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REVIEW ARTICLE

PHTHALATES - WIDESPREAD OCCURRENCE AND THE EFFECT ON MALE GAMETES. PART 2. THE EFFECTS OF PHTHALATES ON MALE GAMETES AND ON THE OFFSPRING

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ABSTRACT

The general exposure to endocrine disruptors, including phthalates, is considered as one of the reason diminished sperm count and deteriorated sperm quality, which may lead to infertility and higher incidence of congenital malformations of the genital tract. This article describes the effects of selected phthalates di(2-ethylhexyl)phthalate (DEHP), dibutyl phthalate (DBP); butylbenzyl phthalate (BBP), diethyl phthalate (DEP), di-isononyl phthalate (DINP) on the male gametes, reproduction and the offspring of exposed animals. Results of several papers *in vitro* showed that above mentioned phthalates are weakly estrogenic, whereas *in vivo* studies showed that they have rather antiandrogenic abilities. Review of papers regarding to laboratory animals confirmed that phthalates cause diminished sperm count, increased frequency of abnormal spermatozoa and DNA damage in germ cells, especially after chronic exposure and in case exposure of immature animals. Phthalates may induce in male gametes mutations leading to increased pre- and postnatal mortality of the offspring and to incidence of congenital malformations, growth retardation, delay in sexual development, shortening of anogenital distance in males, disturbances in sex ratio and diminished quality of semen in F1 generation. The sensitivity on mammalian life stages on phthalates seems to be as follows: fetal>peripubertal>adult. The human studies provided limited evidence of an association between phthalate exposure and semen quality. Concentration of phthalates in semen of men at the level from 0.08 to 1.32 mg/kg was related to declined semen quality and infertility. Majority of human data showed the connection of increased level of phthalates in urine and sperm quality, however on the basis results of other studies, the impact of environmental exposure on sperm parameters seems to be rather small.

Key words: *phthalates, sperm count and quality, pre- and perinatal exposure, mammalian and human effects*

STRESZCZENIE

Powszechne narażenie na substancje estrogenopodobne, w tym na ftalany, jest uważane za jedną z przyczyn zmniejszającej się liczbności gamet męskich oraz pogarszającej się ich jakości, co może prowadzić do niepłodności oraz zwiększonej częstości wad wrodzonych układu rozrodczego. Niniejszy artykuł opisuje wpływ wybranych ftalanów: butylobenzylu (BBP), dibutylu (DBP) i dietyloheksylu (DEHP), dietlylu (DEP) oraz diizononylu (DINP) na gamety męskie, reprodukcję oraz na potomstwo narażanych zwierząt. Wyniki wcześniejszych badań *in vitro* wykazały, że wymienione ftalany wykazują słabe działanie estrogenne, natomiast wyniki *in vivo* świadczą raczej o ich antyandrogennych właściwościach. Analiza publikacji dotyczących zwierząt laboratoryjnych potwierdziła, że ftalany powodują zmniejszenie liczebności gamet męskich, zwiększoną częstość występowania plemników o nieprawidłowej budowie oraz uszkodzeń DNA komórek płciowych, szczególnie w przypadku narażania chronicznego lub narażania zwierząt niedojrzałych płciowo. Ftalany mogą indukować w gametach męskich mutacje powodujące zwiększoną śmiertelność pre- i postnatalną potomstwa, jak również zwiększoną częstość wad wrodzonych, opóźnienia we wzroście i osiąganiu dojrzałości płciowej, skrócenie odległości anogenitalnej u samców, zaburzenia stosunku płci oraz pogorszenie jakości nasienia w pokoleniu F1. Wrażliwość stadiów życiowych ssaków na ftalany przedstawia się następująco: płody>osobniki niedojrzałe>dorosłe.

Znacznie mniej informacji opublikowano na temat wpływu ftalanów na jakość nasienia ludzkiego. Uważa się, że stężenie ftalanów w nasieniu ludzkim od 0.08 do 1.32 mg/kg wpływa na pogorszenie jego jakości i niepłodność. Większość wyników badań na materiale ludzkim wykazała związek podwyższonego stężenia ftalanów w moczu z jakością gamet, jednakże na podstawie innych badań, wpływ narażenia środowiskowego na parametry nasienia wydaje się raczej niewielki.

Słowa kluczowe: *ftalany, ilość i jakość nasienia, narażenie na ftalany, narażenie pre- i perinatalne, wpływ na ssaki i ludzi*

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INTRODUCTION

The social interest of ecological and health impact of endocrine disrupting compounds is of growing concern. The general exposure to endocrine disruptors, which are widely present in the environment, is considered as one of the reason diminished sperm count and deteriorated sperm quality, which may lead to infertility and higher incidence of congenital malformations of the genital tract [23, 30, 142, 148]. Since 90s years of XX century scientists publish papers about the deterioration of male fertility. Firstly, *Carlsen* et al. [30] analysed 61 papers published between 1938 and 1990 years, including data of 14 947 males and observed that average sperm concentration per ml was diminished from 113 mln in 1940 to 66 mln in 1990. Simultaneously, the sperm volume was reduced from 3.40 ml to 2.75 ml, sperm abnormalities were increased and motility was decreased [23, 30]. Above results were confirmed later by *Swan et al.* [153], but not recently by *Axelsson* et al. [16] and *Jorgensen et al.* [91]. Anyway, diminished sperm count and quality leading to increasing reproductive problems of males may be caused among others by widespread exposure to endocrine disruptors, including phthalates.

Phthalates are esters of phthalic acid, containing a benzene ring, two corboxyl groups, and two alcohol groups. They are manufactured by reacting phthalic anhydride with alcohol that range from methanol up to tridecyl alcohol. They are mainly used as plasticizers i.e. substances added to plastics to increase their flexibility, transparency, durability, and longevity. Phthalates are used in many consumer products such as building materials, toys, food packaging, cosmetics, and medical devices [139]. More than 1 000 000 tonnes of phthalates are consumed in Western Europe [4]. There is no covalent bond between the phthalates and plastics, so they are released into the environment, especially after heating or exposure to organic solvents. Phthalates are rapidly metabolized in the body with limitation of half-lives less than 24 h [101]. They are not accumulated and are primarily excreted in the urine.

This article describes the effects of selected phthalates di(2-ethylhexyl)phthalate (DEHP), dibutyl phthalate (DBP); butylbenzyl phthalate (BBP), diethyl phthalate (DEP), di-isononyl phthalate (DINP) on the male gametes, reproduction and the offspring of exposed males. Results of several papers *in vitro* showed that above mentioned phthalates are weakly estrogenic [28, 72, 88], whereas *in vivo* studies showed that they have rather antiandrogenic abilities [66, 81].

THE EFFECTS ON GERM CELLS AND REPRODUCTION ABILITY OF EXPOSED MALES OF LABORATORY ANIMALS

Due to its endocrine disrupting activity, which is capable of perturbing the reproductive process by mimicking or antagonizing steroid action, phthalates have been shown to reduce fertility and induce testicular atrophy in laboratory animals [8, 142]. Phthalates adversely affect the male reproductive system in animals including hypospadias, cryptorchidism, reduced testosterone production and sperm count. The toxic action of phthalates is connectd with inhibiting *Leydig* cell synthesis of testosterone [6]. Diminished sperm count and quality might be caused by disturbances in the spermatogenesis induced by phthalates [5].

The main targets of phthalates are *Sertoli* cells, which does not proliferate after achievement of sexual maturity therefore their damage may significantly affect spermatogenesis [63, 75, 76, 88]. Animal studies showed that DBP and DEHP may affect the structure and function of *Sertoli* and germ cells leading to decrease of *Sertoli* and spermatogonial cell numbers and testosterone secretion [18, 62] and DEHP may affect sperm morphology [58]. Toxicity of phthalates connected with germ cells loss was primarily induced through the effects of testicular cells [75, 99, 108, 109]. Results of numerous researches showed that pubescent animals seems to be more sensitive than adult to the testicular toxicity of phthalates [43, 79]. Dysfunction of *Sertoli* cells induced by phthalate may leads to disturbances in the development and differentiation subsequent stages of spermatogenesis, especially to progressive degeneration of spermatocytes and spermatids [147]. There is known that DEHP induces morphological changes of *Sertoli* cells, necrosis of spermatogonia as well as removing of spermatocytes and spermatids from seminiferous tubules [89, 135]. Moreover, DEHP induced spermatogenetic disturbances and *Leydig* cells dysfunction [117].

Animal studies showed toxic effects of DEHP on the reproduction and development of mammals [38, 95]. It disturbs the expression of genes connected with development of testes and synthesis of steroid hormones [145, 170]. The exposure of adult and pubescent male rodents to this phthalate leads to diminished testosterone and sperm production, reduced testes and epididymis weights as well as to histopathological changes in testes [2, 11, 14, 39, 40, 85, 95, 102, 119, 133, 146]. *Zhang* et al. [175] proposed that the reason of those phenomenon is induced by DEHP diminished expression of following genes DDX3Y, Usp9Y, RBM, E1F1AY, EGF, FSHR,

EGFR. Administration of DEHP to rodents may leads to decline of spermatogenesis and atrophy of testes [1, 85]. Results of *Dostal* et al. [43] showed that exposure of adult male rats for 5 days to doses of 1000 mg/kg and 2000 mg/kg of DEHP daily causes degeneration of spermatogonia and spermatocytes. This phthalate may cause also reduced motility of gametes and enhanced the frequency of morphologically abnormal spermatozoa [2, 39, 40]. Mice received DEHP for 4 weeks at dose of 500 mg/kg/day showed 3-fold enhanced level of DNA mutations in cells of gonads [84]. The spermatozoa of mice treated *in vitro* to DEHP at dose of 1 μg/ml showed significantly diminished reproductive ability [84].

Some papers showed that the male reproductive tract is the most sensitive to DEHP at earlier periods of development [67-68, 119]. *Noriega et al.* [124] observed that treatments to DEHP of pubescent male rats of *Long-Evans* and *Sprague-Dawley* strains induced delay in sexual maturation and reduction in the weight of androgen-dependent tissues. Gonads of immature rodents seems to be more sensitive to damage induced by DEHP, and the changes might me present after shorter than in case of adult animals exposure time [40, 147].

In rats exposed to DBP, BBP, and DINP significantly lowered the sperm count and motility were observed [102]. Two weeks administration of adult rats to 2.5% or 5% BBP in diet cause reduction of testes and epidydymis mass [3]. The exposure lasting to 25 weeks influence on decreased mass of testis, epididymis and prostate, and diminished sperm count [110, 125]. Eight-weeks covering full spermatogenic cycle exposure to BBP induced weak reduction of sperm count and significantly enhanced frequency of morphologically abnormal spermatozoa [161].

DBP influences particularly toxic on the male reproduction because of causing disturbances in the differentiation and development of androgen-dependent tissues, leading to underdevelopment of male gonads, necrosis of seminiferous tubules epithelium and in consequence to diminished reproduction ability [19, 66, 95, 121]. This phthalate induces oxidative stress in rats leading to changes in the structure and function of epididymes [178]. The exposure of adult rodents to DBP causes pathological and biochemical changes in testes, reduction of testes and epididymes weights and hypospermia [22, 115, 140]. Eight-weeks DBP administration to male mice diminished sperm quality, especially enhances frequency of morphologically abnormal spermatozoa [41]. Single exposure of 3-weeks old male rats causes diminished maturation of gametes [7].

There were no testicular effects in rats in chronic studies of DINP at doses up to 600 mg/kg/day [27, 112] nor in 3-weeks study at doses up to 2600 mg/kg/day [111]. Similarly, there were no testicular effects in rats exposed as juveniles and young adults at dose 960 mg/kg daily of DINP [168].

Treatment of 5-week old rats with 2% DEP in diet for 1 week significantly decreased testosterone concentrations in testes and serum, contrary to other phthalates including DEHP and DBP, which increased testosterone level [126]. Dietary administration of 14 weeks mice to DEP did not affect fertility [31, 103, 125].

THE EFFECTS OF PRECONCEPTIONAL, PRENATAL OR PERINATAL EXPOSURE ON THE OFFSPRING

There are many papers described the effect of intrauterine and during lactation exposure of rodents to phthalates and significantly lower number of papers are regarded to preconceptional exposure. Majority of results showed that phthalates may affect fertility of males, pregnancy rate and litter size.

Exposure of pregnant female rats to DEHP and DINP at doses from 300 to 750 mg/kg bw per day may leads to reduced testicular testosterone production and levels in testes and plasma of male foetuses [24]. Intrauterine exposure to the dose of 1000 mg/kg daily caused the decreased foetal weight and skeletal abnormalities [77, 167]. Prenatal exposure of male rats to DINP and DEHP caused genital malformations [66].

The dietary exposure of both sexes of rats to DINP at levels 0.5-2% did not disturb male and female fertility, fecundity, gestational index or length of gestation [168]. Contrary, offspring survival and body weights of foetuses exposed *in utero* and through lactation to DINP at dose 1.5% in diet were reduced [168].

DEHP decreased litter sizes following preconceptional exposure of males [2, 40], of pregnant females [119] or both sexes of rodents [103]. After eight-weeks preconceptional exposure of pubescent male mice to DEHP the significantly enhanced frequencies of unpregnant females and dead foetuses in litters were noted [40]. In case of the exposure of adult male mice to dose of 8000 mg/kg bw DEHP daily, reduced number of live foetuses was observed [39]. Similarly, decreased number of live foetuses was noted in the offspring of F1 generation of male and female mice exposed to DEHP by feed [103]. Prenatal exposure to DEHP induced gross and skeletal malformations in foetuses [40, 66, 77, 144]. Other study showed that exposure to DEHP *in utero* and during lactation induced dose-dependently increased postnatal mortality of the offspring [119]. Then, administration of DEHP to pregnant females of rats at

dose at least 1000 mg/kg bw daily caused decreased number of live foetuses and theirs body weights as well as increased incidence of congenital gross and skeletal malformations of foetuses [66, 77, 119]. Contrary, DEHP given in the diet from 5 to 9 week of age of the F0 generation, and after mating to birth of the F1 generation of mice showed no adverse effect on litter size and weight and on the sex ratio [156, 157].

Treatment of pregnant females with BBP affect the foetuses leading to their death before or after the implantation [5, 55, 56, 123]. Exposure of female *Wistar* rats to doses 500 and 1000 mg/kg/daily of BBP between 15 and 17 day of pregnancy caused reduction of litter sizes [56]. Then, exposure of females from 4 day to the end of the pregnancy induced reduction body weight of foetuses at birth and at 21 postnatal day [5]. BBP or its metabolites, mono-n-butyl and mono-benzyl given pregnant female mice on 8th day of pregnancy at doses of 0.9-5.4 mmol/kg caused concentration related embryolethality and malformations. BBP at the same dose range administered to female rats on 10th of pregnancy induced increase in post-implantation losses and teratogenicity, but with lower susceptibility to toxic effects compared to mice [138]. Exposure of female rats to BBP at 2.0% concentration in feed on gestational days 6-15 resulted in increased incidence of resorption and malformations of foetuses [59]. Similarly, embryotoxicity was observed after exposure of pregnant female rats to 2 % of BBP in diet [47, 48, 51]. Intrauterine exposure to BBP induced also malformations of foetuses [48, 49]. Increase in the incidence of resorption and teratogenic effects (defects of the ribs, vertebral column, cleft palate and fusion of sternebrate) were observed in rats given BBP at doses 750-1250 mg/kg on gestational days 7-9 and 13-15 [50, 53]. Perinatal exposure to BBP diminished mass of testis and sperm count, and delay in achievement of sexual maturity of males [12, 123, 134, 160].

In rats administered with DEP by feed on days 6-15 of pregnancy there were no effects on the number of total, living and dead implants per litter and no gross and skeletal malformations were observed. Only, in high dose group (5% DEP in feed) the incidence of foetuses with extra ribs was significantly higher [60, 136]. Similar skeletal malformations were noted in mice administered from 0 to 17 days of pregnancy with DEP at doses 500-5600 mg/kg bw daily, however the number of malformations did not differ from that of control [155]. In the offspring of female mice exposed to DEP during pregnancy no effects on the litter size, the number of living and dead foetuses was observed [71, 155].

Preconceptional or intrauterine and lactational exposure to phthalates may also affect development of the offspring, especially causing the malformations of male reproductive tract and affecting male germ cells. As results of studies showed, phthalate exposure are more severe after *in utero* than following adult exposure. Exposure of female rats from 14 gestational day to 3 postnatal day to DEHP, BBP and DINP altered sexual differentiation causing for example reduced testis weight, shortened of anogenital distance and reproductive malformations [66].

Exposure of female rodents to BBP during pregnancy and lactation may act as antiandrogen leading to reduced testosterone production in male foetuses and to deformation of genitals as well as to histopathological changes in the structure of seminiferous tubules and decreased production of the sperm [66, 142]. Following exposure of female rats to the dose of 400 mg/kg bw/daily of BBP before conception and during pregnancy reduced testes and epididymes weight and histopathological changes in the structure of seminiferous tubules and *Leydig* cells were observed in F1 generation, whereas in F2 generation reduced anogenital distance was noted [13]. Exposure of female *Wistar* rats to doses 500 and 1000 mg/kg of BBP daily between 15 and 17 day of pregnancy adversely affect the development of male reproductive tract of the offspring leading to cryptorchidism and decrease of anogenital distance in F1 generation [56]. Additionally, the dose of 100 mg/kg of BBP administered *in utero* caused reduction of the reproductive organs weight, reduced sperm count and motility as well as increased frequency of malformed spermatozoa and increased production of testosterone in adult males of F1 generation [5]. BBP administered by gavage in rats at 500 mg/kg on days 15-17 of pregnancy caused undescending of testes and decrease in anogenital distance [56]. Treatment of pregnant females with BBP affect the foetuses leading to reduction of the testes and epididymes weights, decrease of angogenital distance and increased frequency of abnormality in genitals of the offspring [5, 56, 123].

Administration of F0 male mice to DBP at dose of 500 mg/kg bw for 8 weeks did not decrease of their fertility [42]. Other animal studies showed that DBP toxically affect the development of rodent foetuses leading to teratogenic changes at higher doses without the effects in exposed females [52, 143]. Exposure of foetuses *in utero* to DBP may induce disturbances in the expression of genes, which affect the development of androgen-dependent tissues and cause abnormal development of the sexual organs [98]. Other studies showed that exposure to DBP of pregnant females induced disturbances of organogenesis of testes, cryptorchidism, hypospadia, decreased sperm count and testosterone production as well infertility of 60 % male offspring [61, 116, 121, 122]. Intrauterine exposure from 7 to 14 day of pregnancy induced diminished sperm count, viability and motility, and

increased frequency of morphologically abnormal gametes [65]. DBP caused also decreased testosterone production and disturbances in the metabolism of steroid hormones in F1 generation [5, 65, 80, 98, 106, 173]. After exposure of female rats to DBP from 14 day to the end of the pregnancy decreased body weight was observed postnatally in the progeny. Additionally at the dose at least 50 mg/kg bw of DBP decreased reproductive organs weight, sperm count and motility as well as increased frequency of abnormal spermatozoa in adult F1 males was noted [5]. Administration of pregnant female rats to DBP directly before testes differentiation in the offspring induced reduction in the number of germinal cells and limitation of their differentiation [87]. Exposure of foetuses *in utero* and newborn laboratory animals to DBP induced abnormal development of genital tract, diminished sperm production and motility, as well as increased frequency of abnormal spermatozoa in those animals at adulthood [5, 15, 86, 97, 100, 114, 164, 171, 177]. Some papers showed that DBP may more adversely affect fertility and quality of gametes in the progeny of exposed animals than in those animals themselves [33, 169]. *Lee et al*. [105] showed inconsiderable delay in sexual maturity in rats exposed to DBP during pregnancy and lactation. Exposure of females to DBP in the last trimester of the pregnancy induced delay in testes descent of F1 offspring [54]. Then, exposure to doses from 250 to 500 mg/kg bw during pregnancy and lactation caused decrease in the angenital distance in males F1 generation [177]. Administration of F0 male mice to DBP at dose of 500 mg/kg bw for 8 weeks induce growth retardation, disturbances in the sex ratio and delayed vaginal opening in the F1 offspring; and at dose of 2000 mg/kg bw daily increased the number of abnormal spermatozoa [42]. Exposure of pregnant female rats to 500 mg/kg bw of DBP caused abnormal aggregation of Leydig cells in the foetal testis with simultaneous reduction of cell size and number [114].

DEHP, DEP, BBP, DINP administered orally to the dam of rats at 0.75 g/kg from gestational day 14 to postnatal day 3 did not affect litter sizes, however DEHP and BBP reduced pup weight at birth, caused shortened anogenital distance and reduced testis weights in male pups [66]. Intrauterine exposure to DEHP appears to shorten gestational length [104] as does DBP [115] which also can cause litter size reduction or total litter loss in mid-pregnancy. Shortened gestational length represents a risk factor for mortality. Exposure to DEHP of females from 7 to 14 day of pregnancy may be a reason of diminished sperm count and quality in F1-F4 generation of the offspring [44]. Preconceptional 8-weeks treatments of adult male mice to DEHP caused delay in the testes descent of F1 males [39]. In rats exposed to DEHP during pregnancy and lactation an increased frequency of congenital malformation in reproductive tract and sexual abnormality on the male offspring were observed [24, 66, 119, 132]. Exposure of pregnant females to monobenzyl phthalate, the metabolite DEHP may be a reason of elevated incidence of cryptorchidism in their progeny [57]. Treatment of rats with doses 234-1250 mg/kg day of DEHP from gestational day 14 to parturition resulted in increases of the absolute volume of *Leydig* cells per adult testis, and in reduced foetal and adult testosterone production [34]. Other study showed that DEHP has a biphasic effect on *Leydig* cell function with low-dose exposure advancing the onset of puberty [64]. In the offspring of female rats treated with DEHP during pregnancy and lactation the reduced anogenital distance and sperm count, as well as deteriorated sperm quality were noted [10, 35, 66, 162]. Exposure to DEHP of pregnant female mice decreased the testes weight of the offspring [149]. Exposure of F0 males during full spermatogenesis cycle caused reduced mobility of spermatozoa in the progeny [40]. Administration of DEHP at doses from 0.1 to 10 mg/kg/day from gestational day 21 to postnatal day 21 significantly reduced the male-female sex ratio and the sizes of male gonads in the progeny. It was accompanied with lower expression levels of testicular anti-mullerian hormone, androgen receptor, *cyclin A* and *StAR*, *Gnrh* and *Fsh* at the hypothalamic-pituitary levels [172].

There were no testicular effects in rats exposed to DINP *in utero* and through lactation [168]. Exposure of pregnant female rats to doses of 250 and 750 mg/kg/day of DINP from 12 to 19 gestation day could reduce testosterone concentration in the foetal testes and induced incidence of multinucleated germ cells [32]. DINP given pregnant female rats from 12 to 21 gestational day at doses of 10-1000 mg/kg bw daily showed increase of foetal *Leydig* cell size and aggregation, multinucleated gonocytes [107]. Pregnant female rats were gavaged from gestational day 7 to postnatal day 17 with 300-900 mg DINP/kg bw/day and as the results histopathological changes in foetal testes, increased nipple retention, reduced anogenital distance, reduced sperm motility and increased sperm count were observed [21].

In mice treated dietary with DEP for 14 weeks there were no effects on the litter, size, the number of live pups, the viability of pups or pups body weight [31, 103, 125]. In the F1 offspring of mice treated dietary with DEP for 14 weeks beginning at one week before mating epididymal sperm concentration was by 30% reduced and the weight of prostate was increased [31, 103, 125].

THE EFFECTS OF PHTHALATES ON THE HUMAN MALE GAMETES

Little is known about the effects of phthalates on the human reproductive health. The human studies provided limited evidence of an association between phthalate exposure and semen quality.

Concentration of phthalates in semen of men at the level from 0.08 to 1.32 mg/kg was related to declined semen quality and infertility [176]. The *in vitro* study on human semen exposed to DBP showed diminished viability and motility of human gametes [130]. The metabolite of DEHP, mono-(2-ethylhexyl)phthalate (MEHP) has been reported to decrease testosterone production in the human testis *in vitro* [37]. In other study, there were negative association between DEHP and DINP metabolite levels and semen volume [150]. In men from Greenland, Poland and Ukraine significant associations between serum levels of DEHP and DINP metabolites and serum level of testosterone was noted. Additionally, in presence of some metabolites of above phthalates semen volume and sperm count were reduced [150].

In the review paper of *Jurewicz and Hanke* [92] negative association between phthalate level and impaired sperm quality (concentration, motility, morphology) was noted. The urinary concentration of the metabolite of DBP, monobutyl phthalate (MBP), was found to be positively associated with the decreased sperm concentration and sperm count. Significant dose-dependent relationship of urinary level of DEHP metabolites and on increased percentage of abnormal sperm head was also observed [166].

In the semen of men from infertility couples there were correlation between concentration of the metabolite of DBP, MBP, and sperm quantity and quality [45-46, 74]. Results of *Pant et al.* [131] showed that the distribution of phthalate level was significantly higher in infertile than in fertile men and overall elevated levels of phthalate mainly DEP, DBP, DEHP were observed in urban as compared to rural men.

Elevated urinary levels of DEP and DEHP metabolites were associated with increased DNA damage in human sperm [46, 74]. *Murature* et al. [120] found relationship between sperm concentration and DBP level in cellular fraction of ejaculate. *Rozati* et al. [137] observed correlation of mixture of phthalate (including DEP, DBP, BBP, DEHP) concentration and sperm morphology as well as frequency of DNA single strand breaks in sperm, but not ejaculate volume, sperm concentration and motility. In young Swedish men the level of DEHP metabolites was associated with a lower proportion of progressively motile and mature spermatozoa [17].

Several papers on human reported negative association between exposure to DEHP and DBP on sperm motility [45, 73, 82, 83, 93, 129-131]. Association of presence metabolites DBP and DEHP with decreased sperm motility was noted also by *Jurewicz* et al. [93] and *Jonsson* et al. [90]. Exposure to DBP and DEHP has been associated with a lower semen quality [96].

Chinese study on the male cohort at reproductive age showed dose-response relationship between monomethyl phthalate (MMP) presence and sperm concentration and between monoethyl phthalate (MEP) presence and sperm motility [113]. Other study reported that presence of MEHP in semen is associated with increased sperm apoptosis, whereas presence of MMP and MEP in semen is connected with increased sperm DNA damage in Chinese men [174].

A meta-analysis study showed that monobutyl phthalate (MBP) and monobenzyl phthalate (MBzP) were associated with reduced sperm concentration. Then, urinary increased concentration of MBP and MEHP were associated with kind of motility. An increase in MBzP and MEP levels was associated with increase in DNA damage [29]. As *Bloom et al.* [20] reported, urinary concentration of MBzP and monoisononyl phthalate (MNP) were connected with decreased sperm count and concentration, and with increased frequency of morphologically abnormal spermatozoa. Then, MMP presence in urine caused lower sperm motility, whereas MEHP higher sperm motility [20]. Study of *Wang et al.* [165] on males with reproductive problems demonstrated that exposure to DEHP (i.e. presence of their metabolites in the urine) may alter hormone levels, disrupt semen DNA integrity and induce spontaneous apoptosis. Contrary, American study showed that impact of adult fertile men exposure to phthalates, including DEHP, DBP and DEP at environmental levels, on sperm parameters is rather small [158]. Also, *Herr* et al. [78] noted that metabolites of DEHP analyzed in urine of subfertile males are not associated with the quality of human markers of reproductive function (i.e. semen concentration, motility and morphology).

Occupational exposure to DEHP has been linked with decreased sperm motility and with an increased sperm DNA fragmentation [82, 83] and with reduced level of testosterone [128]. Then, occupational exposure to PVC plastics containing phthalates were not associated with increased risk of testicular cancer [69, 70].

Significantly less papers describes the impact of phthalates on the pregnancy duration and on the offspring exposed prenatally. *Latini* et al. [104] demonstrated that *in utero* exposure to DEHP is significantly associated with shorter pregnancy duration. In turn, other authors stated that there were no association between exposure to DEHP of male partners and the time to pregnancy [118]. Then, higher concentration of DEHP, but not DEP, DBP and BBP metabolites in the urine of females in the period around conception and pregnancy was significantly associated with pregnancy loss [159].

Human studies showed that prenatal exposure to phthalates was associated with a shorter anogenital distance in boys, i.e. reduced masculinization [25, 26, 141, 151, 52, 154]. Enhanced concentration of metabolites DEP, DBP and BBP in the urine of pregnant females was related to decreased anogenital distance among male infants [152]. Moreover, shortened anogenital distance was associated with an increased proportion of boys with incomplete testicular descent. Other studies indicated cryptorchidism and hypospadias as the effect of prenatal phthalate exposure [127, 153, 163]. Prenatal exposure may be also a reason of diminished fertility in adult life [36]. In young men born by mother exposed during pregnancy to higher levels of DINP and DEHP diminished testicular and semen volumes were observed [17]. Exposure to phthalates leads to declining proportion of male births, because there is an association between the level of phthalate metabolites in urine an sperm chromosome Y:X ratio [94].

CONCLUSIONS

On the basis of animal studies, the sensitivity on mammalian life stages on phthalates seems to be as follows: fetal>peripubertal>adult. Phthalates may affect male reproductive health of animals and human. They cause reduction of sperm count and increase in the frequency of abnormal spermatozoa and DNA strand breaks. The most dangerous seems to be chronic exposure. Damage to male germ cells may leads to induction of mutation and enhanced pre- and postnatal mortality of the offspring. Congenital malformations, delayed sexual maturation, improper sex ratio, shortening of anogenital distance in boys, and deteriorated sperm quality are possible in F1 offspring.

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