

Phthalate exposure and health outcomes

Abstract

Phthalates are used in commercial products as softeners of plastics, solvents in perfumes and additives to hair sprays, lubricants and insect repellents. The wide spread use of phthalate results in multiple human exposure routes i.e., ingestion, inhalation and dermal exposure. In the present review, a detailed account of respiratory toxicity, reproductive toxicity, developmental toxicity, endocrine disruptors and genotoxicity of human exposure to phthalate is mentioned in detail.

Key words: Exposure, human, phthalate

INTRODUCTION

Phthalates represent a large class of chemicals that are widely used in commercial products. Phthalates are dialkyl or alkyl /aryl esters of 1,2-benzene dicarboxylic acids which have numerous uses as softeners of plastics, solvents in perfumes and additives to hair sprays, lubricants and insect repellents.^[4-5] In the residential construction or automotive industries diethyl hexyl phthalate, dibutyl phthalate and butyl benzyl phthalate are used in floorings, paints, adhesives, wood finishes, wall paper and in PVC products. The high levels of mono ethyl phthalates across the population are most likely associated with the every day use of consumer products that commonly contain diethyl phthalates (DEP), such as detergents, soaps, cosmetics, shampoo and perfumes. Phthalates are multifunctional chemicals used to hold colour and scent in consumer and personal care products. Phthalates are also present in drinking water, air and food. Diethyl hexyl phthalate (DEHP), one of the more commonly used phthalates leaches from blood products, intravenous and dialysate bags and tubings made with PVC.

In particular di - (2-ethylhexyl) phthalate (DEHP) is the most commonly used plasticizer. Globally, more than 18 billion pounds of phthalates are used each year and well above 2 million tons of DEHP alone are produced annually worldwide.^[6] Other important phthalates production and application wise are DEP, dibutyl phthalate (DBP), di-*iso*- and di-*n*-butylphthalate (DiBuP, DnBuP), butyl-benzylphthalate (BBzP), di-isononylphthalate (DiNP) or di-*n*-octylphthalate (DnOP).^[7] The potential for non occupational exposure to

phthalates is high given their use in a vast range of consumable products and because they are not covalently bound to the other chemicals in the formulations. After exposure, phthalates are rapidly hydrolyzed to their respective monoesters which can be further biotransformed to oxidative metabolites.

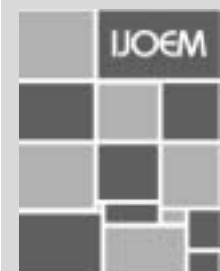
The wide spread use of phthalates results in multiple human exposure routes. Humans are exposed to these compounds through ingestion, inhalation and dermal exposure for their whole lifetime, since the intrauterine life.^[8-10] Dermal and inhalative exposures are considered to be the major route of exposure to DEP that is found in hygiene products such as soap, shampoo and conditioners. DEP and DBP are used extensively in products with volatile components such as perfumes, nail polishes and hair sprays possibly leading to inhalation and efficient absorption through the lungs. Dermal absorption also occurs at a significant rate for phthalates with short side chains such as DEP, DBP and BzBP.^[11] In contrast, for phthalates that are used mainly as plasticizers, such as DEHP, oral exposures predominate.^[12]

METABOLISM OF PHTHALATES

Phthalates are lipophilic compounds that appear not to bioaccumulate.^[13] These are rapidly metabolized to their respective monoesters and further oxidative products which are glucuronidated and excreted through the urine and feces.^[14-16] Recent metabolic studies have shown that long alkyl chain phthalates such as dioctyl phthalate are broken down to small chain phthalates before

**S. K. Rastogi,
C. Kesavachandran*,
Farzana Mahdi,
Amit Pandey**
Era's Lucknow Medical
College and Hospital,
Lucknow,
*Epidemiology Section,
Industrial Toxicology
Research Centre
(CSIR), Lucknow, India

For correspondence:
Dr. S. K. Rastogi,
Department of
Physiology, Era's
Lucknow Medical
College and Hospital,
Lucknow, India.
E-mail:
subhodhrastogi@yahoo.com



elimination from the body.

URINARY MEASURES OF PHTHALATES

Until recently, there was no direct way to measure phthalate exposure in environmentally and occupationally exposed individuals. We also had no population data on urinary phthalates levels and to date there are no published data that indicate sources of exposure associated with phthalates. With the recent studies on phthalates several urinary biomarkers are now available to assess specific phthalate monoesters.^[47] These biomarkers reflect recent exposure and have been demonstrated to be reliable.^[48] The measurement of monoester metabolites have been preferred over the metabolites of diester phthalates because the former have the added advantage of having longer biologic half life (12 hrs) than the latter ones (<3 hrs). Furthermore, most of the human toxicity is associated with the phthalate monoesters. The recent literature has shown that seven urinary monoester metabolites are now measured in spot urine samples using high pressure liquid chromatography mass spectrometry.^[49] Mono benzyl phthalate (MBZP), mono-butyl phthalate (MBP), monocyclohexyl phthalate (MCHP), monoethyl phthalate (MEP), mono-ethyl hexyl phthalate (MEHP), mono-isononyl phthalate (MINP), mono-octyl phthalate (MOP) etc. have been recommended as urinary biomarkers of phthalate exposure.^[49] The National Health and Nutrition examination surveys^[20] which analyzed several hundreds of urine samples indicated that not all metabolites are available in the morning void samples. The four phthalates MBP, MBZP, MEP and MEHP have been detected in most of the urine samples (97 to 99% of the sample analyzed) thereby showing the reliability and sensitivity of these monoester metabolites. However, while conducting such type of estimation it is of utmost importance to have a detailed personal history of the individual undergoing the analysis as sex and cigarette smoking are the confounding factors influencing the urinary metabolites of phthalates. Women have been reported to have higher urinary levels than men.^[24] The fact that women had higher concentration of urinary metabolites than men was most likely attributable to women's increased use of personal care products, such as beauty and hair care products, cosmetics and perfumes. It is not known whether the observed differences in males and females represent different underlying biology or different patterns of exposure. The higher levels of urinary biomarkers in women may be due to their greater exposure via the dermal route whereas men may have greater exposure via inhalation. Similarly adults and adolescents have higher levels than in children are consistent with the known behavioral uses of phthalate containing consumer products. Other factors viz, socio economic status and smoking habit have been shown to influence the level of urinary metabolites of monoester phthalates. The socio economic status appear to have a weak association with

phthalate levels.^[22]

HEALTH OUTCOMES

Human studies are scarce, but suggestive, as frequently reporting an association between phthalate exposure and health risks. The presence of phthalate metabolites in human body fluids does not by itself mean that phthalates cause disease. The adverse health effects of phthalate exposure on human population are most likely associated with the everyday use of consumer products that commonly contain a variety of phthalates like DEP, MEP, MBP etc. The recent studies suggest a broad spectrum of health outcomes associated with phthalate exposure.

RESPIRATORY EFFECTS

Potential phthalate exposure has been associated with respiratory symptoms and disease in young children exposed to building materials, synthetic bedding.^[23-24] Earlier study^[26] observed an increased incidence of lower respiratory symptoms and bronchial obstruction among children in homes with plastic wall materials and PVC building materials. Similar findings have also been reported earlier^[25] on Australian infants using synthetic bedding materials. The children had higher odds of wheeze at 7 years of age than did other children. Earlier report^[26-27,63] show higher rates of respiratory symptoms among beauticians (hair dressers). These respiratory effects could be due to phthalate exposure through inhalation via respiratory routes (air-borne suspended particulates). Earlier report^[27] mentioned that hair dressers had greater reduction in respiratory parameters. The respiratory impact of phthalates in adults was reported earlier.^[28] They assessed the association between phthalate exposure and four pulmonary function parameters (FVC, FEV₁, PEF and MMEF) and found that MBP was significantly associated with decrements in FVC, FEV₁, PEF and MMEF thereby contributing to respiratory impairment. However, MEHP was not adversely associated with any of the pulmonary function parameters evaluated.

REPRODUCTIVE TOXICITY

Evidence of population exposed to phthalates as well as in vitro studies suggest that some phthalates are normally active. The animal studies showed association between some phthalates and testicular toxicity. The National Institute of Occupational Safety and Health has classified DBP as a high priority chemical for study because of its widespread use and its reproductive toxicity. It is toxic to the testes, possibly through its metabolite, MBP.^[29] Of the phthalate most commonly used, DEHP and DBP and their metabolites have the greatest potential for toxicity. DEHP has been reported to suppress the estradiol and ovulation in cycling rats. It is a

reproductive toxicant and is carcinogenic in animal models. The phthalates have been also shown to cause endocrine disruption causing testicular toxicity, decreased fertility, decreased sperm motility and decreased milk synthesis. Several phthalates viz, DEHP, DBP and BZP are teratogenic in animals.^[30,31] Animal toxicology of several phthalates have been studied. DEHP is a rodent liver carcinogen through a mechanism thought to involve peroxisome proliferation.^[32] However, carcinogenicity by this mechanism is unlikely to be relevant to humans.^[33]

Several phthalates and their metabolic products have been shown to be developmental and reproductive toxicants affecting particularly male reproductive development^[34-37] and are suspected of having endocrine disrupting or modulating effects.^[38] An endocrine disruptor is a chemical with the potential to alter hormone action within the body.^[39] Thus these chemicals have been found to interfere with the function of endocrine system which is responsible for growth, sexual development and many other essential physiological functions both in males and females.^[40-41]

Gestational and lactational exposures to large doses of DBP and its metabolite MBP in rats cause male reproductive tract malformation.^[36] DBP reduces the production of testosterone by fetal testis through an antiandrogenic mechanism.^[42] The active testicular toxicant may be DEHP metabolite MEHP.^[43-44]

DEVELOPMENTAL TOXICITY

Results from animal toxicology studies have demonstrated endocrine modulating effects from phthalate exposure.^[31] For example DEHP alters thyroid structure and activity in male wistar rats and produces reproductive and developmental toxicities in rodents.^[45] In male rodents, the testes are a primary target tissue and exposure to high doses of DEHP results in decreased testicular weights and tubular atrophy.^[4] DEHP is a known reproductive and developmental toxicant in animals exerting its toxicity already in utero. Some effects are malformed reproductive organs, a decreased anogenital distance, retained nipples at birth, a general decrease in mating, pregnancy or fertility, reduced prenatal and post natal survival of the offspring, reduced sperm counts or reduced reproductive organ weights.^[45] DEHP is known to produce decreased testicular weight,^[46] severe testicular atrophy and reduced weight of sex organs in adult male rats by a mechanism thought to involve decreased fetal testosterone synthesis during male sexual differentiation.^[35]

Some phthalates and their metabolites act functionally as antiandrogens during the pre natal period^[35,47,48] and cause reproductive and developmental toxicity in animals especially in males. Some developmental effects include reduction in

androgen dependent tissues (Seminal vesicles, epididymis, prostate).^[38,49,50]

ENDOCRINE DISRUPTORS

DEHP is also a suspected human endocrine disruptor/modulator.^[39,40,51-54] Some phthalates are hormonally active^[55,56] and animal studies showed associations between some phthalates and testicular toxicity^[35,57-59] has generated both public and scientific concern about potential reproductive effects of phthalates.

GENOTOXICITY

Recent *in vitro* studies using the alkaline comet assay (single cell gel electrophoresis) found di-n-butyl phthalate (DBP) and di-isobutyl phthalate (DiBP) to be genotoxic in human epithelial cells of the upper aerodigestive tract^[60] as well as in mucosal cells and lymphocytes.^[61] Additionally, the comet assay was used to detect DNA damage in human lymphocytes induced by *in vitro* exposure to DEHP and MEHP.^[62] Using the alkaline comet assay, researchers have found evidence of genotoxicity with *in vitro* studies examining lymphocytes and mucosal cells of digestive tract after exposure to DBP and DiBP.

In another study using the alkaline comet assay on human leucocytes, an association between MEHP and DEHP and increased tail movements was found.^[60-62]

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Source of Support: Nil, **Conflict of Interest:** None declared.

Announcement

INDIAN ASSOCIATION OF OCCUPATIONAL HEALTH

1st - 4th February 2007

Hosted by Tamilnadu Branch

Venue: Hotel Taj Coromandel, Chennai.

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Marudeshwara Enterprises, A/2, Shanthy Apartments, 18 ttk, 1st Cross street, Alwarpet, Chennai - 600 018, phone: 91-44 – 2435 3079, 2432 8152, Tel./Fax : 91-44-2432 0605, E-mail : marudeshwara_tours@vsnl.com, www.marudeshwara.com

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