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EFFECTS OF PHTHALIC ACID ESTERS ON FETAL HEALTH

UTICAJ ESTARA FTALNE KISELINE NA FETALNO ZDRAVLJE

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Summary

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 at 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

Uvod. Ftalati su sintetska industrijska jedinjenja koja imaju sposobnost da remete funkciju endokrinog sistema. Njihovi efekti zavise od doze, dužine dejstva i razvojnog stadijuma jedinke, te su fetus, novorođenče i deca u pubertetu najugroženije kategorije. **Metabolizam ftalata.** Metabolizam ftalata odvija se u najmanje dva koraka − hidroliza i konjugacija. Ekskrecija najvećeg dela ftalata obavlja se urinom, međutim manji procenat se izlučuje fecesom. **Izloženost ftalatima.** Izloženost ftalatima počinje još intrauterino, pošto oni slobodno prolaze placentarnu barijeru. Prisutni su u plastičnim prozvodima, igračkama, medicinskim instrumentima, industrijskim materijalima, hrani, odeći. **Određivanje nivoa ftalata u ljudskom organizmu.** Urin je materijal izbora za određivanje nivoa ftalata, zbog njihovog brzog metabolizma i visokih koncentracija metabolita ftalata u urinu. **Sindrom fetalne testikularne dizgenezije** nastaje kao posledica štetnog dejstva ftalata; podrazumeva anomalije genitalnog trakta: skraćena ano-genitalna distanca, hipospadija, kriptorhizam, malformacije semenih vezikula, prostate, epididimisa. **Drugi efekti ftalata na zdravlje.** Kod osoba ženskog pola negativan uticaj ftalata ogleda se u anovulaciji, preranom pubertetu, promenama u dužini trajanja trudnoće. Smatra se da neželjeni efekti ftalata mogu da se ispolje i kroz neurokognitivne poremećaje, pojavu alergija, astmu, karcinom testisa, oštećenja jetre i bubrega, insulinsku rezistenciju i gojaznost, tiroidnu disfunkciju. **Zaključak.** Neophodna su dalja istraživanja kojima bi se odredile bezbedne koncentracije ftalata, ali i da bi se uočili i do sada neprepoznati neželjeni efekti ftalata na ljudsko zdravlje.

Klučne reči: Ftalna kiselina; Fetus; Endokrina disrupcija; Plastika; Gonadna disgenezija; Insulinska rezistencija

Introduction

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.

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

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Abbreviations

EDCs – endocrine disrupting chemicals
DEHP – di (2-ethylhexyl) phthalates
MEHP – mono(ethyl-hexyl) phthalate
BBzP – butyl benzyl phthalate
DBP – di-n-butyl phthalate
DINP – di-isononyl phthalate
DIDP – di-isodecyl phthalate
DMP – di-methyl phthalate
DnOP – di-n-octyl phthalate
MEP – mono-ethyl phthalate
MBP – mono-butyl phthalate
MMP – mono-methyl phthalate

making the fetus, newborn, and children at puberty the most vulnerable groups [2]. According to the study of Latini et al. from 2003, the exposure to the effects of phthalates begins at the intrauterine stage since the phthalates pass through the placental barrier; another important issue in relation to the phthalates, i.e. EDCs, is that intrauterine exposure may not be manifested until adolescence or even later [1]. It is also known that exposure to phthalates may be manifested only as disorders of the next generations (through modification of factors that regulate gene expression) [1]. Because of the known harmful effects, the European Union countries as well as our country have limited the use of DEHP, butyl benzyl phthalate (BzBP) and di-n-butyl phthalate (DBP) in the production of children's toys and items intended for the child care, while the restrictions on the use of di-isononyl phthalate (DINP), di-isodecyl phthalate (DIDP) and di-n-octyl phthalate (DNOP) apply only to the manufacturers of toys and items intended for child care that children can put in the mouth [3]. Application of DEHP and DBP and BzBP is not permitted in cosmetic production in the European Union because of reproductive toxicity [4].

Metabolism of Phthalates

After they enter the body, phthalates are subjected to hydrolysis and conjugation [4]. Monoestar 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

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.)
Tabela 1. *Diestri ftalata i njihovi metaboliti (preuzeto iz Frederiksen H, Skakkebek NE, Andersson AM. Metabolism of phthalates in humans. Mol Nutr Food Res 2007;51:899-911.)*

Phthalates/*Ftalati*		Metabolites/*Metaboliti*	
di-methyl-phthalate/*di-metil-ftalat*	DMP	mono-methyl-phthalate/*mono-metil-ftalat*	MMP
di-ethyl-phthalate/*di-etil-ftalat*	DEP	mono-ethyl-phthalate/*mono-etil-ftalat*	MEP
di-n-butyl phthalate/*di-n-butil-ftalat*	DBP	mono-butyl phthalate/*mono-butil-ftalat*	MBP
di-n-butil-phthalate/*di-n-butil-ftalat*	DBP	mono-butil-ftalat/*mono-izo-butil-ftalat*	MBP
di-iso-butyl phthalate/*di-izo-butil-ftalat*	DiBP	mono-iso-butyl phthalate/*mono-butil-benzil ftalat*	MiBP
butyl benzyl phthalate/*butil-benzil-ftalat*	BBzP	mono-butyl benzyl phthalate/*mono2-etil-heksil-ftalat*	MBzP
di-2-ethyl-hexyl phthalate *di-2-etil-heksilftalat*	DEHP	mono2-ethyl -hexyl phthalate *mono-2-etil-5 hidroksiheksil ftalat*	MEHP
		mono-2-ethyl-5 hydroxyhexyl phthalate *mono-2-etil-5 oksoheksil ftalat*	5OHMEHP
		mono-2-ethyl-5 oxohexyl phthalate *mono-2-etil-5 karboksipentil ftalat*	5oxoMEHP
		mono--2-ethyl-5 carboxy pentyl phthalate *mono-2-etil-5 karboksipentil ftalat*	5chMEHP
		mono-2-carboxy-hexyl-phthalate *mono-2-carboksi-heksil-ftalat*	2chMMHP
di-iso-nonyl phthalate/*di-izo-nonil-ftalat*		mono-iso-nonyl phthalate/*mono-izo-nonil-ftalat*	MiNP
		mono-hydroxy-iso-nonyl phthalatet *mono-hidroksi-izo-nonil-ftalat*	OH-MiNP
		mono-oxo-iso-nonyl phthalate *mono-okso-izo-nonil-ftalat*	oxo-MiNP
		mono-carboxy-iso-octyl phthalate *mono-karboksi-izo-oktil-ftalat*	cx-MiNP

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 follicule 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 bingind globuline (SHBG) and mono-metyl phthalate (MMP) and MEP and MBP with the ratio of lutenzing hormone (LH) and free testosterone [22].

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].

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

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.

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