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Consumption of Phthalates Coated Pharmaceutical Tablets: An Unnoticed Threat

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Abstract: Phthalates are synthetic chemicals used in many products of both industrial and medical importance. Approximately three million metric tons of phthalates are produced worldwide annually and are used in various sectors. Di-2-ethylhexyl phthalate (DEHP) is one of the most commonly used plasticizers. Chemically, they are loosely attached to Polyvinyl Chloride (PVC) based materials and with passage of time, leach to the surrounding environment. Phthalates are released from various sources and humans are exposed via, ingestion or inhalation. Different types of phthalates are used in the manufacture of coated and sustained releases drug formulations, as approved by FDA. Phthalates have been enlisted as Endocrine Disrupting Chemicals (EDCs) with proven toxicity on various hormone controlled functions. Currently, besides medical devices, over the counter and prescription drugs contain certain quantity of phthalate as excipient. In certain chronic diseases, treating patient with such drugs may be an additional direct exposure to phthalates toxicity. So, on the basis of gathered evidences there is a need to seriously consider this type of direct human exposure and prevent already suffering people from being chronically poisoned with phthalates.

Key words: Endocrine disrupting chemicals, enteric coated medicines, phthalates, toxicity

INTRODUCTION

Phthalates are diesters of phthalic acid, a group of substances being used in variety of products. Di-2-ethylhexyl phthalate (DEHP) is primarily used as plasticizer in polyvinyl chloride (PVC) plastics. Many PVC based products are in direct human use in the form of plumbings, water tanks, cosmetics and some packaging materials (Hauser *et al*., 2004; Green *et al*., 2005). Phthalates are not chemically bound to PVC based materials and with the passage of time may seep out and enter into indoor air, contaminate the atmosphere and finally may get its way to food chain. The rate at which the DEHP leach out from either medical devices or other materials depends upon the type of solution in direct contact, storage temperature, time and amount of DEHP in a particular product (Marcel, 1973). For instance, the leaching rate of DEHP has been measured as 0.25-0.40 mg 100^{-1} mL day^{-1} for blood stored in PVC bags, for 24 days at 4°C (Marcel, 1973). Human exposure to phthalates most commonly occur through direct ingestion or inhalation (Heudorf *et al*., 2007). Apart from environmental exposure, it has been reported that extensive use of PVC based medical devices in clinical settings may lead to higher exposure to DEHP in humans (Green *et al*., 2005).

Global exposure to phthalate compounds: Every year about three million metric tons of phthalates are produced worldwide (Schettler, 2006) among which DEHP is one of the most commonly used plasticizers in numerous products of human use. In the year of 2003, approximately 900,000 tons phthalate consumption has been recorded in Western Europe, among which DEHP was used 24% while more than 50% consumption was recorded for di-iso-nonyl phthalate (DINP) and di-iso-decyl phthalate (DIDP) (http://www.ecpi.org) (Heudorf *et al*., 2007).

Usage of phthalates as a pharmaceutical excipients: The most important among all is the presence of phthalates in over the counter and prescription drugs which could be a source of high exposure for human beings. With the advent of Sustained Release (SR) formulations, the use of different types of phthalates has been dramatically increased in recent years. Many coating polymers used for the design of enteric coated tablets, sustained or controlled releases dosage forms contain different types of phthalates like, diethyl phthalate (DEP), Cellulose Acetate Phthalate (CAP) and Dibutyl Phthalate (DBP), Dimethyl Phthalate (DMP) and Polyvinyl Acetate Phthalate (PVAP) (Hauser *et al*., 2004; Malm *et al*., 1951; Nesbitt *et al*., 1985; FDA, 2010). These compounds have been approved by FDA as excipients with specified

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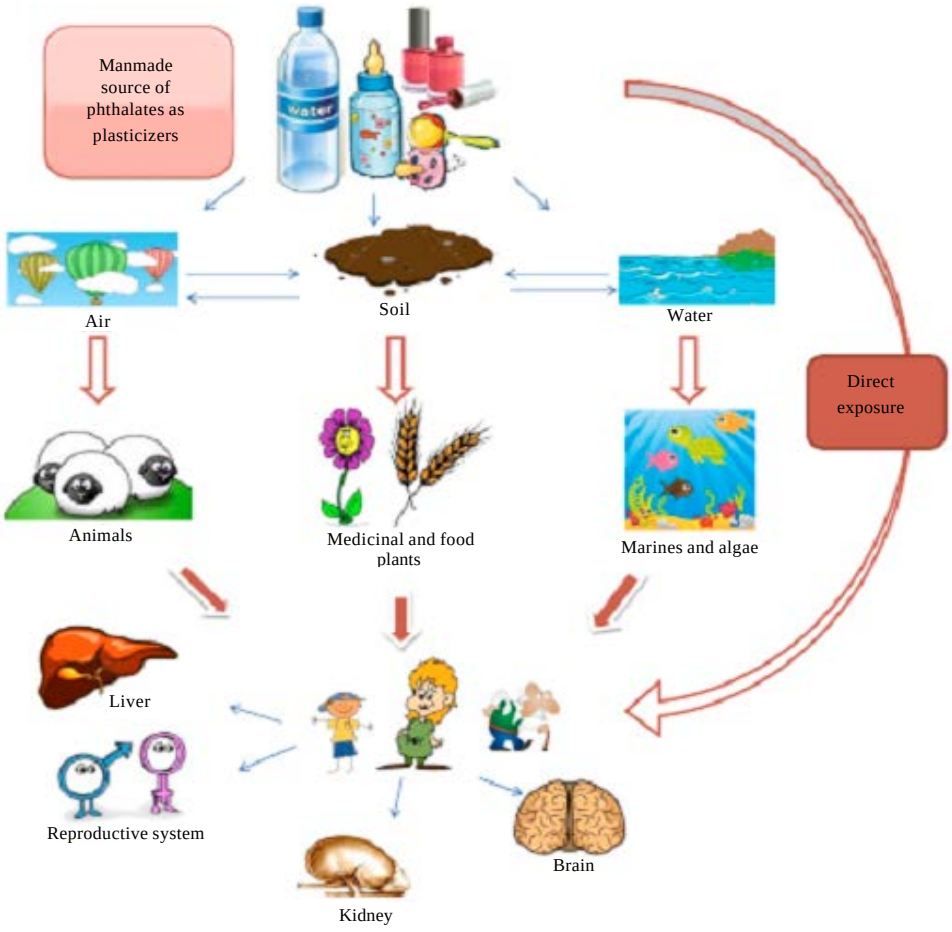

Fig. 1: Natural circulation, deposition and bioaccumulation of phthalates in relation to human exposure and health effects. Adopted under the terms of the creative commons attribution license from (Saeidnia and Abdollahi, 2013)

limits for each formulation and route of administration. The maximum limit of DBP, approved by FDA, for delayed action tablet is 1.70 and 11.18 mg for enteric coated tablet. Similarly permissible limit of DEP for enteric coated, delayed action tablet is 16.8 mg (FDA, 2010).

Evidences regarding the toxic health effects of phthalates: Based on chemical properties, phthalates do not bioaccumulate (Heudorf *et al*., 2007). Generally, different categories of phthalates having pharmaceutical applications have been thought as non- toxic. In humans, phthalates are rapidly hydrolyzed and corresponding metabolites are excreted via urine and feces as evidenced by Hauser *et al*. (2004) in one follow up case (Hauser *et al*., 2004). The half-life of phthalates in humans varies from hours to days subject to the presence of alkyl chain (Schecter *et al*., 2013). As shown in Fig. 1 recently, the concern on the accumulation of phthalates in the herbal medicines has been raised (Saeidnia and Abdollahi, 2013). Accumulation of phthalates can occur in some medicinal plants that are usually grown in water flow in rivers and canals. Therefore, assessment of phthalates in the medicinal and food plants seems necessary to avoid possible human toxicity especially in the cases of chronic uses.

Experimental and some studies from human subjects have suggested that phthalates of pharmaceutical interest such as DBP and DEHP are reproductive and developmental toxicants (Howdeshell *et al*., 2008; Foster, 2005; Swan, 2008; Swan *et al*., 2005). In rats, phthalates exposure have caused seminiferous tubule atrophy and reduction in testicular weight (Kamrin, 2009). Duty *et al*. (2003) have reported sperm DNA damage in adult males exposed to phthalates (Duty *et al*., 2003). Besides altering insulin sensitivity, phthalates have been enlisted as Endocrine

Disrupting Chemicals (EDCs) affecting a wide range of hormone controlled functions and systems (Diamanti-Kandarakis *et al*., 2009; Meeker *et al*., 2007; Huang *et al*., 2007; Svensson *et al*., 2011; Latini *et al*., 2009). Reproductive system is very sensitive to environmental pollutants like phthalates as well as pesticides (Saadi and Abdollahi, 2012; Mostafalou and Abdollahi, 2012) can be listed among causes of human infertilities.

CONCLUSION

The presence of phthalates in many commercial and personal care products and their subsequent release to the environment from either source has been a matter of serious concern since long. Human exposure to phthalates mostly occurs via., inhalation and ingestion. After getting into human body, phthalates are rapidly metabolized and the metabolites are subsequently excreted. Phthalates have been categorized as EDCs and it is evident from experimental and some epidemiological studies, that phthalates are responsible for reproductive toxicity in the form of sperm DNA damage, testicular atrophy and developmental toxicity.

The recent SR technology depends upon the use of certain polymers containing phthalates as plasticizers. The pharmaceutical manufacturers are not required by FDA to disclose the quantity of plasticizers contained in each formulation. Although, toxic outcomes associated with use of plasticizers in drug preparations have not been documented yet, except measuring their metabolites, but we are of the view that in certain chronic diseases, consuming such phthalates coated tablets may leads to high quantity of phthalates exposure. Subsequently in this way a potential unnoticed secondary toxic health effect may be resulted. As per US Environmental Protection Agency phthalate action plan 2012, due to their toxic health effects, phthalates may be substituted with safe alternatives, both in medicine and medical devices.

In addition to look for safe alternatives, additional targeted epidemiologic investigations are needed to objectively assess the potential health effects due to phthalate exposure through medications and other medical devices.

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