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Advances in Clinical Toxicology

Endocrine Disrupting Chemicals used in Plastic Industries: A Cause of Concern and Need for Alternatives

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Review Article

Volume 1 Issue 2

Received Date: October 05, 2016

Published Date: October 17, 2016

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Abstract

Polymer material studies have grown as a multidisciplinary science for combating the demands and challenges of the customers. Plastic and polymeric products have multiple applications ranging from packaging, building materials, nanofabrics, implants, polymer aided drugs to biomedical devices and accessories. Internationally there is increasing concern due to adverse developmental and reproductive effects in mammalian animal models. Phthalic Acid Esters (PAEs) or phthalates have fugitive nature and are extensively used as plasticizers for the production of items of varied composition ranging from daily usage consumer items to personal care products. The annual worldwide production is estimated to exceed five million tonnes. PAEs are issue of great concern worldwide due to toxicity and multidimensional studies have been conducted during last five decades. To meet global challenges of environment friendly solutions, the polymers of current generation are generally superior to any previous generation products due to significant improvement in characterization, machinery, designing tools, fabrication etc. The acceptance of finished products may suffer unless robust quality control steps are followed and legislation is strict for enforcement. The exposure to PAEs may be assessed by several methods viz analyzing urine for their metabolites as it is rapidly metabolized to its monoester and also glucuronidated. The extensive in vitro and in vivo toxicity studies had been conducted for understanding the mutagenic, developmental, reproductive, neurobehavioral implications. They may bioaccumulate in invertebrates, fish and plants but do not get biomagnified as higher animals efficiently metabolize and excrete phthalates. It may leach from the plastics that are dumped at municipal landfills. Efforts are being made to search or develop comparatively safe plasticizers preferably from natural resources. The synergy between natural polymers and the safe additives sciences are appreciated and efforts for translational R & D are in progress. Innovative and stimulated development of several value added degradable functional polymers in electronics, architecture, intelligent packaging are the need of the present times. Computer aided polymer designing using structure activity relationship, functional techniques with appropriate sequencing may offer uniformity and quality control. Relevance of both clinical and non clinical data along with knowledge of the technical specifications of polymeric product, toxicity profile and regulatory guidelines at International platforms can never be underestimated. Dissemination of the state of art knowledge to the beneficiaries must be percolated as per needs. They are needed to holistically plan for appropriate usage with appropriate preventive measures for minimizing the adverse implications. In order to meet future requirements, capacity building for systematic sampling, monitoring and management are to be created under guidance of trained manpower.

Keywords: Plasticizers; Toxicity; Health; Regulatory Requirements; Management

Introduction

Endocrine disrupting chemicals (EDCs) are detected in varied products viz plastics, pesticides, additives/contaminants in food and personal care products. The endocrine system consists of glands,

secreted hormones and associated receptors. They have been reported to be associated with changed reproductive function with increased incidence of abnormal growth patterns, neurodevelopment changes in children, immune function etc. The exposure to them may occur through ingestion of food and water, dust inhalation, exposure to toxic gases and particulates in the air or through the dermal route. They may be transferred from the pregnant woman to the developing fetus or child through the placenta and breast milk. Expecting mothers and children are comparatively vulnerable populations to be affected by exposures. They may be released into the environment after prolonged exposure to acidic pH, sunlight, heat or reaction with simulating solvents. Due to the ubiquity of plastics in modern lifestyle we are exposed to some level of PAEs. The exposure may be through direct use or by indirect means via leaching and general environmental contamination. They are not covalently bound to plastics and leach from products into the environment. Several studies have reported that Bisphenol A and phthalates induce adverse health effects in vertebrates, wildlife while few studies have addressed their toxicity to non-mammalian species [1-17]. The concerns related to estrogenic characteristics had arisen from studies indicating that the binding of 17 beta estradiol to isolated oestrogen receptors and stimulated the in vitro expression of cellular oestrogen sensitive endpoints. The toxicity profiles and potency may vary from phthalates to phthalates and depending on routes as well as concentration of exposure beside the implications of mixtures. They may be associated with the neurodevelopment, carcinogenicity, reproductive, developmental effects etc. With increasing awareness about phthalates and restrictions for its usage the search is continued for alternatives which may be non-toxic compounds and that will not leach out of the plastics and polymeric products. Soyabean oil and Polycaprolactone (PCL) is being tried with few limitations and getting future directions through concept of green chemistry.

Commonly used Phthalates

Exposures to these plasticizers from products may occur during their lifecycle or even through degradation after normal shelf life. Commonly prevalent phthalate compounds are di ethyl phthalate (DEP), di-n-butyl phthalate (DBP), di-iso-octyl phthalate (DIOP), bis (2-ethylhexyl) phthalate (DEHP), di-isobutyl phthalate (DIBP) and diallyl phthalate (DAP). They are known to depict rapid metabolism in humans by biotransformation to their respective monoesters. They are normally colorless, odorless liquids produced by reacting phthalic anhydride with an appropriate alcohol .The Consumer Product Safety Commission (CPSC) has convened a chronic hazard advisory panel on PAEs found in children's toys, childcare products and in products used by women of childbearing age. Biomonitoring and toxicology data reveals the basis for a mixture risk assessment and need to focus on routes and sources amidst uncertainties. They interfere with hormone signaling, which is especially critical to early childhood development and few are known reproductive and developmental toxicants. In view of this it is that phthalate plasticizers be minimized or eliminated from the environment. In response to consumer and regulatory pressures manufacturers have begun to offer phthalate-free products and comparing with diisononyl phthalate (DINP). Newer Phthalate-free plasticizers raise fewer concerns as plasticizers. As they are ubiquitous in the environment and we have to learn to live with them safely and protecting ourselves. Few organizations are actively devoted to convert waste to wealth by recovering the useful moieties.

Phthalates from Packaging or Indirect Exposure through Diet Routes

Di (2-ethylhexyl) phthalate (DEHP) and other phthalates may reach the general population through food chain or fatty foods or packaging materials of unregulated quality. Phthalate esters are the dialkyl or alkyl aryl esters of phthalic acid. They have a clear syrupy liquid consistency and show low water solubility, high oil solubility and low volatility. They are divided into two distinct groups, with different applications, toxicological properties and classification. They are used to impart flexibility and plasticity. Lower-molecular-weight phthalates are being gradually replaced in several countries due to health concerns and are replaced by high-molecular-weight phthalates or non-phthalate plasticizers to minimize the adverse implications on health. Di-n-butyl phthalate (DBP) and di-(2-ethylhexyl) phthalate (DEHP) have been detected in several water samples of river, well and tap water. In studies of rodents exposed to certain phthalates, high doses have been shown to change hormone levels and cause birth defects. Different moieties of phthalates have been detected in a wide range of food products, vegetables and breast milk. Milk analyses demonstrate that background levels in unprocessed milk may be usually low and dietary products fat-enriched food may have DEHP. Plasticized PVC from tubes, conveyor belts, or disposable gloves used in food processing may be also a source for contamination of food. Non-occupational exposure to PAEs may lead to adverse effects on testicular/Leydig cell function owing to

the ubiquitous multisource exposure. Levels of DEHA have been determined in representative samples and observed to be above the European specific migration limit of 18 mg/kg for DEHA in food or food stimulants [1-22]. In another study of Norwegian foods and beverages the estimated dietary exposures to phthalates and BPA were determined to be considerably lower than their respective tolerable daily intake (TDI) values established by European Food Safety Authority (EFSA).

Metabolites, Urine Analysis and Biological Markers for PAEs

Metabolites are believed to be responsible for the biologic activity attributed to phthalate exposure, and metabolite measurements may be more relevant in studies investigating associations between phthalate exposure and adverse health outcomes. In absence of comprehensive information about the biologic activity of the oxidative metabolites it is felt that toxicological data on the metabolites of phthalates are needed. Reliable biologic markers will enable application in epidemiologic studies as well as development of questionnaires that may help to identify key predictors of phthalates. The toxicological properties of different phthalates vary thus biological markers may be useful for assessing exposure to phthalates and risk assessment. It is suggested to have repeated-measures studies for addressing the temporal variation of phthalate exposure over the course of days, weeks and throughout the year. Biomarkers may serve as useful tools to determine human exposure and to determine the sources and further evaluate potential health effects associated with exposure. Analytical data of urine samples from experimental animals indicates release of low concentration levels and becomes useful to assess sensitization of direct exposed workers. The measurement of phthalate metabolites in people is not adequate to conclude that phthalates are primarily responsible without adequate epidemiological data. In view of this additional research are required to supplement and determine whether specific exposure to phthalates at the levels found in the general population is a cause for health concern. The NIEHS and other international organizations are supporting studies to determine whether exposure to endocrine disruptors is resulting in human health effects viz lowered fertility or an increased incidence of endometriosis and some cancers. They may pose risk during prenatal and early postnatal development when organ and neural systems are developing. Dermal exposure of EDCs may be through complex process of contact between a relevant substance and the skin over a period of time. The diseases resulting from dermal exposure and consequently absorption may have a significant impact on human health. The modern analytical equipments have plastic components and thus the phthalates may be in detected in traces quantities from plastic wares or equipments accessories. During monitoring blank or control should be run and Limit of detection (LOD), limit of confirmation (LOC) as well as limit of quantification (LOQ) monitored during quality control and assurance.

Interlinkages between Plasticizers, Monomers and other Additives

Polycarbonate plastics have many applications including use in some food, water and drink packaging, baby feeding bottles, compact discs, impact-resistant safety equipment, and medical devices. Epoxy resins are used as lacquers to coat metal products such as food cans, bottle tops, and water supply pipes. Some dental sealants and composites may also contribute to BPA exposure. The sources of exposure to Bisphenol A are also through the diet, water and beverages. Bisphenol A may leach into food from the protective internal epoxy resin coatings of canned foods and from consumer products such as polycarbonate tableware, food storage containers, water bottles, and baby bottles. The degree to which BPA leaches from polycarbonate bottles into stored in liquid may depend on the temperature of the liquid, bottle other than the age of the container. BPA may also be found in breast milk. Fertility may be decreased in adults exposed to Bisphenol A. A preponderance of evidence for a low dose of BPA given to pregnant rats suggests changes in brain development and behavior in their offspring. There is some evidence of low-dose effects on brain processes involving the neurotransmitter dopamine, thyroid hormone, and regulation of ovulation. Some studies have implicated low doses of BPA in behavior changes related to aggression, pain response, anxiety, motor activity and others. There are other chemicals such as parabens, pesticides, Poly brominated Diethyl Ethers (PBDEs), poly chlorinated bi phenyls (PCBS) which may exhibit interlinkages with phthalates and serve as EDCs which may accumulate in river and marine sediments. Isolation, removal, devising technologies and strategic planning for remedial procedures is critical in view of movement in the ecosystem and bio accumulation.

Smart Polymeric Materials and Natural Chemistry

Nanostructured functional smart polymeric materials are critically vital for energy harvesting storage, environmental control, water purification, controlled

release of incorporated agents, transportation, construction, appliances etc. The prerequisites for development of materials encompass precise synthetic, processing techniques, characterization with unique properties of natural chemistry. It may include multidimensional chromatography; hyphenated spectroscopic methods, thermo mechanical methods, scanning microscopy with high resolution for identification, standardization, characterization and validation. Thus polymer or bioplastics may range from synthetic and novel biobased items such as palm oil, gums, resins etc for variety of applications.

Safe Alternatives

A panel of novel compounds with satisfactory plasticizer properties and biodegradability may be in use as commercial plasticizers, such as diisononyl-cyclohexane-1,2-dicarboxylate (DINCH). MEHP, the monoester metabolite of DEHP may also be included as reference compound. As phthalates target mainly testicular function i.e. androgen production and spermatogenesis, researchers have used the mouse MA-10 Leydig and C18-4 spermatogonial cell lines as surrogates to evaluate cell proliferation, steroidogenesis and mitochondrial integrity. Dose-response studies revealed the toxicity of most maleates and fumarates, while identifying several dibenzoate and succinate plasticizers as innocuous on Leydig and germ cells. Few commercially available products of established certification may serve as safe alternative. MEHP is the only plasticizer inducing the formation of multinucleated germ cells (MNG) in organ culture. The adoption of such collaborative approaches for developing new chemicals may help to prevent the development of compounds potentially harmful to human health.

Advanced Degradable Polymers and Medical Treatment

Degradable polymers may be used for cancer treatment, dental implants or general accessories in surgical operations. The degradable polymers may be thermo, photo or oxo degradable in nature depending on inherent compositions. A range of biodegradable polymeric drug delivery systems designed for localized and systemic administration of therapeutic agents as well as tumor-targeting macromolecules has entered into the clinical phase of development, indicating the significance of biodegradable polymers in cancer therapy. Biodegradable and biocompatible polymeric nanocarriers due to several unique properties such as excellent biocompatibility, prolonged gene circulation time, prevented gene degradation, passive targeting by using the enhanced permeability and retention (EPR) effect, and possibility of modulating polymers structure to obtain desirable therapeutic efficacy, are among the most promising systems for gene delivery. However, biodegradable gene delivery systems have some limitations such as inadequate stability and slow release of therapeutics which have to be overcome. Advanced functional biodegradable and compatible delivery systems with more efficient gene delivery activity has recently been introduced as safe carriers for oligonucleotide delivery. ISO, IS, DIN, ASTM, WHO and OECD guidelines or specifications are being updated towards improvement in quality and harmonization. The coupling of drugs to macromolecular carriers has received an impetus of polymer-drug conjugates. Water-soluble polymers viz. poly (ethylene glycol), poly[N-(2-hydroxypropyl) methacrylamide), poly(l-glutamic acid) and dextran have been investigated for application in clinical research. The reports of clinical trials with polymer-drug conjugates viz paclitaxel, doxorubicin, camptothecins etc indicates positive utility of few degradable polymers as drug delivery vehicles.

Developments and New Strategies for Application of Polymers

Over the last two decades stent technology has progressed from bare metal stents to drug eluting stents (DES) to thin strut, biodegradable polymer coated DES to totally bioabsorbable DES. Each step was marked by improvements in safety and benefits. It involved investments in R&D, animal testing, clinical trials, post market surveillance and long term follow up. These were made to ensure new devices were significantly better than previous devices. Long term safety data and effectiveness data are necessarily needed prior to FDA approval. These data are collected through large multi centre randomized, clinical trials with rigorous statistical rationale, independent safety monitoring, adverse event adjudication. In consideration to chemical toxicity, it is vital to identify modifiable sources of exposure that need to be targeted for exposure reduction strategies. In addition simulated exposure modeling, observational epidemiologic studies, stringent monitoring and management, intervention studies are suggested by experts for understanding exposure pathway for both high-molecular-weight phthalates and BPA. The economy, acceptance by the community and safety towards environmental sustainability are the prime considerations. Utilizing the green chemistry concepts and need for functionality combined with innovation

based on renewable feedstock the tailor-made, and easily accessible polymer additives solutions are in process of development with stringent quality standards.

Disposal of Medical Waste Containing Plastics and Plastic Waste Management

Although there are rules for Plastic Biomedical Waste Management but they need improvements to improve the health and sanitation as they are not adhered due to varied reasons. The situation is different in countries to countries and requires specific location based solutions with awareness. Uncontrolled incineration of plastic packaging material or biomedical may lead to emissions into the air, and products in landfills may leak hazardous substances into the nearby environment, aquifers over a long period of time. Recovery or recycling, dismantling without appropriate scientific safety approaches may lead to exposure. The accumulated data reveals that many adult diseases have fetal origins, but the causes have remained unexplained. The improving fetal and child health may influence the whole life of an individual and improve the wellbeing of our society. They may degrade through abiotic means which proceeds via hydrolysis and photolysis involving reactions with hydroxyl ions to form carbon dioxide and methane. The conditions in the lower landfill layers are high temperature and pressures with wide pH fluctuations.

We must attempt towards promoting innovation of new efficient clean technologies. The adoption of the Polluter Pays Principle, the Use Pays Principle or the Precautionary Principle may ensure the best technology available to meet the predefined specifications by the manufacturers in preventing and controlling pollution. We should try to protect our environment from overburden of toxic chemicals and indiscriminate injudicious usage [4-8,13-23]. Environmental phthalate exposure may be associated with attention deficit disorders in children. A study has been conducted with initial hypothesis that in children treated in the pediatric intensive care unit (PICU), circulating phthalates may migrate from indwelling medical devices and may contribute in their long-term attention deficit. The association with the attention deficit has been confirmed in the validation cohort (all $P \leq 0.01$) and phthalate exposure effect explained half of the attention deficit in post-PICU patients by Verstraete et al. The clinical studies carried out by Ishfaq et al in have indicated that several phthalates are linked to adverse implications on development and function of human and animal systems. Sex hormone-binding globulin is a plasma carrier protein that binds androgens and estrogens and represents a potential target for phthalate endocrine disruptor function in the body. A preliminary study conducted by Lulia et al of Romania related to tobacco smoke indicates that there is no statistically significant association between the urinary levels of arsenic, cotinine, and phthalates metabolites and the response to cervical cancer treatment but still suggest that phthalates metabolism may be associated with response to treatment for locally advanced cervical cancer.

Conclusion

Plasticizers, which are well known EDCs, are being utilized for enhancing the flexibility of polymeric materials and their technical properties. Thus combination of additives to monomers ranging from stabilizers, colourants flame retardants, fillers are the important ingredients of the plastic industry to impart the desired characteristics and formulations. PAEs and Bisphenol A may leach, migrate, or off-gas from products over time and enter the human body through different routes of exposure as they are used in floorings, fragrances, pesticide carriers, repellents, cosmetics, paints, adhesives, upholstery etc. The natural chemistry or green chemical approaches are being taken for advanced and safe chemicals or intermediates in view of environmental sustainability and maintenance of ecological equilibrium.

PAEs and BPA are quickly metabolized and excreted in urine, with elimination half-lives less than 24 hours. They are established endocrine disruptors and are group of aromatic chemicals containing a phenyl ring with two attached and acetate groups. Globally, chemicals in environment or food are issues of health concern. In few cases they are cause of trade obstacles and thus potentially affecting the economy. We must consider the cumulative exposure to all PAEs investigated and possible dose-additive endocrine effects in the target organism. Efforts are also being made for Research & Development, risk assessments and updating of International standards by prominent regulatory agencies and academic institutions. We should strategically plan and regulate for their reduction and periodical monitoring in different parts of the world due to varied pattern of lifestyle and usage.

References

1. Agency for Toxic Substances and Disease Registry, [ATSDR] 2008.

2. Zota AR, Phillips CA, Mitro SD (2015) Recent Fast Food Consumption and Bisphenol A and Phthalates Exposures among the US Population in NHANES, 2003–2010, Environ Health Perspect 124(10):1521–1528.

3. Bang du Y, Lee IK, Lee BM (2011) Toxicological characterization of Phthalic Acid. Toxicol Res 27(4): 191-203.

4. Boisvert A, Jones S, Issop L, Erythropel HC, Papadopoulos V, et al. (2016) In vitro functional screening as a means to identify new plasticizers devoid of reproductive toxicity Environ Res 150: 496-512.

5. Cao XL, Zhao W, Churchill R, Hilts C (2014) Occurrence of Di-(2-ethylhexyl) adipate and phthalate plasticizers in samples of meat, fish, and cheese and their packaging films. J Food Prot 77(4): 610-620.

6. Doppalapudi S, Jain A, Domb AJ, Khan W (2016) Biodegradable polymers for targeted delivery of anti-cancer drugs. Expert Opin Drug Deliv 13(6): 891-909.

7. Hashizume K, Nanya J, Toda C, Yasui T, Nagano H, et al. (2002) Phthalate esters detected in various water samples and biodegradation of the phthalates by microbes isolated from river water. Biol Pharm Bull 25(2): 209-214.

8. International Programme on Chemical Safety (2014) Environmental Health Criteria 242 Dermal Exposure Inter-Organization Programme For The Sound Management Of Chemicals. A cooperative agreement among FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD.

9. Sheikh IA, Turki RF, Abuzenadah AM, Damanhouri GA, Beg MA (2016) Endocrine Disruption: Computational Perspectives on Human Sex Hormone-Binding Globulin and Phthalate Plasticizers. PLoS One 11(3): e 0151444.

10. Ito Y, Hasuda H, Morimatsu M, Takagi N, Hirai Y (2005) A microfabrication method of a biodegradable polymer chip for a controlled release system. J Biomater Sci Polym Ed 16(8): 949-955.

11. J Ortiz-Colón AI, Piñero-Santiago LE, Rivera NM, Sosa MA (2016) Assessment of Concentrations of Heavy Metals and Phthalates in Two Urban Rivers of the Northeast of Puerto Rico. Environ Anal Toxicol 6(2).

12. Kappenstein O, Vieth B, Luch A, Pfaff K (2012) Toxicologically relevant phthalates in Food. EXS 101: 87-106.

13. Sundar DS, Antoniraj MG, Kumar CS, Mohapatra SS, Houreld NN, et al. (2016) Recent Trends of Biocompatible and Biodegradable, Nanoparticles in Drug Delivery: A Review. Curr Med Chem.

14. Tarapore P, Hennessy M, Song D, Ying J, Ouyang B, et al. (2016) spermatogenesis. Reprod Toxicol pii: S0890-6238(16)30339-2.

15. Velusamy P, Kumar GV, Jeyanthi V, Das J, Pachaiappan R (2016) Bio-Inspired Green Nanoparticles: Synthesis, Mechanism, and Antibacterial Application. Toxicol Res 32(2): 95-102.

16. Verstraete S, Vanhorebeek I, Covaci A, Güiza F, Malarvannan G, et al. (2016) Circulating phthalates during critical illness in children are associated with long-term attention deficit: a study of a development and a validation cohort. Intensive Care Med 42(3): 379-92.

17. World Health Organization (2013) State of the Science of Endocrine Disrupting Chemicals. WHO and UNEP Report.

18. Centers for Disease Control and Prevention (1998) Community exposure to toluene diisocyanate from a polyurethane foam manufacturing plant--North Carolina, 1997. MMWR Morb Mortal Wkly Rep 47(22): 455-457.

19. Domínguez-Morueco N, González-Alonso S, Valcárcel Y (2014) Phthalate occurrence in rivers and tap water from central Spain. Sci Total Environ 500-501: 139-146.

20. Li HL, Song WW, Zhang ZF, Ma WL, Gao CJ, et al. (2016) Phthalates in dormitory and house dust of northern Chinese cities: Occurrence, human exposure, and risk assessment. Sci Total Environ 565: 496-502.

21. Seth PK (1982) Hepatic effects of phthalate esters. Environ Health Perspect 1982 45: 27-34.

22. Shen HY (2005) Simultaneous screening and determination eight phthalates in plastic products for food use by sonication-assisted extraction/GC-MS methods. Talanta 66(3): 734-739.

23. Lo Turco V, Di Bella G, Potortì AG, Tropea A, Casale EK, et al. (2016) Determination of plasticizers and BPA in Sicilian and Calabrian nectar honeys by

selected ion monitoring GC/MS. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 11: 1-7.

24. Mathieu-Denoncourt J, Wallace SJ, de Solla SR, Langlois VS (2015) Plasticizer endocrine disruption: Highlighting developmental and reproductive effects in mammals and non-mammalian aquatic species. Gen Comp Endocrinol 219: 74-88.

25. Mokhtarzadeh A, Alibakhshi A, Yaghoobi H, Hashemi M, Hejazi M, et al. (2016) Recent advances on biocompatible and biodegradable nanoparticles as gene carriers. Expert Opin Biol Ther 16(6): 771-785.

26. National Institute of Environmental Health Sciences [NIEHS].

27. Park JH, Ye M, Park K (2005) Biodegradable polymers for microencapsulation of drugs. Molecules 10(1): 146-161.

28. Qureshi MS, Yusoff AR, Wirzal MD, Sirajuddin, Barek J, et al. (2016) Methods for the Determination of Endocrine-Disrupting Phthalate Esters. Crit Rev Anal Chem 46(2): 146-159.

29. Sarah Lott (2014) Phthalate-free Plasticizers in PVC By Sarah Lott Phthalate-free Plasticizers in PVC.