DI-2-Ethylhexyl Phthalate and Endocrine Disruption: A Review

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Abstract: Esters of o-phthalic acid are widely distributed in the ecosystem. The phthalate acid esters (PAE's) are used as plasticizers in enormous quantities for a variety of industrial uses in the formulation of plastics. They are also used as solvents in certain industrial processes and as vehicles for pesticides and have been described as being among the most abundant man-made environmental pollutants. Plasticizers have been shown to elute at a constant rate from plastic products to the environment. Increasing chemical use needs a better understanding of how these pollutants may affect human health. In particular, certain members of this chemical class, such as di-[2-ethylhexyl]-phthalate (DEHP), have been shown to cause reproductive and developmental toxicity and are suspected to be endocrine disruptors.

Keywords: Phthalate esters, Plasticisers, Di-[2-ethylhexyl]-phthalate, Endocrine disruptor, Fertility, Reproduction.

INTRODUCTION

Polyvinyl chloride plastics (PVC), made flexible through the addition of phthalates, are used in the production of a wide array of PVC formulations, including vinyl floors, interior building surfaces, shoe soles, food wraps, cosmetics, medical devices, toys and baby-care commodities [1, 2]. Phthalates are not chemically bound to PVC and, with time and use, release from vinyl products, hence becoming regular contaminants in ambient air, drinking water, and food products, all of which are potential exposure sources for the general population [3-11].

Globally, more than 18 billion pounds of phthalates are used annually, primarily as plasticizers in flexible PVC products [12] and up to 1 % of all phthalate content of PVC products is leached out into the environment each year. Di-2-ethylhexyl phthalate (DEHP) is by far the most commonly used plasticizer, annual production being 1-4 million tons. From the late 1960s, leaching of DEHP from PVC formulations, human exposure and, more recently, tissue deposition have been documented [13, 14]. In particular, DEHP induces a wide range of developmental and reproductive toxicities in mammals [15], while its ability to produce toxicity to humans remains uncertain. Limited studies in human populations suggest an association between phthalate exposure and adverse reproductive health outcomes in both genders. In fact, chronic occupational exposure to high levels of phthalates is associated with decreased rates of pregnancy and higher rates of miscarriage and anovulation in female factory workers [16, 17]. Moreover, higher urinary phthalate levels correlated with pregnancy complications such as anemia, toxemia, and preeclampsia in women living near a plastics manufacturer [18]. More recently, we found an association between DEHP exposure and endometriosis, suggesting a possible role of phthalate esters in the pathogenesis [19].

On the other hand, long term exposure to DEHP resulted in a reduction of human sperm motility [20]. Moreover, both the Center for the Evaluation of Risks to Human Reproduction (CERHR) of the National Toxicology Program [2, 21] and the Center for Devices and Radiological Health, U.S. Food and Drug Administration [22] concluded that there exists a serious concern that DEHP exposure may adversely affect male reproductive health. In particular, there is increasing evidence that DEHP is an endocrine disruptor, which is an environmental contaminant capable of perturbing the reproductive process by mimicking or antagonizing steroid hormones action [23].

HUMAN DEHP EXPOSURE

Humans are potentially exposed to DEHP from several different sources and exposures may follow different routes, occurring either sequentially or separately. We have recently shown that DEHP exposure begins during intrauterine life [24] and more recently we have observed that even lactational exposure from healthy mothers may occur [Latini G. and associates, unpublished data]. The exposures may also vary in frequency, occurring at different ages, and for different durations. It is apparent that exposure to DEHP occurs for a lifetime, but the amount, frequency and source can change. The Agency for Toxic Substances and Disease Registry (ATSDR) estimates that the daily exposure to DEHP for the general population may grow up to about 2 mg/day. Occupational and medical exposures can reach much higher levels [25]. The tolerable daily intake (TDI) value settled by the EU Scientific Committee for Toxicity, Ecotoxicity and the Environment (CSTEE) is 37 micrograms/kg body weight/day [26] and the reference dose [RfD] of the U.S. Environmental Protection Agency (EPA) is 20 μg/kg body weight/day. Recently, for DEHP a median

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intake of 13.8 µg /kg body weight/day and an intake at the 95th percentile of 52.1 µg/kg body weight/day have been assessed [27]. In children highest estimated intakes [19 µg/kg body weight/day] are at the age 0.5-4 years [28]. DEHP concentrations in water, fresh soil and sediment have been estimated to be 3 to 20 times higher than the Environmental risk limits (ERLs) [29]. Although exposure to the developing fetus *in utero* during critical points in development is a concern, the most dangerous risk of exposure for humans is probably the release of DEHP from PVC medical devices into the biological fluids which they contain [13, 14, 22, 30]. DEHP is lipid soluble, so when PVC medical devices are contiguous with lipid containing body tissues (e.g. blood), this plasticizer leaks out, accumulating in blood and tissues, particularly in the liver, kidney and lung, especially if renal function is impaired [31]. Consequently medical devices become more rigid [32]. DEHP is released from several medical devices, including feeding tubes, infusion tubing systems, umbilical catheters, respiratory tubing systems, PVC blood bags, transfusion tubing systems, hemodialysis systems, cardiopulmonary bypass, continuous peritoneal dialysis, extracorporeal membrane oxygenation circuits (ECMO) [31-57]. More recently we observed DEHP release also from endotracheal tubes [58]. The rate of extraction of DEHP from PVC medical devices depends highly on the surrounding temperature and the time of contact between solution and tubing [59]. Neonates in the NICU environment represent a population at particularly increased toxicity risk, due to multiple medical device-related DEHP exposure, also because neonates exposed to DEHP and MEHP from PVC devices may have been previously exposed to phthalate esters *in utero* [22, 24, 60]. Thus, it is conceivable that prenatal and postnatal exposures may have synergistic and cumulative actions in producing adverse effects, especially for very low birth weight premature infants.

DEHP AS A DEVELOPMENTAL AND REPRODUCTIVE TOXICANT

DEHP is a well-known developmental and reproductive toxicant working by similar mechanisms in males and females and toxicity seems to occur at an older age in females than in males [61]. DEHP and its main metabolite mono(2-ethylhexyl)phthalate (MEHP) appear to target analogous sites within the testis (Sertoli cells) and ovary (granulosa cells). In males DEHP is a testicular toxicant [62] and its target is likely to be located in the Sertoli cell membrane, by inhibiting follicle stimulating hormone (FSH) signal transduction [63]. Potential adverse effect on male reproductive tract consists into hormonal disturbance of the fetal testis development [22]. Development of a fetus into a phenotypic male depends, firstly on testis formation and secondly on hormone production by the fetal testis [23]. In particular, involvement of the production and action of hormones, such as androgens and anti-mullerian hormone is required and chemical exposures, which may interfere with the production or action of these hormones, can partially or completely prevent masculinization. Abnormal development of the testis in fetal or neonatal life can have life-time consequences on all aspects of reproductive function in adulthood, including sperm counts [23]. Moreover, DEHP effects on Leydig cell steroidogenesis are influenced by the stage of development at exposure [64].

In contrast to the male, development of a fetus into a female is largely hormone-independent, though development along this pathway is still susceptible to hormonal disruption, e.g. masculinization of the female fetus by exposure to androgens [23]. DEHP, through its metabolite MEHP, acts through a receptor-mediated signaling pathway to alter estradiol production in the ovary [65]. Therefore, DEHP is not only the most important phthalate with respect to its production, use, occurrence and omnipresence but also the phthalate with the greatest endocrine disrupting potency.

DISCUSSION

There is increasing concern about endocrine-disrupting chemicals (EDCs), which are suspected of interfering with the production, release, transport, metabolism, binding action, or elimination of natural ligands responsible for the maintenance of homeostasis and the regulation of developmental processes and therefore, may produce adverse health effects in humans.

During the 20th century, there has been an increased risk from environmental by-products that may disrupt reproductive function in humans. In particular, infants, whose growth and development are highly dependent upon the endocrine system, are vulnerable to endocrine disruptor exposure. Recent research has identified environmental chemicals that disrupt reproductive processes by altering the actions of endogenous steroid hormones [23]. Phthalate esters, a large group of chemical agents used predominantly as plasticizers in the plastics industry and described as being among the most abundant man-made environmental pollutants, are now regarded as endocrine disruptors. In particular, DEHP, which belongs to the class of peroxisome proliferators, has been suspected of possessing endocrine disruptor properties, by antagonizing the effects of sex hormones or altering the actions of endogenous steroid hormones, in animal models [29, 61, 63-72]. In fact, it is known that DEHP acts by reducing testosterone to female levels in the fetal male rat during a critical stage of reproductive tract differentiation [72]. In particular, perinatal DEHP exposure inhibits fetal testicular testosterone production demasculinizing the males [73]. Moreover, DEHP effects on Leydig cell steroidogenesis may occur through modulation of testosterone-biosynthetic enzyme activity and serum LH levels [64]. Furthermore, DEHP expresses estrogen-like activity through estrogen receptors and the inhibitory effect of phthalates on nAChR-coupled Ca[2+] response is an indication of their nongenomic estrogen-like activity [67]. On the other hand, DEHP may also be an endocrine disruptor in women and its potential target has been shown to be the ovary. Its action mainly consists in an alteration of the natural ovulation times, resulting in hypoestrogenic anovulatory cycles and polycystic ovaries [74]. Thus, DEHP, through its metabolite MEHP, acts through a receptor-mediated signaling pathway to suppress estradiol production in the ovary, leading to anovulation. The pathways leading to ovarian hormone production are similar in rodents and humans, and it is reasonable to assume that MEHP would suppress aromatase

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in the human ovary. MEHP has been shown to alter the levels or availability of aromatase in the granulosa cell either by decreasing synthesis or increasing degradation of the enzyme [65]. Recent studies demonstrated that MEHP decreased aromatase RNA message and protein levels in a dose-dependent manner [75].

Moreover, MEHP activates the peroxisome proliferators receptors [PPARs] to suppress aromatase in the granulosa cells [65]. Finally, DEHP administration has been shown to alter the expression of genes associated with testis development, such as Vanin-1, and steroid hormone synthesis, thus providing additional evidence for the endocrine disrupting potential of DEHP [76]. In particular, an association between phthalates exposure and premature thelarche in a human female population has been recently reported [77]. In conclusion, although these compounds have been shown to be endocrine disruptors in experimental animal models, a close cause-and-effect relationship between DEHP exposure and adverse health effects on the endocrine system in the human population remains to be established. Future epidemiological and toxicological studies are needed to determine to what extent human exposure to phthalates impairs reproductive function and hence, human health. However, the available toxicity data and the limited but suggestive human exposure data causes the serious concern that DEHP exposure may be detrimental to human fertility and reproduction. Therefore, over the years many investigators have proposed discontinuing the use of plastic items containing extractable materials that may come in contact with human tissues and urgently encouraging research into alternatives to DEHP-containing products [30, 40, 46, 78, 79]. Accordingly, we have recently reported polymeric admixtures, which could represent a solution to the problem of obtaining safe and stable PVC formulations as compared to overall performance as DHEP-plasticized PVC [80]. Furthermore, since 2000 new plasticisers for PVC formulations are presently being studied in the frame of a four years Brite-Euram Project, entitled "*Biocompatible flexible polymer alloys based on polyesters from removable resources for mass-consumer applications involving contact with human fluids and tissues*" (Bioflex-Renew), approved and funded by the European Union (Contract N. QLK5-CT-1999-01355) in which the Brindisi Hospital has been serving as a Project Partner. The overall goal of this Research Project is to develop industrial technologies for the production from renewable resources of polymeric plasticisers capable of replacing phthalates in flexible PVC for mass-consumer applications involving contact with human fluids and tissues, particularly medical devices and toys.

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ABBREVIATIONS

DEHP = Di-(2-ethylhexyl)-phthalate

MEHP = Mono-ethylhexyl phthalate

PVC = Polyvinylchloride

EDC = Endocrine-disrupting chemical

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