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REVIEW ARTICLE

PHTHALATES - WIDESPREAD OCCURRENCE AND THE EFFECT ON MALE GAMETES. PART 1. GENERAL CHARACTERISTICS, SOURCES AND HUMAN EXPOSURE

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ABSTRACT

Phthalates are widely present in human environment. Widespead exposure to those agents, which are compounds of numerous daily use products, is unavoidable. In the current paper following phthalates benzylbutyl phthalate (BBP), di-n-butyl phthalate (DBP), di(2-ethylhexyl)phthalate (DEHP), diethyl phthalate (DEP), di-isononyl phthalate (DINP) are described.

Phthalates mainly enter to the composition of plastic goods, like boxes and containers for storage of foods, toys, medical devices, and also cosmetics, personal care products, as well as paints, vanishes, printing inks. This paper describes the occurence of individual phthalates in the environment (water, air) and in different products. During production, transportation, manufacturing of goods and improper disposal, phthalates released into soil, water and air. For example indoor air included 13 mg/m^3 phthalates, where 72 % of all constitutes DEP (2.29 mg/m^3), BBP (3.97 mg/m^3) and DEHP (2.43 mg/m^3). Exposure to phthalates take place mainly by ingestion or inhalation air or through the skin. Presence of phthalates were observed in numerous food products and is connected with migration of those compounds from food storage containers to preserved food. They could mirgate to salivia during sucking and chewing of toys and this way increased exposure to of children. The results of studies regarding to concentration of phthalates in human tissues and excretions are also described. The level of phthalates were measured in numerous of human biological samples. For example, DEHP, DEP and DBP were detected at levels of 5.71 mg/L in blood serum, of 0.30 mg/L in semen and of 0.72 mg/kg in fat samples.

Key words: *phthalates, occurence and sources of exposure, concentration in human tissues and excretions*

STRESZCZENIE

Ftalany są szeroko rozpowszechnione w środowisku człowieka. Powszechne narażenie na te związki, które wchodzą w skład wielu produktów codziennego użytku jest nieuniknione. W niniejszej pracy opisano ftalany butylobenzylu (BBP), dibutylu (DBP) i dietyloheksylu (DEHP), dietlylu (DEP) oraz diizononylu (DINP).

Ftalany przede wszytkim wchodzą w skład wyrobów plastikowych, takich jak pojemników do przechowywania żywności, zabawek, wyrobów medycznych oraz kosmetyków środków higieny osobistej, a także farb, lakierów, tuszów drukarskich. W niniejszej pracy opisano występowanie poszczególnych ftalanów w w środowisku (np. w wodzie, powierzu) oraz w różnych produktach. Podczas produkcji, transportu, wyrobu produktów oraz niewłaściwej utylizacji, ftalany przenikają do gleby, wody i powietrza. Na przykład, w powietrzu w pomieszczeniach stwierdzono 13 mg/m^3 ftalanów, z których 72% of stanowiły DEP (2,29 mg/m^3), BBP (3,97 mg/m^3) i DEHP (2,43 mg/m^3). Narażenie na ftalany nastepuje głównie drogą pokarmową, inhalacyjną oraz poprzez skórę. Obecność ftalanów stwierdzono w wielu produktach żywnościowych, co jest związane z migracją tych związków z opakowań do przechowywanej w nich żywności. Mogą migrować do śliny podczas ssania i żucia zabawek i w ten sposób powodują zwiększone narażenie niemowląt i małych dzieci. Omówiono także wyniki badań dotyczących stężenia ftalanów w tkankach i wydalinach ludzkich. Stężenie ftalanow mierzone było w różnych thankach ludzkich. Przykładowo, obecność DEHP, DEP i DBP stwierdzono w surowicy krwi (5,71 mg/l), w nasieniu (0,30 mg/l) oraz w tłuszczu (0,72 mg/kg).

Słowa kluczowe: *ftalany, występowanie, źródła narażenia, stężenia w tkankach i wydalinach ludzkich*

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INTRODUCTION

Humans and animals are continously exposed to wide range of natural and synthetic estrogens. The most important seems to be xenoestrogens, called also endocrine disruptors, endocrine disrupting compounds, hormone disruptors, xenobiotics or estrogen mimicking chemicals. The name "xenoestrogen" comes from Greek language. 'Xeno' means foreign, so xenoestrogens are compounds that act like estrogens from a foreign source. They possess heterogenous chemical structure. Endocrine disruptors are chemicals which interact with hormonal system, mimic estrogens and impact hormone balance in the body, and may also have antiandrogenic ability. Due to structural similarity to estrogens, they may easily bind to hormone receptors and block the action of natural hormones. They may also affect the synthesis, metabolism, binding or cellular responses of natural estrogens [50].

Xenoestrogens including some pharmaceutics (i.e.contraceptive), metals (i.e. aluminum, arsenite, barium, cadmium, chromium, lead, mercury), parabens, used as preservatives in cosmetic and pharmaceutical products, detergents and plasticizers (i.e. bisphenol A, phthalates).

The general population is exposed to phthalates, because they are ubiquistos environmental contaminant [25, 60]. Humans are exposed to phthalates directly or indirectly, by multiple routes, depending on the kind of phthalate. One of the most important way of exposure is ingestion (via phthalate-contaminated food, water and other liquids and in case of children through mouthing of toys and teethers) or also dermal exposure (via cosmetics and other personal care products). Exposure can also result via inhalation; because they volatilize from phthalate-containing products, and directly via blood from blood storage bags, catheters and haemodialysis instruments [18]. The total daily phthalate exposure in US was estimated as 0.27 mg daily for ambient, 0.25 mg daily from food, 0.002 μg daily through water and 0.4 μg daily by air [56].

This paper describes sources of selected phthalates in the environment and their concentration in products and human tissues. The following phthalates were chosen to this review di(2-ethylhexyl)phthalate (DEHP), dibutyl phthalate (DBP); butylbenzyl phthalate (BBP), diethyl phthalate (DEP), di-isononyl phthalate (DINP).

GENERAL CHARACTERISTIC AND OCCURRENCE OF SELECTED PHTHALATES

Di(2-ethylhexyl)phthalate (CAS No 117-81-7) known also as bis(2-ethylhexyl) phthalate, diethylhexyl phthalate, di-sec octylphthalate or octylphthalate, is an oil liguid of low volalility used in chemical industry. DEHP is the most often used plasticizer (approximately 50% of total used phthalates) in polyvinyl chloride (PVC), polyethylene and polypropylene products. Plastics may contain from 1-40% DEHP by weight. It is a component of many consumer products such as artificial leather, waterproof clothing, footwear, upholstery, floor tiles, various types of furnishing, industrial tubing, wires and cables, tablecloths, shower curtains, wraps and boxes for food, children's toys, and a variety of medical plastic devices like blood storage bags, catheters and haemodialysis instruments. Among others DEHP is also used in a hydraulic and dielectric fluids, liquid detergents, decorative inks, industrial lubricating oils, paints, glues [4, 15, 17, 46].

Dibutyl phthalate (CAS No 84-74-2) is called also di-n-butyl phthalate, butyl phthalate, n-butyl phthalate, 1,2-benzenedicarboxylic acid dibutyl ester, o-benzenedicarboxylic acid dibutyl ester, Palatinol C, Elaol, dibutyl-1,2-benzene-dicarboxylate. DBP is colourless or light yellow liquid with weak similar to ether smell and expressive bitter savor. It is soluble in various organic solvents like alcohol, ether and benzene. DBP is commonly used plasticizer and as an additive to adhesive and printing ink, as a solvent for paints, for impregnation of tissues and as antifoamer. DBP is a component of plastic goods, containers for food preservation, plastic pipes, glues, perfumes, nail polishes and washers, shadows, hair sprays [11].

Diethyl phthalate (CAS No 84-66-2) known also as diethyl ester of phthalic acid and ethyl phthalate is a colorless liquid at room temperature and is only slightly denser than water. DEP has a faint, disagreeable odor, when burned, produces toxic gases [5]. DEP like other phthalates is commonly used to make plastics more flexible. Products in which it is found include toothbrushes, automobile parts, tools, toys, and food packaging. DEP can be released fairly easily from these products. It is also used as solvent, fixative or alcohol denaturatant in many personal care products and cosmetics, like fragrances, skin lotions, nail polishes and removers, eye shadows, hair sprays [5, 36]. DEP may be used also for solvent for insecticides and mosquito repellents, as well as detergent bases and aerosol sprays. It is used in aspirin coatings and in different medical devices inluding dialysis tubing [3, 22, 58]. Moreover, DEP has been used a componet of food and pharmaceutical packaging [5, 34].

Benzylbutylphthalate (CAS No 85-68-7) also named n-butyl benzyl phthalate or benzyl butyl phthalate, Palatinol BB, Unimoll BB, Sicol 160 or Santicizer 160 is a colorless liquid with weak smell. It is used mainly as plasticizer during manufacturig of goods containing PVC. BBP may be a component of vinyl floor tiles, traffic cones, conveyor belts, roof covers, upholsterer's padding, artificial leather, industrial solvents, adhesives, plastic wraps for food, toys, cosmetics, personal care products [25].

Diisononyl phthalate (CAS Nos 28553-12-0 and 68515-68-0) is named also isononyl alcohol phthalate, Palatinol DN, Palatinol N, 1,2-benzenedicarboxylic acid diisononyl ester, bis(7-methyloctyl) phthalate, di(C8-C10) branched alkyl phthalate, Vestinol 9, Vestinol NN, Vinylcizer 90, or Witamol 150. DINP is typically a mixture of chemical compounds consisting of various isononyl esters of phthalic acid. It is clearly viscous liquid, insoluble in water. DINP is mainly used as additives in plastics to make them more flexible, and also in varous products like electrical wire and cables, coated fabrics, automotive parts, building and construction (waterproofing), vinyl flooring, footwear, sealings, lamination film and in PVC-containing school supplies (such as scented erasers and pencil case). This phthalate can be blended into a paste (plastisol), for coating (tarpaulins, synthetic leather and wall covering) and rotomoulding (toys, play and exercise balls, hoppers) applications. Moreover, DINP is used in non-polymer applications such as adhesives, paints, surfactants and printing inks for T-shirts. It can be found in plasticine, in several categories of toys (plastic books, balls, dolls and cartoon characters) and in baby products (changing mats/cushions) which could be placed in the mouth. DINP has been found in other articles that may come into contact with children (clothes, mittens, coverage of pacifiers, PVC-containing soap packaging and shower mats) [14].

SOURCES AND LEVELS OF HUMAN EXPOSURE

As was stated earlier, phthalates are widely present in human environment. Indoor air included 12 mg/m^3 of phthalates, where 72% of all constitutes DEP (2.29 mg/m^3), BBP (3.97 mg/m^3) and DEHP (2.43 mg/m^3) [47]. The median concentration of sum of phthalates in house dust was measured as 362 mg/kg, including DBP at the level of 14 mg/kg and DEHP at the level of 4 mg/kg [1].

The main routes of exposure to phthalates are consumptions of contaminated food and drinking of contaminated water, inhalation, which is highly toxic, and dermal exposure. Phthalates are released into the environment during production, transportation, manufacturing and improper disposal. They are also released from products into soil, water and air.

Four phthalates or their metabolites concentrations were measured in personal air samples of pregnant women in New York City (US) and in Kraków (Poland). The concentarions of them in air samples were as follows DEP 0.26-7.12 μg/m^3, DBP 0.11-14.76 μg/m^3, DEHP 0.05-1.08 μg/m^3 and BBP 0- 0.63 μg/m^3 [2].

Concentration of DEHP in residences was detected at level from below than 0.002 μg/l to 5 ng/m^3 [20], whereas at work place approximately of 60 ng/m^3 [35].

One of the most impartant sourece of exposure to DEHP is drinking water. It has been detected there at different levels depending on the country, for example in Poland and Germany at 0.05-0.06 μg/l, in Greece at 0.93 μg/l, in US at 0.95 μg/l, in China at 3.47 μg/l [12, 64]. The daily dose of DEHP taken by human general population with food is estimated as about 25 μg/kg bw/day [43]. Concentration of DEHP in food varied depeding on products, for instance in fishes from 129.5 to 253.9 mg/kg of dry mass [29]. In European countries, DEHP among others was detected in milk at average 12 mg/L, and in cheease at average 2000 mg/L [51]. On this bases, the dose taken by ifants with mothers and cow milk was estimated as 1-10 μg/kg daily [30]. In children between 0.5 to 11 years old daily DEHP intake was estimatated as 14-19 μg/kg/day [52]. The exposure coming from cosmetisc, personal care products and children toys was estimated as from 8.2 to 25.8 μg/kg/day [33].

DBP was detected in surface waters of Europe and United States at concentration from 0.01 to 622.9 μg/dm^3 [62]. On the basis of measuration in several factories produced DBP in Europe, it was detected at majority of work place at the level below 0.5 mg/m^3, although somewhere this level was 10-fold higher. Concentration of DBP during manufacturing of goods containing this phthalate was from <0.008 mg/m^3 to 0.75 mg/m^3 [49]. DBP was found in home dust at the level from 36 to 50 mg/kg [28, 42]. It was detected in 19 of 21 nail polishes and in 11 of 42 perfumes at concentration from 444.567 to 1671.139 μg/ml [37]. Occupational exposure to DBP, which take place mainly by inhalation and sometimes by dermal way, was estimated as approximatelly 143 μg/kg bw/day, whereas the exposure of general population mainly by ingestion as 2-10 μg/kg bw/day [44].

The main way of occupational exposure to BBP is inhalation. The concentration of BBP in the air during manufacture of phthalates was estimated as 1 mg/m^3, whereas during manufacture of PVC as 2 mg/m^3. This is the equivalent of staff exposure to doses of 143 μg/kg bw/day and 286 μg/kg bw/day, respectively [49]. Exposure of general population is connected with presence of BBP in daily use products and take place mainly through drinking water, food and home dust. *Nagorka* et al., [42] showed approximately 48 mg of BBP per kg of home dust. Daily exposure to BBP of adult was estimated as 2 μg/kg body mass, whereas of children 3-fold higher [32].

DEP has been found in ground water at 0.0125 ppm, in soil at 0.039 ppm, in drinking water from 0.00001 to 0.0046 ppm, in indoor air 0.00018-0.00022 ppm, in outdoor air 0.00004-0.00006 ppm [13]. Other study reported the concentration of DEP in indoor air from 1.60 to 2.03 μg/m^3, in outdoor air from

0.4 to 0.52 μg/m^3 [53]. Human exposure to DEP can result from eating food contaminated from packing materials and contaminated seafood, or drinking contaminated water, or breading contaminated air or as result of medical treatment [13]. DEP from plastic packaging may gets into food and has been found in packaged food at the level of 2-5 ppm, The daily human intake of this phthalate has been estimated to be 4 mg based on the food intake [31]. DEP was detected in pies (average 1.8 μg/g), in crakers (5.3 μg/g), and in chockolate bars (5.3 μg/g) [45]. The anuual exposure from drinking contaminated water has been estimated to be 0.0058 mg/year/person [13]. Because of DEP was present mainly in fragrance products, dermal exposure seems to be the most important. It was found in 35 of 36 perfume products sold in Europe with the highest concentration of 2.23% [24]. The median value of DEP in fragrance products was 1679 μg/g [36]. Based on the level of DEP in cosmetic and personal care products, children's exposure to this phthalate was estimated as 42 μg/kg bw daily for babies, as 20 μg/kg bw daily for toddlers, and as 18 μg/kg bw daily for female adults [36]. Moreover, people receiving medical treatment that involve the use of PVC tubing may be exposed to DEP of its leaching from tubing [13].

The concentration of DINP in home dust was estimated as 184 mg/kg [42]. The average DINP concentration level in 24 kinds of food was 0.24 mg/kg. [41]. DINP was detected in baby snaks at the level of 1.83 μg/g and it is equivalent of 0.77 μg/kg bw [57]. The average dietary intake of this phthalate was estimated as 4.39 μg/kg/day in general population, 8.91 μg/kg in children aged 2 to 6 years, 6.53 μg/kg in children aged 7 to 12 years [41]. DINP intake in German students ranged from 0.02 to 20.2 μg/kg bw/day [61]. The estimated DINP exposure in European Union through the use of concumer products in infants is 249.9 μg/kg bw/day, whereas in adults 10.8 μg/kg bw/day [16]. Then, in Canada DINP exposure of ifants was estimated to range from 5 μg/kg bw/day to 45.8 μg/kg bw/day [27]. The exposure of 12-123 months old children to DINP was estimated from 1.3 to 3.2 μg/kg daily [7].

The average and high daily intakes for infants were estimated on the basis of phthalate concentration in breast milk. They are as follow 0.6 μg/kg bw and 2.1 μg/kg bw for DEHP, 0.1 μg/kg bw and 0.5 μg/kg bw for DBP, 3.2 μg/kg bw and 6.4 μg/kg bw for DINP, respectively [21].

The important potential health effects of pthalates is connected with children exposure from toys and other sources [46]. Infantas and young children could be under higher phthalate exposure. As phthalates plasticizers are not chemically bound to PVC, they could migrate to salivia during sucking and cheving of toy and this way increasing exposure. Nowadays, the presence of phthalates, like DEHP, DINP, DBP and BBP, in toys is prohibited by European Union directive. Unfortunatelly, toys produced in Asia still contained phthalates.

PHTHALATES CONCENTRATIONS IN HUMAN TISSUES

The level of phthalates were measured in numerous human biological samples. Three phthalates DEHP, DEP and DBP were detected among others in biological samples of people residing in Shanghai area with median levels of 5.71 mg/L in blood serum, 0.30 mg/L in semen speciments and 0.72 mg/kg in fat samples [63].

Exposure to phthalates is usually determined by measuring metabolite levels in the urine. The urinary level of several phthalate metabolites in different human populations have been measured. The concentration of phthalate metabolites in the urine of pregnant women in US were as follows; 26.7-5.52 x 10^3 μg/g creatine for DEP, 21.3-105 μg/g creatine for DBP, 5.6-120 μg/g creatine for BBP and 1.8-449 μg/g creatine for DEHP [2]. The levels of phthalate metabolites in the urine in men of reproductive age was as follows 5.6-53.5 μg/l for DEHP, 4.9-15.2 μg/l for BBP, 26.6-278 μg/l for DEP, 16.3-38.1 μg/l for DBP [26]. The highest levels of metabolites of following phthalates were detected in the urine of adult American population DEP (16 200 ng/ml, 6790 μg/g creatinine), DBP (4670 μg/g, 2760 μg/g creatinine), BBP (1020 ng/ml, 540 μg/g creatinine [8]. DEP metabolites were detected in the urine of 6 year old children at the concentration of 171 μg/l and in persons over 6 years at 1160 μg/l [9]. In the urine of pregnant women from Taiwan 0.09-859 μg/l, metabolites of DEHP, <0.25-55 μg/l metabolites of BBP, 1.02-269 μg/l of DBP metabolites, and 0.25-36.5 μg/l of DINP metabolites were detected. In the urine of their 2 years old children from 1.25 to 8.81 μg/l of DEHP, from 1.02 to 269 μg/l of DBP, approximately 3.86 μg/l of BBP and <0.25 – 398.84 μg/l of DINP metabolites were detected. In the urine of their children aged 5 years from 1.04 to 1390 μg/l of DEHP, from 4.16 to 165 μg/l of DBP, approximately 3.66 μg/l of BBP and 0.6 - 1188 μg/l DINP metabolites were found [39]. The concentration of phthalate metabolites in the urine of young (17.5-20.5 years old) Swedish men were as follows 2-6900 μg/ml for DEP, 1-690 μg/ml for DBP, 0.5-260 μg/ml for BBP, < level of detection – 1900 μg/ml for DEHP, < level of detection – 980 μg/ml [6].

In the study, of women after delivery the mean concentrations of DBP were measured as follow in the peripheral blood 84.75 μg/ml, in umbilical cord blood 52.23 μg/ml, in milk 57.78 μg/ml and in the urine 24.93 μg/ml [10]. Chineese study showed concentration

approximatelly of 8.84 mg/L DEHP and 7.67mg/L of DBP in the blood of mothers after delivery. Simultaneously they detected 5.20 mg/L DEHP and 5.71 mg/L DBP in umbilical blood [38]. In urine samples of healty Danish children and adolescents the median concentration of several phthalate metabolites were detected as follows 29 ng/ml for DEP, 17 ng/ml for DBP, 111 ng/ml for DEHP, and 31 ng/ml for DINP. On the basis of above results, the median of estimated daily intake was 4.29 µg/kg bw/24 h for DBP, 4.04 µg/kg bw/24 h for DEHP, 1.70 µg/kg bw/24 h for DINP, 1.09 µg/kg bw/24 h for DEP and 0.62 µg/kg bw/24 h for BBP [19].

In breast milk of women in Bavaria were found the following median concentration of phthalates 3.9 ng/g for DEHP, 0.8 ng/g for DBP [21]. In other study the mean concentration of DINP metabolites study in breast milk was measured less than 0.25 µg/l, and in cord blood samples < 0.25 – 4.05 µg/l. The levels of DEHP metabolites were detected from <0.25 to 46.53 µg/l and from 0.25 to 32.20 µg/l, respectively, whereas metabolites of BBP from <0.25 to 39.70 and from <0.25 to 39.70 µg/l, respectively [39].

The concentrations of phthalates in the blood of human were measured in several countries. In 2004 World Wilde Fund for Nature Poland measured the level of several phthalates in the blood of 15 voluntaries. The concentration of DEHP varied from 49 to 293 ng/kg of blood, whereas of DBP from bottom limit of notation to 103 ng/kg of blood. DEP, DINP and BBP were not found [55]. In the blood serum of Hong-Kong inhabitants from 3.51 to 28.45 ng DEHP/ml, from 0.82 to 1.97 ng BBP/ml, from 0.77 to 12.50 ng DBP/ml and from 1.02 to 5.91 ng DINP/ml were detected [59]. Elevated DEHP residue concentration has been found in the blood and tissues of patients after numerous transfusions [17, 40, 54]. Above group of people may receive considerably higher doses of DEHP compared to general population. Amount of DEHP entering dialyzed patient ranged ranged from 9 to 150 mg in a 5-hr hemodialysis session [23] or from 23.8 to 360 mg in a 4-hr dialysis period [48]. Patients subjected dialyses may be exposed to dose of 12 g of DEHP per year [17]. In case of pregnant females, where the exposure to DEHP coming from dialysis treatment or blood transfusions, the health consequences might be present in their children [46]. Neonatales may be heavily exposed to DEHP and its metabolites receiving blood products by usage of PVC comtaining medical devices. For example to DEHP exposure per exchange transfusion may be up to 3.3 mg/kg [54].

CONCLUSIONS

Taking into consideration numerous sources, diversity and application of of phthalates it seems to be important to inform widely of society about the hazard carrying by them. Particularly important is escape of heating up of food and drinks in cans and in plastic containers. It is also important to pay attention on presence of phthalates in toys, and personal care and daily use aricles assigned for infants and small children.

Conflict of interest.
The author declares no conflict of interest.

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