Health Hazards of Phthalates vis-à-vis Idiopathic Male Infertility

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Abstract: The use of plastics has increased many-folds worldwide. Phthalate compounds, which are used as plasticizers for the manufacture of plastics, leach in to the surrounding medium and pose an environmental threat to developing countries including India. Now it is established that many chemicals exhibit biological activities associated with female sex hormone oestrogen. Untimely exposure to natural or synthetic estrogens can adversely affect human health, particularly with regards to the reproductive cycle and reproductive function. In recent years, there have been a plethora of publications discussing man-made oestrogen-mimicking chemicals, the so-called xenoestrogens. Reports of declining semen quality have been followed by hypotheses that this phenomenon may be linked to an increase in the exposure of humans to xenoestrogens, specifically *in utero*. Evidence of the estrogenic behaviour of certain phthalates *in vitro* has previously been reported. These environmental oestrogens may bind with hormone receptor in the body and inhibit the activity of natural hormone or elicit hormone like effects by themselves. There may be several other mechanisms that may be responsible for reproductive abnormalities induced by these chemicals.

While several investigators have recorded the effects of phthalate compounds on reproductive parameters in experiments conducted on laboratory animals, there have been conflicting reports about effects of phthalates on human reproductive system. Thus, in view of the recent studies on the role of endocrine disrupters in reproductive dysfunction and reported declining trend of human semen quality, it is essential that a planned study be undertaken to fulfil the gaps in the database on human exposure to phthalates and correlate phthalate levels in the human body with various health hazards especially male infertility.

Key words: Plastic, Phthalate, Endocrine Disruptor, Male Infertility, xenoestrogens, sperm, testis

Plastics have been recognized as one of the greatest discovery of the millennium becoming an integral part of our life. Nobody can just think life without plastics. We start our day with a plastic tooth brush and end it by going to bed on pillows & mattresses made up of some form of plastic (foam). During the day, we use cars, computers, television, cell phones etc. with each of them having several plastic components. It is used for packaging goods, for insulating electric wires and cords, in building and construction as well as in automotive industries.

Unveiled by Alexander Parkes in 1862 at the Great International Exhibition in London, these synthetic polymers have the capability of being moulded, extruded, cast into various shapes and

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meeting the wide range of needs of the society. Several types and variants of plastics have been developed, viz., bakelite, polyvinyl chloride (PVC), polyethylene, polyurethane, polyester, polypropylene, polycarbonate etc. The polymer industry in India has been growing at about 12 to 15% annually and demand for plastics is expected to touch 12.4 million tons by 2010-11, becoming third largest consumer after US and China.

The two most common plastics in the world, in terms of production volume are polyethylene and PVC. Both are used in medical devices, packaging, electrical insulation, flooring, and some auto components. Additionally about 60% of PVC production is destined for the construction industry, where it is used for everything from water pipes to siding. Most of the remaining 40 percent is used in consumer goods. PVC is the only major commercial plastic that contains up to 45 percent chlorine by weight which renders the raw PVC useless making it brittle and prone to degrade rapidly when exposed to UV light and necessitating addition of several other chemicals such as antioxidants, lubricants, pigments, flame retardants and plasticizers to the resin to achieve desirable qualities. Almost all such PVC additives are a health concern; but in terms of the quantities used, the most important additives are plasticizers.

Plasticizers (Phthalates)

Plasticizers are materials incorporated into certain plastics to increase flexibility and workability. These are not chemically bonded to the resin, so they may migrate to the surface of the material and leak (off-gas) into the surrounding environment. Off-gassing increases with mechanical stress (i.e., bending, pressure, and chewing) and exposure to solvents such as fats, oils, saliva, and temperatures over 85°F.

Almost 90% of plasticizers belong to a family of industrial compounds called phthalates (PAEs) which are used for a variety of purposes, including personal care, paints, industrial plastics, building materials, food packaging, clothing, toys, blood bags, intravenous fluid bags and infusion sets, and other medical devices (Huber *et al.,* 1996). They are also used in detergents, solvents, lubricating oils, fixatives, adhesives, printing inks, aerosols, antifoaming agent, and coatings for paper (NTP-CERHR, 2003). The lipophilic nature of these chemicals indicates that fatty food such as cream, cheese, and butter are most likely to be subject to contamination. Very roughly, global phthalate production appears to be in the range of 5.5 million tons a year. DEHP is the most commonly used plasticizer with an annual production of about 2 to 4 million tons. Different important PAEs and their major applications are listed in Table I.

Health Hazards of Phthalates

PAEs are not chemically bound to the plastic so they can be released from consumer products into the environment thus becoming ubiquitous environmental contaminants. Over a period of time, these accumulate in body tissues, and have been shown to damage liver, lungs, and reproductive organs in lower mammals. Population studies show that virtually everyone carries some level of phthalates in their body. According to U.S. EPA scientist Robert Menzer (1991) "It has become very difficult to analyze any soil or water sample without detecting phthalate esters". Some experts argue that even supposedly pure laboratory materials may be

contaminated with phthalates, making it difficult to establish baseline levels of exposure.

Some of the most common phthalates are persistent organic pollutants (POP) or POP-like compounds. In both wildlife and laboratory animals, these have been linked to a range of adverse reproductive effects, viz., reduced fertility, miscarriage, birth defects, abnormal sperm counts, and testicular damage. Some of the phthalate compounds such as BBP and DBP some food additive like butylated hydroxyanisole (BRA) are reported to be weakly estrogenic *in vitro* (Jobling *et al.,* 1995; Soto *et al., 1995*) as well as *in vivo* (Sharpe *et al.,* 1995). Experimental studies have further suggested that oestrogenic and anti-androgenic properties of xeno-estrogens can cause an increase of testicular tumours, hypospadia, cryptorchidism, and reduction of sperm density. Prenatal exposure to DBP, BBzP, DEHP, and DINP has been shown to disrupt reproductive tract development in male rodents through an anti-androgenic mechanism. Mylchreest *et al.,* (1998) reported that DBP specifically impaired the androgen dependent development of the male reproductive tract suggesting that DBP may not be estrogenic but anti androgenic in rats at high dose levels.

Circumstantial evidence indicative of disruption in human reproductive processes (Chalmers *et al*., 1984, Anonymous, 1986, Giwercman and Skakkebaek, 1992) by these environmental xenobiotics has resulted in a great deal of concern about their developmental and reproductive toxicity particularly in males. Harris *et al.* (1997) observed that some phthalates are estrogenic *in vivo* and hence may disrupt normal male development. DEHP has been recognised for many years to be reproductive toxicants (Gangolli 1982, Gray and Gangolli 1986,

Table 1: Important pthalates and their application

Full Name	Acronym	Examples of Applications
Di-Ethyl-Hexyl-Phthalate	DEHP	Perfumes; medical devices (transfusion tubing blood bags, gloves, catheters), flexible PVC products (food containers, shower curtains, diapers, plastic film for food packaging)
Di-Iso-Decyl-Phthalate	DIDP	Vinyl wall coverings, food packaging & gloves
Di-Iso-Nonyl Phthalate	DINP	Toys, vinyl flooring, gloves, food packaging, garden hoses, drinking straws, etc.
Di-Butyl-Phthalate	DBP	Insecticides; perfumes, deodorants, nail polish, hair sprays; printing ink, electron microscopy resin
Di-Ethyl-Phthalate	DEP	Perfumes, deodorants, hair gels, shampoos, soaps, body lotions, nail polish, hair sprays
Butyl-Benzyl-Phthalate	BBP	Perfumes, hair sprays, vinyl flooring, glues & adhesives
Di-Octyl-Phthalate	DOP	Flexible plastic-based products
Di-Methyl-Phthalate	DMP	Deodorants

Siddiqui and Srivastava 1992). However, it demonstrated no estrogenic potential in the assay used by Harris *et al.* (1997). Moreover DEHP is suspected to be an endocrine disruptor through reduction in testosterone levels and there is a controversy as to whether it is a carcinogen.

Impairment of foetal testicular testosterone production can lead to cryptorchidism, hypospadia, and reduced fertility. According to a study by the National Human Adipose Tissue Survey, 31% of 46 composite human adipose tissue specimens analysed had detectable levels of DEHP. Persons receiving medical care may be exposed to much higher concentrations of phthalates than the general population. The reproductive toxicity of DEHP is attributable to the action of its primary metabolite, mono (2-ethylhexyl) phthalate (MEHP), in Sertoli and germ cells (Sjoberg *et al* 1986, Li *et al.*, 1998), although disruption of Leydig cell structure and function has also been reported (Mylchreest *et al.,* 2000, Jones *et al.*, 1993).

Given their high production volume, common use and wide spread environmental contamination; humans are exposed to these compounds through ingestion, inhalation, and dermal exposure on daily basis. Table 2 lists some of the sources of human exposure to PAEs.

Numerous studies show that people are probably being contaminated by substantial quantities of PAEs although no 'safe' level of exposure has been suggested in humans. Hospital patients receiving intravenous infusions have been shown to be at risk of exposure to DEHP, which can directly leach out from intravenous tubes into patients' bloodstreams. Similarly neonates in Neonatal ICU environment are particularly at high risk to DEHP exposure from multiple medical devices due to their small body size, their physical condition combined with their developmental vulnerability. Various studies have also shown that children who chew on PVC toys-such as teething rings-absorb phthalates into their bodies. Young children may absorb phthalates from vinyl flooring and have been shown to have an 89% greater chance of developing bronchial obstruction and asthma than the control group. Recently, phthalates have been detected in urine from women of child-bearing age, at levels that cause foetal abnormalities in laboratory animals. Male workers in PVC plants have risk of developing seminoma which is six times greater than the general population.

Several studies on low-dose effects of different phthalates have revealed even more disturbing trends. *In utero* exposure to DEHP or DBP can deform the male sex organs and cause other types of 'demasculinization' in laboratory animals at levels far below the reported levels of previous toxicological concern. Swan *et al.* (2005) found an inverse relationship between prenatal phthalate levels and anogenital distance in male infants. In another study Puerto Rican girl, aged 6 months to 2 years, showed premature breast development and the level of DEHP in their blood was observed to be seven times the normal level.

A study of 85 infant boys found a correlation between increased exposure to some forms of the chemical phthalate and smaller penis size and incomplete testicular descent. Strangely these infants didn't experience levels even close to the high doses used in rat experiments and the boys' exposures, measured by analyzing their mothers' urine during pregnancy, were similar to those

Table II: Sources of pthalate exposure on human beings

Source of exposure	Exposed Group
Breast Milk and Formula (Dietary)	Children
Toys, milk bottles and teethers	Children
Food processing & packaging (Dietary)	All
Household Products	All
Cosmetic products (Dermal)	Adults/?All
Medical devices (Leaching)	All
Dust	All
Food	All
Off-gassing from building materials (Inhalation)	All

found among the general population. Blount *et al.* (2000) suggested that health-risk assessments for phthalate exposure in humans should include diethyl, dibutyl, and benzyl butyl phthalates in addition to DEHP and DINP

The controversy

The applicability of animal toxicity studies to humans remains incompletely characterized and controversial because of limited and conflicting human studies which are suggestive of an association between phthalate exposure and health risks. Further, the presence of phthalate metabolites in human body fluids by itself does not mean that PAEs can cause disease. As early as 1970s, scientists had observed that chicken embryos died when subjected to a 0.4 percent solution of DEHP. Although this concentration may appear very high by the standards of modern toxicology, it has been reported that human blood stored in vinyl bags can reach this level in a day or two. People can get exposed to DEHP at much higher levels than previously believed and the exposure of children in terms of body weight is twice as high as that of adults (Koch *et al.,* 2004). Yet, cause-and-effect relationships in the human population remain unresolved.

Carlsen *et al.* (1992) reported a decrease in the quality of human semen in terms of progressive reduction in sperm counts and decreased fertility during the past 50 years. It is now being slowly realized that there may be some adverse effects of environmental chemicals particularly estrogenic compounds on the reproductive function of human as well as animals. Sharpe and Skakkeback (1993) have postulated that apparent drop in sperm count may be due to the developmental exposure to estrogenic xenobiotics. The endocrine disruptor hypothesis suggests that a global decrease in male

reproductive capacity and increased incidence of breast cancer in women may be due to background environmental exposures to endocrine disruptors. But this hypothesis has become quite controversial, and resolution of this debate will depend upon future evaluations of human cohorts.

One school of investigators are of the opinion that environmental contamination with POP residues may be an important etiologic factor in breast cancer and reproductive toxicological disorders while the other school states that the levels of PAEs at which adverse health effects have been observed in experimental animals are unlikely to reach human body and thus correlative studies do not uniformly support a role for these chemicals in such disorders. Yet, in spite of apparently no toxicity of PAEs in adult humans in acute low doses, the toxic effects of cumulative exposure when ingested chronically (over a long period of time) cannot be ruled out.

Conclusion

Hence, it is right time that concerted multi-disciplinary and multi-institutional studies should be undertaken to:

- Monitor and establish a reference range of phthalates, pesticides and other POPs in the Indian population and fully characterize the risk of these compounds to human health.
- Assess health hazards & risk of various POPs including PAEs on human reproduction.
- Determine the effects of oral exposure on pre- & postnatal development in non-rat species.
- Examine the effects of PAEs on reproductive development, structure and fertility in a multigenerational study of rodents.
- Effects in non-rodents using non-oral routes of administration.

In nutshell planned animal studies as well as monitoring and correlation of POPs with human health status is the needed urgently. With further data on the toxicology of phthalates, and the human burden of exposure, we will hopefully be able to more accurately characterize the potential for human effects from these ubiquitous environmental contaminants.

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