Unpacking Phthalates from Obscurity in the Environment

Subjects: Chemistry, Analytical

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Phthalates (PAEs) are a group of synthetic esters of phthalic acid compounds mostly used as plasticizers in plastic materials but are widely applied in most industries and products. As plasticizers in plastic materials, they are not chemically bound to the polymeric matrix and easily leach out. Logically, PAEs should be prevalent in the environment, but their prevalence, transport, fate, and effects have been largely unknown until recently. This has been attributed, inter alia, to a lack of standardized analytical procedures for identifying them in complex matrices.

Keywords: phthalates ; environmental contamination ; extraction ; detection

1. Introduction

Phthalic acid esters (PAEs), popularly known as phthalates, are a class of lipophilic chemicals widely used as plasticizers and additives in plastics to improve plasticity, flexibility, durability, and resistance to UV degradation and combustion [1][2]. PAEs are used in nearly every industry and are broadly found in construction materials, printing inks, varnish, latex paint, cosmetics and personal care products, clothing, food packaging, pharmaceutics, medical products, intravenous cannulas, and insecticides. Some of the most widely used PAEs include butyl benzyl phthalate (BBP), dibutyl phthalate (DBP), di(2-ethylhexyl) phthalate (DEHP), di-isononyl phthalate (DINP), and di-isodecyl phthalate (DIDP).

Until recently, despite being widely utilized and present in the environment, the prevalence, transport, and destiny of numerous PAEs were largely undiscovered, making them less noticeable on the radar of awareness regarding chemical pollution [3]. They have not gained as much prominence as microplastics despite having a higher potential for environmental hazards. Partially, this can be attributed to the challenges in determining PAEs in different environmental matrices that have mostly led PAEs to remain below the pollution radar. In addition, direct analysis of PAEs is complicated due to their low concentrations in complex matrices (**Figure 1**).

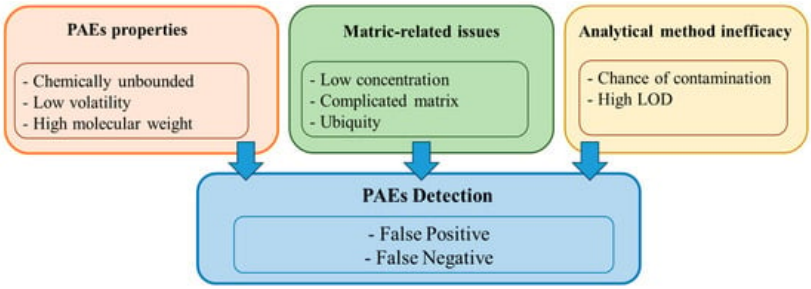

Figure 1. Factors contributing to PAEs' detection uncertainty.

2. Phthalates

2.1. Physicochemical Properties

PAEs are esters of phthalic acids. They are also known as esters of benzene-1,2-dicarboxylic acid. A benzene ring with an ester functional group is their structure character. They are commonly produced by a reaction of phthalic anhydride with alcohol. Their properties can be tuned by changing the alcohol type, allowing for an almost limitless range of products, although only around 30 are, or have been, commercially important. This reaction can be catalyzed via base catalysis or may happen at a reflux in hexane. Either of them concludes with the production of monoester PAEs. By having a high

temperature or being catalyzed by metal complexes, heteropolyacids, or p-toluenesulfonic acid, this reaction produces diester phthalates (reactions are described in **Figure 2**).

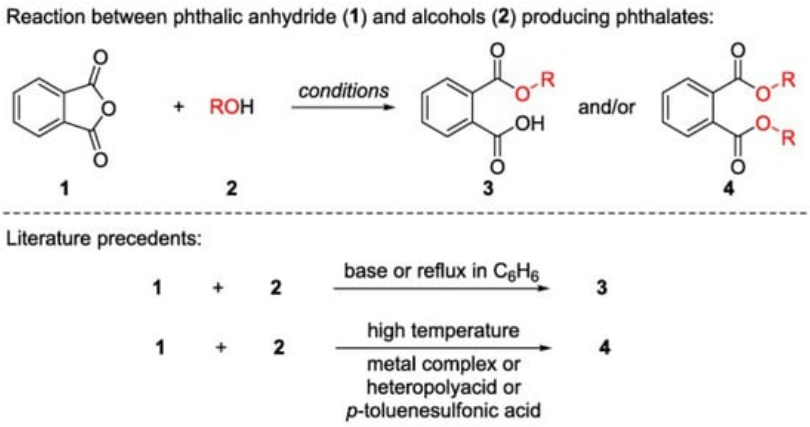

Figure 2. Synthesis of PAEs using base- or metal compound-based catalysis [4].

PAEs, as oily liquids, have high boiling temperatures, good solubility in most organic solvents, and weak solubility in water. Their solubility in water decreases by extending their carbon chain or increasing their molecular weight. Due to their structure and physiochemical properties, PAEs have been good candidates for being plasticizers since 1921. Their high compatibility with various polymers enables them to disperse uniformly within polymer matrices, resulting in a homogenous, durable product.

2.2. Environmental Sources and Fates

PAEs are becoming ubiquitous environmental contaminants because of their widespread use, allied in almost all industries. They can enter the environment not only during the manufacturing process but also through the daily use of various produced items, such as food packaging, toys, paints, construction materials, personal care items, cosmetics (e.g., nail varnish), and electronic and medical devices (e.g., bags for intravenous fluids, breathing masks or umbilical catheters). Within any material, PAEs are not chemically bound to the matrices, allowing them to migrate to the surface of the products and accumulate in the environment by leaching, migration, and oxidation during manufacture, storage, usage, or disposal.

PAEs can enter wastewater streams through domestic or industrial discharge. During the wastewater treatment process, they can accumulate in sewage sludge, which is commonly used as agricultural fertilizer. In addition to this pathway, soil can become contaminated with PAEs through leaks from agriculture machinery and the deposition of air or organic fertilizers.

Due to their high molecular weight, PAEs have low vapour pressure and do not tend to evaporate into the air. Furthermore, they resist degradation and do not easily break down via natural processes, such as sunlight or microbial activities. Their hydrophobic nature causes them to bind to the organic compounds in the environment. These properties lead to their accumulation in the soil, water, and sediment for extended periods. Their resistant nature allows them to undergo long-range transport by wind, water currents, or other driving forces. This ability allows PAEs to spread beyond their original release point and impact remote areas. The combination of their high environmental resistance and ability to migrate over long distances results in a widespread distribution of PAEs in the environment. Once released, they can contaminate the air, soil, and water, entering the food chain through bioaccumulation (**Figure 3**).

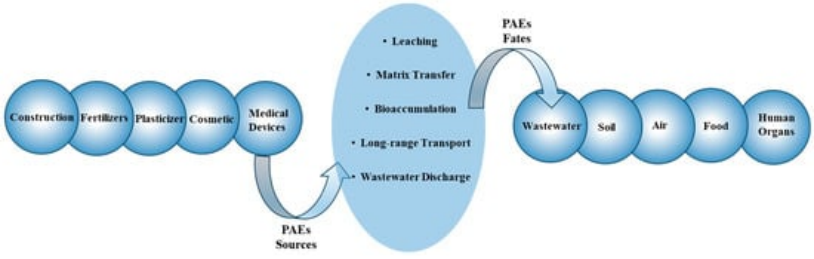

Figure 3. Sources and fates of PAEs in the environment.

2.3. Phthalates Effect

2.3.1. Environmental Toxicity

Once PAEs reach water sources, they can affect aquatic organisms, ranging from fish to algae. The primary effect that has been extensively studied is their impact on reproductive systems. Certain PAEs can disrupt the endocrine system of aquatic organisms, especially fish, leading to impaired fertility and reduced successful hatching. They can also cause the feminization of male fish, alter the sex ratios of the fish population, and result in reduced fertility.

PAEs can reach plants through contaminated soil, fertilizers, water, or air. Plants cannot degrade or metabolize PAEs, so they translocate and accumulate in different parts of the plants. This accumulation can harm the plant and any organisms that consume it, leading to a broader distribution. Exposure to PAEs can reduce the germination rate of plants, resulting in alterations to the plant species's population. They can also affect root elongation and branching, leading to stunted rooting. Since the roots are crucial for nutrient and water uptake, defective roots impact the overall health and productivity of the plants. PAEs in plant components can decrease chlorophyll content, reduce photosynthetic efficiency, and compromise plant growth and productivity.

2.3.2. Human Toxicity

The primary source of human exposure in the general population is ingesting food contaminated during production, processing, and packaging. However, indoor air exposure, cosmetic products, and contact with medical devices should be considered as the other possible sources of PAEs. PAEs have not only been detected in human urine, breast milk, and amniotic fluid but can also cross the placenta, leading to fetal exposure closely linked to maternal exposure [5].

Upon human exposure, PAEs undergo a metabolic pathway consisting of at least two steps. The first step is hydrolysis, followed by a conjugation process. In the hydrolysis step, which takes place in the intestine and parenchyma, diester phthalates are hydrolyzed by the catalytic activity of lipase and the catalytic activity of esterases, resulting in the formation of primary monoester phthalates. Although the first step in typical metabolism is often detoxification, the hydrolyzed structure regarding diester phthalates is more bioactive. Short-branched PAEs are primarily excreted in urine after the initial metabolic step as monoester phthalates. Long-branched PAEs undergo several biotransformations, such as hydroxylation and oxidation, before they can enter the second phase of metabolism and be excreted in the conjugated form in urine and feces. This conjugation process is usually catalyzed by the enzyme uridine 59-diphosphoglucuronyl transferase, forming a hydrophilic glucuronide conjugate that can be excreted in urine [6].

Since PAE possesses endocrine-disrupting properties, high exposure concentrations can lead to a range of adverse effects, such as fetal death, cancer, malformations, liver and kidney injuries, and reproductive toxicity. Additionally, since PAEs can transfer from the mother to the fetus via the placenta and to neonates through breast milk, the potentially harmful effects during development are concerning. Neonates have lower levels of pancreatic lipase, which results in considerably reduced metabolic capacity compared to adults.

3. Regulatory Framework

The toxicity of PAEs and their potential health effects have raised significant concerns, prompting both researchers and regulatory bodies to monitor the presence of different PAEs in various consumer products, such as food or cosmetic items, as well as the environment. By determining the level of PAEs in any sample, the assessment of their potential health risk, the identification of their source, and the pathway of their exposure can be studied.

Regulatory agencies, such as the Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA), have established limits and guidelines for the permissible levels of PAEs in different matrices. These regulatory standards are vital to ensure consumers' safety and protect human health. To meet these stringent requirements, developing accurate and precise analytical methods capable of detecting PAEs qualitatively and quantitatively has become a significant research focus in recent years.

Sensitive and reliable analytical methods are essential for accurately detecting even trace amounts of PAEs, as even low levels of PAE exposure can lead to adverse health effects. Achieving regulatory compliance requires advancing analytical techniques, including sample preparation and detection methods, which will be discussed in detail in the following sections.

4. Contemporary Analytical Procedure

4.1. Extraction or Pre-Treatment Methods: Potential and Challenges

In addition to sampling and homogenization, efficient preconcentration and cleanup steps are necessary for assessing PAEs due to the complexity of the matrices and their low concentration levels [7]. However, it is important to know that samples can easily become contaminated during laboratory activities by glassware, solvents, and reagents; analyzing PAEs in various matrices is a challenging task that requires precautions to avoid contamination.

A significant challenge in the analysis of PAEs is the proper preparation of blank samples for analytical measurements since they are widespread compounds present in the laboratory's environment air [8], organic solvent, chemicals [9], as well as laboratory materials such as tubing, caps, and filter papers [8].

Depending on the sample matrices, which may contain lipids, various extraction methods are available. These include liquid–liquid (L–L) extractions or micro extractions with organic solvents, solid-phase extractions (SPE) using cartridges, and solid-phase micro-extraction (SPME). It is worth noting that when the matrix, such as milk or oil, contains lipids, phthalate analysis requires additional steps such as headspace SPME and gel-permeation chromatography (GPC). This is necessary because the aforementioned methods may co-extract lipids and organic compounds along with the PAEs.

4.1.1. Solid-Phase Extraction (SPE)

The brilliant properties of solid-phase extraction (SPE), such as ease of operation, semi-automation capabilities, low solvent consumption, high enrichment factor, and speed, have kept it in the spotlight as the dominant method for treating water samples for years [10]. Additionally, SPE can be fully automated via a direct connection to a chromatograph.

Various activated solid phases, shaped as discs or cartridges, have been employed to extract PAEs from water samples and were subsequently eluted with organic solvents. The efficiency of SPE relies on the selectivity and development of the sorbent. A wide range of polymeric sorbents with a hydrophilic–lipophilic balance, such as Oasis HLB and Strata X, have demonstrated their effectiveness in extracting different PAEs from aqueous samples using different organic solvents as eluents, including acetone, dichloromethane (DCM), ethyl acetate (EtOAc), methanol, and n-hexane. The choice of the sorbent-eluant influences the recovery rate of PAEs. In the case of water samples with low-suspended solid materials (SSM) (≤1 g/L), PAEs can be extracted through SPE without any prior filtration [11]. However, when dealing with higher levels of SSM, pre-filtration becomes essential, which may result in potential errors up to a 20% inclination of the total PAE concentration due to the contamination risks [12]. Commercial SPE cartridges are not the only option for use as the extractant in SPE.

Dispersive solid-phase extraction (DSPE), in which the adsorbents are dispersed in the sample, offers different advantages. This includes applicability to a wide variety of PAEs, high cost-effectiveness, minimal use of glassware/plasticware, and easy automation, all of which help minimize potential PAEs contamination. Additionally, this procedure achieves a higher recovery rate than the traditional SPE without the concerns of cartridge or disk blockage or the need to control the sample flow rate [13].

4.1.2. Solid-Phase Microextraction (SPME)

SPME is another method based on sportive extraction, where the analyte is extracted from the sample using a liquid polymer or a solid phase coated on a fiber. This method is considered environmentally friendly due to its nearly solvent-free approach and has gained popularity for PAE analysis. It has the potential to combine sampling, extraction, enrichment, and analysis into one single step, minimizing the risk of contamination for analyzing PAEs. After extraction, the SPME fiber can be transferred to the GC injection port for thermal desorption of PAEs, followed by analysis. A variety of polymers, including polydimethylsiloxane and divinylbenzene (PDMS-DVB), handmade polyaniline, and polyacrylate fibers, have been successfully used as solid coatings for SPME fibers for the analysis of the six main PAEs listed by the US-EPA [14].

Stir-bar sorptive extraction (SBSE) is a sub-category of SPME in which the sorbent is coated on a stir bar and can be followed by thermal desorption. In SBSE, the sorbent amount is considerably larger, resulting in a higher sample capacity and lower LODs. Moreover, in the case of liquid samples, SBSE can eliminate the need for a cleanup step, potentially reducing the chance of PAE contamination. Despite these advantages, it is worth noting that SBSE requires a longer extraction time compared to SPME, limiting its suitability for daily use.

4.1.3. Liquid–Liquid Extraction (LLE)

LLE has been widely utilized for extracting PAEs from various samples due to its simplicity and convenience [15]. Since the transfer of the analytes between two liquid phases depends on their solubility in each phase, PAEs can be extracted from aqueous samples using suitable organic solvents. Common solvents for extracting PAEs include propanol and hexane, while adding an organic modifier like methanol can enhance the extraction of nonpolar PAEs such as DEHP and DNOP [16]. The efficiency of the extraction process can also be improved by adding inorganic salts and controlling pH.

To address the limitations mentioned above, various modifications have been made to LLE methods for the PAE extractions. One such modification is solid-supported LLE (SLE), in which the extractant phase is supported on an inert solid phase and packed into a disk or cartridge. After introducing the sample, the analytes were selectively eluted with a suitable organic solvent, minimizing interferences of the matrices [17].

4.1.4. Liquid-Phase Microextraction (LPME)

The miniaturized form of LLE, which limits the considerable volumes of organic solvent to a few microliters, is known as LPME. LPME offers several advantages, including simplicity, rapidity, low sample volume, low cost, and high enrichment factors. It can be categorized into three main types, each with potential sub-groups: (a) single-drop microextraction (SDME); (b) hollow-fiber liquid-phase microextraction (HF-LPME); and (c) dispersive liquid–liquid microextraction (DLLME) [18][19].

SDME, first reported in the 1990s, overcame many limitations of SPME and limited organic solvent consumption to a few microliters. It involves a micro syringe needle immersed directly into the aqueous sample (known as direct immersion or DI-SDME) or fixed above the sample (known as headspace SDME or HS-SDME). This method requires inexpensive equipment and combines extraction, preconcentration, and sample introduction into a single step, minimizing potential contamination. Although their method significantly reduced the amount of organic solvent used, using multiple solvents remained a drawback. Subsequent modification simplified these methods using single solvents like toluene or introducing innovations like the bubble-in-drop (BID-)HS-SDME method. With these improvements, the LOD of these methods reached an ng mL^{-1} level for up to 17 PAEs in aqueous samples [20][21].

To address the drop instability issue, HF-LPME was introduced as a revolution in comparison to SDME. It uses a hydrophobic porous hollow fiber, such as polypropylene, connected on one side to the needle tip of a micro syringe while leaving the other end suspended in the sample solution to protect the single drop [22]. This method achieved LODs in the range of 0.23–0.69 µg L^{-1} for PAEs and offered advantages such as low cost, full automation capability, and the disposability of the used fiber, minimizing cross-contamination risks [20][21].

4.1.5. Other Methods of Extraction

In addition to the previously mentioned methods, which have been the primary procedures for PAE extraction from various samples, other reported methods include the following:

Cloud-point extraction (CPE)—This procedure involves extracting PAEs into a very small volume of a non-volatile surfactant-rich phase. In the research by Ling et al., this method was coupled with UPLC, and the obtained hydrophobic analytes extract was analyzed to achieve LOD levels in the ng mL^{-1} range for PAEs [23].

Accelerated solvent extraction (ASE)—This extraction method involves using an organic solvent at high temperature and pressure to extract analytes quickly and efficiently. ASE, when coupled with GC-MS, can be used for PAE extraction from various matrices, including food, soil, and plastics [24][25][26][27]. This method can be automated, offering benefits such as low solvent consumption, short extraction time, and high recovery. However, the high temperature and pressure during this process have the potential to hydrolyze PAEs, leading to the cleavage of carbon–oxygen bonds and isotopic enrichment of carbon and hydrogen, which can pose challenges for detection [28].

Continuous-flow microextraction (CFM)—In this method, the extraction solvent drop is injected into a glass chamber using a micro syringe and held at a tubing outlet where the samples flow through it and into the waste [29]. Continuous extraction occurs, resulting in a rapid process. The extraction solvent can then be transferred to GC-MS for analysis.

4.2. Comparison between Different Methods of Extraction

The selection of an extraction method not only depends on the sample type and its physiochemical characteristics but can also be determined by the priorities and concerns of the analysis. **Table 1** summarizes the advantages and disadvantages of the above-discussed methods from the perspective of PAE extraction.

Table 1. Comparison of different extraction methods.

Method	Advantages	Disadvantages
SPE	Simplicity, accuracy, high throughput and high recovery, low solvent consumption, ease of automation	Inability to extract from large sample volumes, susceptibility to sorbent vulnerability, high probability of column blockage [30]
SPME	Simplicity, rapidity, minimal solvent usage, ease of automation	The short lifespan of the fiber, high cost, potential for cross-contamination [31]
SBSE	High sample capacity, high recovery and sensitivity, and low detection limits eliminate the need for a cleanup step in liquid samples.	Limited repeatability [32]
LLE	Simplicity, convenience, popularity	Time consuming, labor intensive, requires large sample volumes, involves toxic organic solvents, and is inapplicable for trace analytes [33]
LPME	Low cost, limited organic solvent consumption, simplicity and possibility of full automation, low chance of cross-contamination	Time consuming, limited sample volume [34]
SLE	Limited organic solvent consumption, higher selectivity compared to LLE extraction	Potential of cross-contamination, low stability of the extractant [35]
MMLLE	Capability to operate online with GC and HPLC	Limited selection of organic solvents suitable for all PAEs [16]
SDME	Limited organic solvent consumption, fast merging sample preparation, preconcentration, and introduction step minimized the risk of cross-contamination.	Requires multiple solvents [20]
HF-LPME	Capability for full automation, minimization of cross-contamination	There is a high risk of contamination during the fiber placement process [36]
DLLME	Simplicity, high efficiency, rapidity, low sample volume requirement, cost-effectiveness, high enrichment factor	Use of toxic organic solvents, difficulty of automation, high-cost preparation process, low stability of the extractant drop [37]
CPE	Environmentally friendly	Incompatibility with GC [38]
ASE	Compatibility with different matrices, fast and low-solvent consumption	Utilizes harsh physical conditions and has a high risk of detection errors [24][39]
CFM	Rapid and online extraction	Limited reproducibility [40]

4.3. Potential and Challenges of Contemporary Analytical Procedures

4.3.1. Gas Chromatography (GC) Analysis

Due to the thermal stability and volatility of PAEs, GC coupled with a mass spectrometer is the most common detection method. This is generally conducted using a nonpolar column and Helium as the mobile phase [41]. PAEs can be analyzed in split or spitless mode, with or without pulsed mode.

4.3.2. Liquid Chromatography (LC) Analysis

LC can be a reliable method for analyzing PAEs due to its excellent selectivity. C18 is the commonly used column for PAE analysis because of the nonpolar nature of these compounds. Typically, a mixture of ACN/water and MeOH/water is the suitable mobile phase, often buffered or acidified by an isocratic or gradient elution to enhance the ionization efficiency [42][43][44][45]. Heating the column to temperatures between 25 and 80 °C can also improve separation.

4.3.3. Micellar Electrokinetic Capillary Chromatography (MEKC)

MEKC is a capillary electrophoresis method that combines electrokinetic chromatography and micellar chromatography, allowing the separation of PAEs with several advantages, including high efficiency, high output, and less consumption of reagents. In this method, analytes are separated by different partitioning between micelles and the surrounding aqueous buffer solution. MEKC has been employed to analyze PAEs in various sample matrices such as water and soil. It has been coupled with DLLME and diode-array detection to achieve a limit of quantification (LOQ) of 2.7 µg/L for PAEs [46].

4.3.4. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR, which provides a fingerprint signal for any analyte and offers high output, speed, simplicity, high sensitivity, and internal calibration, can be employed to detect PAEs in various physical states of samples. Although FTIR is more cost-

effective, rapid, and involves fewer essential sample preparation steps than GC-MS, it is less sensitive and can detect the total amount of PAEs rather than specific phthalate compounds.

4.3.5. Colorimetric Analysis

Colorimetric methods, which involve measuring an analyte with the aid of a color agent, using organic or inorganic compounds, and with or without an enzymatic step, have been widely utilized to determine PAEs. For instance, anhydrous phthalate can be hydrolyzed with sodium hydroxide and then dehydrated to form phthalate anhydride. Subsequent reaction with resorcinol in concentrated sulfuric acid results in the conversion to fluorescein, forming a color. This color change can be detected using absorbance spectroscopy with LODs of less than a µmol, depending on the phthalate type [47].

4.3.6. Immunoassay-Based Techniques

Immunoassay sensors that utilize immunochemical reactions coupled with a transducer provide specific recognition for detecting PAEs, particularly from plastic matrices. Several reported methods for quantifying PAEs in water samples are fluorescence-based, offering LODs in ng L^{-1} ranges and high recoveries [48][49]. Besides the limited required sample preparation, the main advantages of this method include its reliability and selectivity, which allows the analysis of the samples without any specific manipulation.

5. Emerging Trends and New Perspectives

In the recent decade, considerable advancements have been made in phthalate extraction and analysis techniques. Numerous pre-treatment techniques and detection methods can now be applied to identify and quantify these compounds in various environmental matrices, including atmospheric aerosols, indoor and outdoor air, municipal solid waste compost, sludge, fresh water and marine waters, soil, and sediments. Consequently, our understanding of the fate and effects of PAEs is improving daily.

The primary separation and detection methods are GC with flame ionization or mass spectrometry and HPLC with ultraviolet or mass spectrometric detection. These analytical techniques have witnessed a significant shift towards high-throughput screening methods, aiming for rapid and comprehensive assessments of PAEs. Liquid chromatography–mass spectrometry (LC-MS) and gas chromatography–mass spectrometry (GC-MS) techniques have been refined and optimized for improved sensitivity and specificity.

Machine learning algorithms and data-driven approaches have become integral in handling the complexity of phthalate datasets [50][51]. These computational methods allow for the extraction of meaningful patterns, aiding in the interpretation of intricate relationships within large datasets.

Despite these advancements in the PAE detection pathway, the challenges in analyzing phthalate in environmental samples still exists, making a call for further enhancements. These challenges originate from two perspectives. First, the real concentrations of phthalate contaminants are often underestimated in environmental samples because they exist in complex matrices where contaminants are typically present in trace levels. These trace concentrations of PAEs in environmental samples make the development of efficient pre-treatment methods for extracting the target contaminants extremely challenging.

References

1. Kumar, R.; Verma, A.; Shome, A.; Sinha, R.; Sinha, S.; Jha, P.K.; Kumar, R.; Kumar, P.; Das, S.; Sharma, P. Impacts of plastic pollution on ecosystem services, sustainable development goals, and need to focus on circular economy and policy interventions. Sustainability 2021, 13, 9963.
2. Huang, L.; Zhu, X.; Zhou, S.; Cheng, Z.; Shi, K.; Zhang, C.; Shao, H. Phthalic acid esters: Natural sources and biological activities. Toxins 2021, 13, 495.
3. Tran, H.T.; Lin, C.; Bui, X.-T.; Nguyen, M.K.; Cao, N.D.T.; Mukhtar, H.; Hoang, H.G.; Varjani, S.; Ngo, H.H.; Nghiem, L.D. Phthalates in the environment: Characteristics, fate and transport, and advanced wastewater treatment technologies. Bioresour. Technol. 2022, 344, 126249.
4. Bajracharya, G.B.; Koju, R.; Ojha, S.; Nayak, S.; Subedi, S.; Sasai, H. Plasticizers: Synthesis of phthalate esters via FeCl3-catalyzed nucleophilic addition of alcohols to phthalic anhydride. Results Chem. 2021, 3, 100190.

5. Latini, G.; De Felice, C.; Presta, G.; Del Vecchio, A.; Paris, I.; Ruggieri, F.; Mazzeo, P. In utero exposure to di-(2-ethylhexyl) phthalate and duration of human pregnancy. Environ. Health Perspect. 2003, 111, 1783–1785.
6. Dutta, S.; Haggerty, D.K.; Rappolee, D.A.; Ruden, D.M. Phthalate Exposure and Long-Term Epigenomic Consequences: A Review. Front. Genet. 2020, 11, 405.
7. Haji Harunarashid, N.Z.I.; Lim, L.H.; Harunsani, M.H. Phthalate sample preparation methods and analysis in food and food packaging: A review. Food Anal. Methods 2017, 10, 3790–3814.
8. Fankhauser-Noti, A.; Grob, K. Blank problems in trace analysis of diethylhexyl and dibutyl phthalate: Investigation of the sources, tips and tricks. Anal. Chim. Acta 2007, 582, 353–360.
9. Grob, K.; Biedermann, M.; Scherbaum, E.; Roth, M.; Rieger, K. Food contamination with organic materials in perspective: Packaging materials as the largest and least controlled source? A view focusing on the European situation. Crit. Rev. Food Sci. Nutr. 2006, 46, 529–535.
10. Zhang, Z.; Luo, L.; Cai, R.; Chen, H. A sensitive and selective molecularly imprinted sensor combined with magnetic molecularly imprinted solid phase extraction for determination of dibutyl phthalate. Biosens. Bioelectron. 2013, 49, 367–373.
11. Du, X.; Li, X.; Luo, T.; Matsuur, N.; Kadokami, K.; Chen, J. Occurrence and aquatic ecological risk assessment of typical organic pollutants in water of Yangtze River estuary. Procedia Environ. Sci. 2013, 18, 882–889.
12. Isobe, T.; Nishiyama, H.; Nakashima, A.; Takada, H. Distribution and behavior of nonylphenol, octylphenol, and nonylphenol monoethoxylate in Tokyo metropolitan area: Their association with aquatic particles and sedimentary distributions. Environ. Sci. Technol. 2001, 35, 1041–1049.
13. Socas-Rodríguez, B.; Herrera-Herrera, A.V.; Asensio-Ramos, M.; Hernández-Borges, J. Dispersive solid-phase extraction. Anal. Sep. Sci. 2015, 1525–1570.
14. Li, H.-y.; Qu, J.-h.; Liu, H.-j. Removal of a type of endocrine disruptors—Di-n-butyl phthalate from water by ozonation. J. Environ. Sci. 2006, 18, 845–851.
15. Lv, X.; Hao, Y.; Jia, Q. Preconcentration procedures for phthalate esters combined with chromatographic analysis. J. Chromatogr. Sci. 2013, 51, 632–644.
16. Bergström, S.; Barri, T.; Norberg, J.; Jönsson, J.Å.; Mathiasson, L. Extracting syringe for extraction of phthalate esters in aqueous environmental samples. Anal. Chim. Acta 2007, 594, 240–247.
17. Dévier, M.-H.; Le Menach, K.; Viglino, L.; Di Gioia, L.; Lachassagne, P.; Budzinski, H. Ultra-trace analysis of hormones, pharmaceutical substances, alkylphenols and phthalates in two French natural mineral waters. Sci. Total Environ. 2013, 443, 621–632.
18. Rezaee, M.; Assadi, Y.; Hosseini, M.-R.M.; Aghaee, E.; Ahmadi, F.; Berijani, S. Determination of organic compounds in water using dispersive liquid–liquid microextraction. J. Chromatogr. A 2006, 1116, 1–9.
19. Prosen, H. Applications of liquid-phase microextraction in the sample preparation of environmental solid samples. Molecules 2014, 19, 6776–6808.
20. George, M.J.; Madala, N.E.; Dubery, I.A. Extraction of phthalic acid esters from soil samples using aqueous room temperature sonication coupled to bubble-in-drop single-drop microextraction. Int. J. Environ. Anal. Chem. 2019, 99, 1198–1210.
21. Tegladza, I.D.; Qi, T.; Chen, T.; Alorku, K.; Tang, S.; Shen, W.; Kong, D.; Yuan, A.; Liu, J.; Lee, H.K. Direct immersion single-drop microextraction of semi-volatile organic compounds in environmental samples: A review. J. Hazard. Mater. 2020, 393, 122403.
22. Shen, G.; Lee, H.K. Hollow fiber-protected liquid-phase microextraction of triazine herbicides. Anal. Chem. 2002, 74, 648–654.
23. Ling, W.; Jiang, G.-B.; Cai, Y.-Q.; Bin, H.; Wang, Y.-W.; Shen, D.-Z. Cloud point extraction coupled with HPLC-UV for the determination of phthalate esters in environmental water samples. J. Environ. Sci. 2007, 19, 874–878.
24. Khosravi, K.; Price, G.W. Determination of phthalates in soils and biosolids using accelerated solvent extraction coupled with SPE cleanup and GC–MS quantification. Microchem. J. 2015, 121, 205–212.
25. Yan, R.; Shao, M.; Sun, C.; Liu, X.; Song, D.; Zhang, H.; YU, A. Determination of 11 phthalic acid esters in soil by accelerated solvent extraction-liquid chromatography tandem mass spectrometry. Chin. J. Anal. Chem. 2014, 897–903.
26. Hai-Yang, S.; Gang, X.; Ming-Hong, W.; Liang, T.; Ning, L.; Wen-Hui, Q. Determination of phthalate esters in sediment using accelerated solvent extraction and gas chromatography-mass spectrometry. Chin. J. Anal. Chem. 2013, 41, 1315–1321.

27. Aipeng, H.; Yulan, L.; Mingming, Z. Directly determination of phthalate acid esters in oil feedstock by gas chromatography-mass spectrometry. Food Sci. 2016, 37, 146–151.

28. Min, N.; Yao, J.; Amde, M.; Wu, L.; Sunahara, G.; Li, H.; Chen, Y.; Liu, J.; Mihucz, V.G. Accelerated solvent extraction combined with GC–MS: A convenient technique for the determination and compound-specific stable isotope analysis of phthalates in mine tailings. Microchem. J. 2020, 153, 104366.

29. Liu, W.; Lee, H.K. Continuous-flow microextraction exceeding1000-fold concentration of dilute analytes. Anal. Chem. 2000, 72, 4462–4467.

30. Ferrone, V.; Bruni, P.; Catalano, T.; Selvaggi, F.; Cotellese, R.; Carlucci, G.; Aceto, G.M. Development of a SPE-HPLC-PDA Method for the Quantification of Phthalates in Bottled Water and Their Gene Expression Modulation in a Human Intestinal Cell Model. Processes 2022, 11, 45.

31. Alshehri, M.M.; Ouladsmane, M.A.; Aouak, T.A.; ALOthman, Z.A.; Ahmed, A.Y.B.H. Determination of phthalates in bottled waters using solid-phase microextraction and gas chromatography tandem mass spectrometry. Chemosphere 2022, 304, 135214.

32. Gebrehiwot, D.G.; Castro, R.; Hidalgo-Gárate, J.C.; Robles, A.D.; Durán-Guerrero, E. Method development of stir bar sportive extraction coupled with thermal desorption-gas chromatography-mass spectrometry for the analysis of phthalates in Peruvian pisco. J. Chromatogr. A 2023, 1711, 464470.

33. Wang, W.; Kannan, K. Leaching of Phthalates from Medical Supplies and Their Implications for Exposure. Environ. Sci. Technol. 2023, 57, 7675–7683.

34. Merlo, F.; Profumo, A.; Fontas, C.; Anticó, E. Preparation of new polymeric phases for thin-film liquid phase microextraction (TF-LPME) of selected organic pollutants. Microchem. J. 2022, 175, 107120.

35. Grau, J.; Chabowska, A.; Werner, J.; Zgoła-Grześkowiak, A.; Fabjanowicz, M.; Jatkowska, N.; Chisvert, A.; Płotka-Wasylka, J. Deep eutectic solvents with solid supports used in microextraction processes applied for endocrine-disrupting chemicals. Talanta 2023, 368, 125338.

36. González-Sálamo, J.; González-Curbelo, M.Á.; Socas-Rodríguez, B.; Hernández-Borges, J.; Rodríguez-Delgado, M.Á. Determination of phthalic acid esters in water samples by hollow fiber liquid-phase microextraction prior to gas chromatography tandem mass spectrometry. Chemosphere 2018, 201, 254–261.

37. Notardonato, I.; Passarella, S.; Iannone, A.; Fiore, C.D.; Russo, M.V.; Protano, C.; Vitali, M.; Avino, P. Comparison of two extraction procedures, SPE and DLLME, for determining plasticizer residues in hot drinks at vending machines. Processes 2021, 9, 1588.

38. dengan Spektrofotometri, S.S.T.B. Removal of phthalates in aqueos samples using non-ionic silicone surfactant mediated cloud point extraction via spectrophotometry. Malays. J. Anal. Sci. 2019, 23, 839–848.

39. Hu, A.; Qiu, M.; Liu, H.; Xu, Y.; Tao, Y.; Yang, G.; He, Y.; Xu, J.; Lu, Z. Simultaneous determination of phthalate diesters and monoesters in soil using accelerated solvent extraction and ultra-performance liquid chromatography coupled with tandem mass spectrometry. J. Chromatogr. A 2020, 1626, 461347.

40. Liang, P.; Li, Q.; Xu, J.; Du, D. LC determination of phthalate esters in water samples using continuous-flow microextraction. Chromatographia 2008, 68, 393–397.

41. Sanchis, Y.; Yusà, V.; Coscollà, C. Analytical strategies for organic food packaging contaminants. J. Chromatogr. A 2017, 1490, 22–46.

42. Yadav, S.; Rai, S.; Srivastava, A.K.; Panchal, S.; Patel, D.; Sharma, V.; Jain, S.; Srivastava, L. Determination of pesticide and phthalate residues in tea by QuEChERS method and their fate in processing. Environ. Sci. Pollut. Res. 2017, 24, 3074–3083.

43. Rian, M.B.; Vike-Jonas, K.; Gonzalez, S.V.; Ciesielski, T.M.; Venkatraman, V.; Lindstrøm, U.; Jenssen, B.M.; Asimakopoulos, A.G. Phthalate metabolites in harbor porpoises (Phocoena phocoena) from Norwegian coastal waters. Environ. Int. 2020, 137, 105525.

44. Saliu, F.; Montano, S.; Lasagni, M.; Galli, P. Biocompatible solid-phase microextraction coupled to liquid chromatography triple quadrupole mass spectrometry analysis for the determination of phthalates in marine invertebrate. J. Chromatogr. A 2020, 1618, 460852.

45. Tsochatzis, E.; Karayannakidis, P.; Kalogiannis, S. Determination of selected dichloroanilines and phthalates in lyophilised mussels samples with ultra-high performance liquid chromatography-tandem mass spectrometry after QuEChERS clean-up. Food Addit. Contam. Part A 2019, 36, 1253–1260.

46. Sun, J.; He, H.; Liu, S. Determination of phthalic acid esters in Chinese white spirit using dispersive liquid–liquid microextraction coupled with sweeping β-cyclodextrin-modified micellar electrokinetic chromatography. J. Sep. Sci. 2014, 37, 1679–1686.

47. Yanagisawa, H.; Fujimaki, S. Simple colorimetric determination of phthalates in polymers by dye formation. Anal. Sci. 2019, 35, 1215–1219.
48. Zhang, M.-C.; Wang, Q.-E.; Zhuang, H.-S. A novel competitive fluorescence immunoassay for the determination of dibutyl phthalate. Anal. Bioanal. Chem. 2006, 386, 1401–1406.
49. Sun, R.; Zhuang, H. Biotin-streptavidin enzyme-linked immunosorbent assay for the determination of dibutyl phthalate in beverages and drinking water using a specific polyclonal antibody. Food Anal. Methods 2015, 8, 1990–1999.
50. Rijavec, T.; Ribar, D.; Markelj, J.; Strlič, M.; Kralj Cigić, I. Machine learning-assisted non-destructive plasticizer identification and quantification in historical PVC objects based on IR spectroscopy. Sci. Rep. 2022, 12, 5017.
51. Midya, V.; Alcala, C.S.; Rechtman, E.; Gregory, J.K.; Kannan, K.; Hertz-Picciotto, I.; Teitelbaum, S.L.; Gennings, C.; Rosa, M.J.; Valvi, D. Machine learning assisted discovery of interactions between pesticides, phthalates, phenols, and trace elements in child neurodevelopment. Environ. Sci. Technol. 2023, 57, 18139–18150.