than 60% is excreted in 24 hours [1, 9].

Exposure to Phthalates

Low molecular weight phthalates, for example di-methyl phthalate (DMP), DBP, are present in cosmetic products (nail polish, perfumes, facial creams, shampoos, body lotions...), while high molecular weight phthalates, for example DEHP, BBzP, DNOP, DINP, DIDP, are present in plastic containers, adhesives, clothes of raincoat type and plastic products with polyvinyl chloride which is added in order to improve flexibility [4]. Phthalates are also found in medical instruments such as central venous and urinary catheters, as well as in packaging for total parenteral nutrition and intravenous infusion. They are also present in some medications [11]. Foodstuffs, such as cereals, bread, biscuits, cakes, nuts, oils and fats, can be found in packaging made of plastics containing DEHP, DBP and DEHP and di-isobutil phthalate (DIBP), and thus they are in contact with phthalates [12].

Toys are another important source of exposure to phthalate (soothers, teethers, bath toys), and they can enter the body either orally, or by inhalation, through skin and parenterally [1,10].

Determination of Phthalate Levels in Humans

Phthalates do not tend to bioaccumulate and their half-life is less than 24 hours [1,10]. There have been attempts at determining phthalate levels in saliva, serum, seminal fluid, meconium and placenta but, the validation of these procedures have shown that phthalates are excreted in a very small percentage in this way [13, 14]. Urine, maternal milk, serum and amniotic fluid are most frequently used nowadays as material to assess the presence of phthalates in the body [15]. Urine was proven to be the best sample in epidemiological studies in regards to the rapid metabolism of phthalates and high concentrations of the metabolites in the urine. Further advantages of urine as material for determining levels of phthalates is that it can be collected in a noninvasive way and may reflect exposure to phthalates in the last few days, even weeks [16, 17]. In all the above mentioned samples, the level of monoesters, i.e. phthalates metabolites, are determined because the level of monoesters is higher than the level of diesters of phthalic acid, and the contamination of the sample by ubiquitous diesters during the collection, storage and analysis itself is avoided [18].

Fetal Testicular Dysgenesis Syndrome

In the last fifteen years, a number of studies on experimental animals (rats) have proven that phthalates, especially DEHP, DBP, BBzP, when acting in a critical period of the development of genital tract, lead to disturbances in androgen-signaling pathway [18,19]. In almost all previous studies, the anti-androgen effect of phthalates in newborn males was examined, but it was also shown that the negative effects of phthalates on female health are reflected in anovulation, premature puberty, changes in the duration of pregnancy and other disorders [2, 10].

Fetal testicular dysgenesis syndrome (“phthalate syndrome” in rodents) involves disorders of male genital tract in terms of shortened anogenital distance, hypospadia, cryptorchidism, malformations
of the seminal vesicles, prostate, and epididymis [18, 20]. According to contemporary literature, the stated syndrome is a consequence of reduced level of fetal testosterone, insulin-like growth factor-3 (IGF-3) and follicle stimulating hormone (FSH) [18, 21]. A negative correlation between levels in breast milk and free testosterone of babies was observed, while there was a positive correlation between mono-ethyl phthalate (MEP) and mono-butyl (MBP) with sex hormone binding globuline (SHBG) and mono-metyl phthalate (MMP) and MEP and MBP with the ratio of lutenizing hormone (LH) and free testosterone [22].

Recent research suggests a possible effect on neurocognitive development, as well as on the development of allergies, asthma, testicular carcinoma, hepatic and renal damages, insulin resistance and obesity, thyroid dysfunction [18].

An interesting fact is that exposure to a certain type of phthalates varies among different socioeconomic groups, which is probably the consequence of certain products whose use is significantly different among these groups [24].

**Conclusion**

Considering the widespread use of phthalates and exposure of large human population to phthalates in the environment, food or items for personal use their harmful impact on health need to be tested. Numerous experimental, epidemiological and observational studies of human population have suggested their most common side effects, but there are still many uncertainties. It is characteristic that detrimental effect is not only dose dependent. The duration of exposure is rather important: exposure to low doses of phthalates over a long period of time can lead to endocrine and metabolic disorders. Especially sensitive categories are the fetus and newborn, as well as pubertal

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**Table 1. Phthalate diesters and their metabolites** (taken from Frederiksen H, Skakkebek NE, Andersson AM. Metabolism of phthalates in humans, Mol Nutr Food Res 2007;51:899-911.)

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**Other effects of phthalates on health**

Exposure to phthalates is significantly associated with the duration of pregnancy [2]. According to some studies, the chemical structure of DEHP and prostaglandin/thromboxane, interleukin-1 connects the phthalates with induction of intrauterine inflammatory processes as well as shortening of pregnancy [2, 23]. Some results suggested an association between levels of mono-(2-ethylhexyl) phthalate in preconceptional period and early pregnancy loss, while many authors pointed out the impact of phthalates on the low birth weight [9, 16, 18].

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children. Endocrine disrupting chemicals have the epigenetic influence and these disorders can be manifested in the next generations. Further research aimed at timely recognition of adverse effects and adjusting the concentrations of the chemical compounds in products is needed in order to avoid their adverse effects on human health.

References