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Review

Can Phthalates Be Considered as Microplastic Tracers in the Mediterranean Marine Environment?

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Abstract: Plastics are a major environmental concern, not only because of their uncontrolled dispersion in the environment, but also because of their release of chemical additives, such as phthalates (PAEs), particularly in water bodies. Key land–water interfaces, such as coastal zones, has always represented a complex and dynamic nexus for plastic pollution, as they are sites often densely populated, with major pollution sources. The Mediterranean basin, for example, is known to be a global hotspot of plastic waste, with a microplastic concentration approximately four times greater than the North Pacific Ocean. However, differently from the overviewed issue of plastic litter and microplastics, the occurrence, distribution, and impact of PAEs on the abiotic and biotic compartment of marine ecosystems of the Mediterranean area have still not been reviewed. Hence, this review provides an introductory section on the plastic pollution issue and its close relationship, not only with microplastics, but also with the leaching of toxic PAEs. To follow, the most relevant analytical approaches for reliably assessing PAEs in abiotic and biotic marine matrices are discussed. The analysis of the main anthropogenic sources of PAEs, their occurrence and spatiotemporal trends in the Mediterranean Sea is conducted. Finally, the potential correlation between PAE pollution and the abundance of microplastics are critically examined to evaluate their effectiveness as tracers of microplastic pollution.

Keywords: microplastics; phthalates; plasticizers; analytical methods; seawater; sediments; biota; marine environment

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1. Introduction

Plastic is a low cost and long-lasting material, can be made in almost any shape, is easy to transport due to its light weight, contributes to the reduction in food waste and deforestation, and has a lower carbon footprint than many other materials. These properties, together with a broad range of uses and applications, have inevitably led to an increase in its production over the last century. The global plastic annually produced has increased from 2 million tons in 1950 to over 400 million tons in 2022, and its production is expected to continue growing, because of its undeniable necessity in many everyday contexts. In this scenario, China has produced almost 1/3 of global plastic (~115 million tons), followed by North America (~68 million tons) and Europe (~56 million tons). More than 90% of such plastic still derives from fossil-based feedstock; nearly 10% is plastic from post-consumer (mechanical or chemical) recycling, and only 0.1% corresponds to bio-based-plastics. Packaging—often used once and then thrown away (44%)—and building and construction (18%) are the two markets where plastics found the greatest application [1]. The increase in production has predictably been accompanied by a more than two-fold increase in waste generation. Indeed, around 353 million tons of plastic waste have been produced in the last two decades and, as mentioned above, only 10% is properly recycled. A total of 10% of the remaining waste is incinerated, 50% is landfilled, and 22% is mismanaged,

since it is dumped in uncontrolled landfills, burned in open pits, or directly released into the surroundings [2].

Hence, it is fully understandable that the main problem with plastic is its consequent dispersion in the environment, particularly in water bodies. Although there is no general rule on the degradation process, which depends not only on the type of plastic polymer, but also on the presence of additives and coloring agents, and should be studied on a case-by-case basis, plastics generally degrade very slowly and remain in the environment up to hundreds of years. Plastics in the environment are subjected to different physical, chemical, and biological processes that are known to stimulate the leaching of additive chemicals along with the fragmentation, thus contributing to the progressive modification of the polymer. In the long and slow process of degradation, plastics are able to fragment into virtually ubiquitous nanoplastics (<100 nm), microplastics (<5 mm), mesoplastics (5–25 mm), and macroplastics (>25 mm). On this basis, plastics can enter the environment as primary microplastics (i.e., plastic debris already manufactured with a microscopic size range) or as secondary plastics (i.e., macroplastics or mesoplastics broken down into smaller microplastics or nanoplastics by biotic and abiotic factors), and the hazard is basically related to the physical damage induced by the plastic debris of various sizes to exposed organisms [3–11]. However, regardless of size, plastics also pose a risk through external chemical toxicity, which is related to a variety of contaminants vectored by the polymer itself into the surroundings [12], and internal chemical toxicity, which is linked to the plastic additives used during the manufacturing of polymers with high potential to leach out and enter the environment [13–15]. A recent report from the UN Environment Programme [16] has stated that more than 13,000 compounds are intrinsically associated with plastics and ten groups of chemicals (based on chemistry, uses, or sources) are of major concern due to their toxicity and potential to be released into the environment. They include specific flame retardants, UV stabilizers, perfluoroalkyl and polyfluoroalkyl substances (PFASs), phthalates (PAEs), bisphenols (BPs), alkylphenols and alkylphenol ethoxylates, biocides, certain metals and metalloids, and polycyclic aromatic hydrocarbons (PAHs).

Among the cited additives, PAEs are used in the manufacturing of thermoplastics (mainly polyvinyl chloride [PVC], but also polyethylene [PE], polyethylene terephthalate [PET], and polypropylene [PP]) for increasing the mobility of molecular chains, weakening their intermolecular forces, and making these materials more flexible and, thus, exploitable in a wide range of sectors and product value chains. Moreover, PAEs are exploited for the same softening properties in a variety of non-plastic products, such as cosmetics, textiles, paints and varnishes, emulsifiers, and lubricants. Just to obtain an idea of the massive use of these compounds, Net and colleagues reported that an estimated 6 to 8 million tons of PAEs are consumed every year [17]. PAEs are classified into low molecular weight substances, e.g., dimethyl phthalate (DMP), di-ethyl phthalate (DEP), di-butyl phthalate (DBP), benzyl butyl phthalate (BBP), and di-iso-butyl phthalate (DIBP), mainly used in childcare and body care products, printing inks, lacquers, sealants, paints, etc., and high molecular weight plasticizers, including bis (2-ethylhexyl) phthalate (DEHP), diisononyl phthalate (DINP), diisodecyl phthalate (DIDP), and di-n-octyl phthalate (DnOP), mainly employed in food packaging, toys, floorings, home furnishings and other building material, and medical devices [18]. While PAEs may enter the environment through abrasion or leaching from plastic products because there is no covalent bond between them and the polymer which they are mixed in, their release appears also to be accelerated as plastics age and break down into microplastics [19]. As a result, PAEs are commonly detected in densely populated and highly industrialized areas, such as land–water interfaces (i.e., coastal zones, lakes, rivers, and lagoons) [20–23], and are differentially distributed in abiotic (i.e., air, water, sludge and sediments) and biotic compartments (i.e., food webs) [24–27]. Overall, although it is still under debate whether PAEs can be reliable indicators of microplastic pollution, they can be reasonably considered as reliable tracers of the occurrence and extent of plastic pollution in ecosystems.

A few key physicochemical properties of PAEs, including the water solubility (WS), the octanol−water partition coefficient (K_{OW}) and its logarithm (log K_{OW}), the organic carbon–partition coefficient (K_{OC}), the air−water partition and octanol–air partition (K_{AW} and K_{OA}) coefficients and their logarithms (log K_{OA} log K_{AW}), define their behavior, transport, and fate in their environment, and their partition between the different compartments as well [24]. Table 1 shows that the WS of PAEs is generally low and decreases with increasing carbon chain length. K_{OW} has been used to predict the tendency of PAEs to concentrate in aquatic biota, since it translates the affinity of PAEs for the lipids present in living organisms. Log K_{OW} increases with increasing carbon chain length, indicating a greater bioconcentration in the organism. The study of the K_{OC}, log $K_{AW,}$ and log K_{OA} allows the modeling of PAE distribution in different environmental compartments. Due to the association of PAEs with organic matter, K_{OC} is calculated to describe the partitioning behaviors of PAEs in the water-suspended particulate matter (SPM) system [24,25]. Log K_{AW} and log K_{OA} increase with the increasing alkyl chain length. High values of log K_{OA} suggest that the PAEs present in the atmosphere will be appreciably sorbed to aerosol particles, soil, and vegetation, whereas high values of log K_{AW} suggest that PAEs potentially evaporate more rapidly from water. Consequently, low molecular weight PAEs will volatilize rapidly from the pure state, but only very slowly from aqueous solution due to their high WS. Conversely, the higher molecular weight PAEs will potentially evaporate more rapidly from water, but this behavior is mitigated by high K_{OW} and K_{OC}, which make these compounds generally more persistent in the aquatic environment [24].

Table 1. Main physicochemical properties of most common PAEs.

PAE	CAS N.	Mw (g/mol)	Carbon Atoms per Chain	WS (mg/L) [28]	Log K_{OW} [28]	K_{OC} (L/kg) [24]	Log K_{AW} [24]	Log K_{OA} [24]
DMP	131–11–3	194.2	1	4000 at 25 °C	1.54	55–360	−5.40	7.01
DEP	84–66–2	222.2	2	932 at 20 °C	2.20	69–1726	−5.01	7.55
DBP	84–74–2	278.4	4	10 at 20 °C	4.46	1375–14,900	−4.27	8.54
DIBP	84–69–5	278.4	4	13.8 at 20 °C	4.11	-	−4.27	8.54
BBP	85–68–7	312.4	4,6	2.69 at 25 °C	4.84	9×10^3–17×10^3	−4.08	8.78
DEHP	117–81–7	390.6	8	0.003 at 20 °C	7.50	87,420–51×10^3	−2.80	10.53
DINP	28553–12–0	418.6	9	0.0006 at 21 °C	8.80	-	−2.43	11.03
DIDP	26761–40–0	446.7	10	0.0004 at 20 °C	9.46	286×10^3	−2.06	11.52

Depending on the plasticizer and its physicochemical properties, the route of exposure and the type of organism exposed, PAEs may lead to different adverse outcomes and levels of chronic and acute toxicity. In fact, although all PAEs have not been thoroughly investigated, there is evidence that some of them may interfere with the hormonal system and damage the reproductive function, with potential transgenerational or multigenerational effects [29]. In males, they are considered a risk factor for altered puberty and infertility; in women, they can affect the reproductive function and health, with important repercussions on the pregnancy and embryonal and fetal development [29]. Also, a positive correlation between the exposure to PAEs and an increased level of biomarkers of oxidative stress, chronic inflammation, hepatotoxicity, cardiovascular disease, metabolic syndrome, diabetes mellitus, and tumors has been extensively addressed and reviewed in the literature [30–34].

Diverse international legislations have introduced restrictive measures to limit the production and use of PAEs, with the ultimate aim of protecting human health and the environment and moving towards more sustainable and ecofriendly economies. The EU legislative framework (Regulation (EC) No.1907/2006 [35]), for example, regulates only those PAEs with high rates of application, and thus, a high risk of exposure, which have been classified as toxic to reproduction (Repr. 1B substances). In this Regulation, Annex XIV lists nine PAEs subject to authorization before use, as they have been already identified as substances of very high concern (SVHC) for their adverse effects to human health and/or environment; while Annex XVII specifies the restrictions on the manufacture and placing on

the market for eleven PAEs, of which eight substances (i.e., DEHP, DBP, BBP, DIBP, DMEP, DIPP, DPP, DnHP) have been already declared as SVHCs and are subject to authorization according to Annex XIV (Table 2).

Table 2. List of PAE subject to authorization (Annex XIV) and restrictions on their manufacture and placing on the market (Annex XVII) according to the Regulation (EC) No. 1907/2006 [35].

PAEs Subject to Authorization (Annex XIV)	
Phthalate	Reason for authorization
Bis(2-ethylhexyl) phthalate (DEHP)	-Toxic for reproduction -Endocrine disrupting properties (effects to environment and human health)
Dibutyl phthalate (DBP)	
Benzyl butyl phthalate (BBP)	-Toxic for reproduction -Endocrine disrupting properties (effects to human health)
Di-isobutyl phthalate (DIBP)	
Di-*n*-hexyl phthalate (DnHP)	-Toxic for reproduction
Dipentyl phthalate (DPP)	
Di-isopentyl phthalate (DIPP)	
Bis(2-methoxyethyl) phthalate (DMEP)	
n-pentyl-isopentyl phthalate	
Restrictions on the Manufacture, Placing on the Market and Use of Certain Dangerous Substances,Mixtures and Articles (Annex XVII)	
Phthalate	Restriction
Bis (2-ethylhexyl) phthalate (DEHP)	The four PAEs shall not be used at 0.1% or above by weight of the plasticized material, individually or in any combination in toys and childcare items. Toys and childcare items should not be placed on the market if either their individual concentration of DEHP, DBP, and BBP or their combination is equal to or greater than 0.1% in their plasticized material. DIBP shall not be placed on the market in toys or childcare items, individually or in any combination with DEHP, DBP, and BBP, in a concentration equal to or greater than 0.1% of the plasticized material. The four PAEs shall not be placed on the market in articles, individually or in any combination, in a concentration equal to or greater than 0.1% of the plasticized material.
Dibutyl phthalate (DBP)	
Benzyl butyl phthalate (BBP)	
Di-isobutyl phthalate (DIBP)	
Di-isononyl phthalate (DINP)	The three PAEs shall not be used as substances or in mixtures, in a concentration equal to or greater than 0.1% of the plasticized material, in toys and childcare articles which can be placed in the mouth by children. Toys and childcare items with the three PAEs in a concentration greater than 0.1% of the plasticized material shall not be placed on the market.
Di-isodecyl phthalate (DIDP)	
Di-*n*-octyl phthalate (DnOP)	
Bis(2-methoxyethyl) phthalate (DMEP)	The four PAEs shall be used at a maximum concentration of 1000 mg/kg (individually or in any combination
Diisopentylphthalate (DIPP)	
Di-*n*-pentyl phthalate (DPP)	
Di-*n*-hexyl phthalate (DnHP)	

However, in addition to the EU, other regions, such as the US, Canada, Latin America, and Israel have also set restrictions for PAEs in children's toys or articles intended to be put in their mouths, food contact materials, and electronic and electric products [36–39].

The Mediterranean Sea has been recognized as the sixth-highest accumulation hotspot for marine litter [40]. The shores of this regional semi-enclosed sea house around 10% of the global coastal population and constitute one of world's busiest shipping routes. The basin is in communication with the Atlantic Ocean via the Strait of Gibraltar, and with the Indo-Pacific region, thanks to the Suez Canal. It receives waters from densely populated rivers (e.g., Nile, Ebro, and Po), and has a water residence time as long as a century [41]. According to Cozar et al. [42], there is a total load of floating plastic debris amounting to 1000–3000 tons in this sea. This magnitude of plastic pollution is comparable to that revealed in the five oceanic gyres and makes the Mediterranean basin an additional major accumulation area of plastic litter at a global scale. The plastic pollution in the Mediterranean surface waters is dominated by millimeter-sized debris and a higher proportion of large plastic objects (mesoplastics) that reflect a closer connection with pollution sources [42], while the presence of microplastics is much higher in sediments [43,44]. Consequently, the migration of hazardous additives, such as PAEs, from plastic debris is also a major concern in this area for both short- and long-term effects on the abiotic and biotic compartments. In particular, the marine web may be exposed to PAEs either directly (i.e., uptake of leached PAEs via inhalation or digestion) or indirectly (i.e., uptake of microplastics containing PAEs via

ingestion, inhalation, and entanglement). In any case, the trophic transfer of PAEs from the base of the web to higher trophic levels cannot be ignored. Indeed, due to an intrinsic hydrophobicity, these pollutants may bioaccumulate within the fatty tissues of marine species and pass up the food chain [26].

Based on these premises and the intrinsic link between plastics and PAEs in the issue of plastic pollution, this review first provides an overview of the analytical approaches used to monitor these substances in diverse marine matrices (i.e., seawater, sediments and biota), also with reference to their limits and future perspectives in the context of green analytical chemistry. Then, the studies on the occurrence of PAEs and their spatial and temporal distribution in the Mediterranean coastal ecosystems are comprehensively reviewed to achieve a detailed picture of PAE pollution in the Mediterranean Sea. Finally, the anthropogenic sources of PAE pollution and the potential correlation between PAE pollution and the abundance of microplastic debris are critically examined to evaluate their effectiveness as tracers of microplastic pollution.

2. Methods of Analysis

As a matter of fact, the accurate and precise determination of PAEs in environmental samples is a challenging task, as PAEs congeners, such as DEHP, DBP, DIBP, DINP, and DIDP [45–48], are ubiquitous in the ambient of the laboratory of analysis (i.e., air, work surfaces, material, and reagents), and the background contamination at different stages of the analytical procedure can often lead to false positive or overestimated results. Indeed, sample preparation can be a source of PAE contamination via solvents, chemicals, glassware, tubes, stoppers, etc., and the possibility of contamination increases as the number of steps and time involved in the extraction process increases. Also, the analysis typically conducted by gas chromatography (GC) may cause contamination via the carrier gas, the injector liner, the septa, the ferrules, the vial caps, the washing solvent, and the syringe [46–48].

As a result, strict quality control (QC) and quality assurance (QA) procedures must be implemented to maintain low background contamination throughout the workflow.

2.1. Quality Control and Quality Assurance (QC/QA)

QC includes all the procedures established to ensure accurate and reliable results and to measure any non-conformance in PAE analysis.

Ideally, a dedicated room with a purified air filter should be used for PAE analysis. Since PAEs are contained in plastics (10–60%), the use of plastic materials is prohibited throughout the workflow, except for in PAE-free nitrile gloves. Cartridges, filters, vial caps, syringes, and septa should also be checked to ensure they are PAE-free [46]. Only glass, polytetrafluoroethylene (PTFE), aluminum, or stainless-steel materials should be handled during sampling and sample preparation. In addition, these materials and, more generally, all the laboratory equipment, should be pre-washed with a suitable organic solvent such as *n*-hexane, cyclohexane, isooctane, or methanol [46]. All glassware, sampling materials, tubes, and columns should be then kept in a suitable box sealed with a glass or PTFE lid or calcined aluminum foil to prevent the adsorption of PAE from the ambient air. PAEs, such as DBP and DEHP, have often been reported in some organic solvents, such as *n*-hexane, even in the order of µg/L [47]. For this reason, all the solvents should be of high quality (i.e., Suprasolv, Ultra Trace, or MS grade) and should be routinely checked to be free of PAE. However, organic solvents may be distilled to increase their purity [46]. Attention should also be given to the use of ultrapure water from the Milli-Q® system (Millipore Corp., Milford, MA, USA) which may cause PAE contamination due to leaching from the tubing [47,48]. Chemicals, such as aluminum oxide, silica, sodium carbonate, sodium chloride, and sodium sulfate, should be decontaminated via calcination at 400–550 °C from 4 h to overnight.

Differently from QC, QA is the system of verification that the whole process of PAE analysis is within acceptable limits.

The use of blanks during the sampling and analysis of environmental samples is essential in any QA program to ensure reliable and reproducible data quality [49]. A blank is an artificial sample designed to monitor the introduction of artifacts into the analytical process [50]. There are many different types of blanks, and they can be conveniently grouped as either field blanks—prepared during sample collection and transport—or methods blanks—prepared within the laboratory (i.e., procedural, solvent, and matrix blanks).

A field blank is a sample usually constituted by ultrapure water in place of the matrix that is handled (i.e., collected, transported, and stored) in the field. It is treated in the laboratory as a test sample and is used to document that PAE contamination is not introduced during the sampling phase [51]. A procedural blank also consists of ultrapure water, but, differently from the field blank, it is prepared in the laboratory, carried through the analytical procedure, and analyzed in the same way as a test sample. This type of blank assesses the PAE contamination caused by materials, solvents, and reagents introduced during any step of the measurement procedure [52,53]. A solvent blank is made up of the solvent(s) of the final solution presented to the instrument. It can assess any interferences present in the solvent and indicate possible carry-over effects from one sample to the next [53]. A matrix blank is a sample matrix with no PAEs present, e.g., a saline solution representative of seawater. Sample blanks may be difficult to obtain, but they are necessary in QA to give a realistic estimate of interferences that would be encountered in the analysis of test samples. A matrix blank can establish if there are matrix components that may interfere with the selectivity of the analytical procedure, namely the ability of the method to measure PAEs of interest [54]. Additionally, this blank should be used in the preparation of the so-called "matrix-matched" standards (i.e., a matrix blank spiked with known amounts of analytical standards) for conducting a proper analytical validation. In fact, matrix-matched standards are useful for determining the working range, the LOD, and the LOQ, and, when reference materials are not available, the trueness, precision, and ruggedness of the method [55].

Field and method blanks should always be run along with each environmental sample batch to track the source(s) of PAE contamination and, thus, find appropriate solutions. PAEs in blanks should be $\leq$LOQ and, if they are present at higher levels, they must be eliminated according to the QC measures described above. If they cannot be eliminated, they must be quantified and subtracted from the sample measurement.

The recovery assessment is another essential component of the QA program, as well as of the optimization of sample preparation protocols discussed in Section 2.2.1. Indeed, recovery tests are advantageous, not only to check that the experimental data do not suffer from background contamination and that one is operating analytically correctly, but also to improve a given extraction protocol, for example, by reducing the solvent/reagent volume and/or operating time, or even to prefer one extraction technique over another. Under this perspective, recent reviews report the comparison of recovery rates obtained from different extraction techniques of PAEs [24,45].

However, other extraction techniques have also been developed not only to reduce the solvent volume and extraction times but also to improve the precision of the recovery.

The recovery of target PAEs in the environmental sample of interest should be evaluated by spiking known amounts of relative analytical standards into a matrix blank, with a concentration similar to those found in the real samples, and performing the analytical workflow of sample preparation and analysis. The recovery rates should be within the acceptable limits (i.e., 70–120% [56,57]) to ensure either good efficiency and no significant loss, or interference during the analytical procedure. The recoveries of PAEs in real samples can be different from one PAE to another, as it may be affected by the organic matter of the matrix blank and the extraction efficiency of the protocol of sample preparation [24,58].

In the development of a QA program, a planned and reasoned choice of method of quantification is necessary to provide quality data.

It is strongly recommended to carry out the quantification of PAEs via the internal standard(s) (IS) method [24]. This method contemplates the spiking of a known amount

of IS to both the sample and the calibration solutions prior to sample preparation. After the entire analytical procedure has been made, the PAE of interest is determined in the test sample, not by the absolute instrumental response of the target analyte, but rather by its relative response, intended as the analyte/IS response ratio. Hence, the use of IS allows for the normalization of the instrumental response and the correction of the overall analytical variation in the measurement process resulting from random errors (e.g., sample preparation) and/or systematic errors due to the presence of interfering compounds, such salts or undetected metabolites, in the matrix. In this respect, the IS also allows the monitoring of the matrix effect [59,60]. The IS method is very useful in the case of PAEs, because low-molecular-weight PAEs (e.g., DMP, DEP and DBP), for example, are quite volatile, and can be significantly lost during the concentration phase of sample preparation. It is generally recommended to use IS isotopically labeled with ^{13}C or ^{2}H (or simply d4) analogs of the target compounds. In the literature, deuterated PAEs such as DMP-d4, DEP-d4, DBP-d4, DEHP-d4, DiDP-d4, DnOP-d4, and DiNP-d4 were most often used and proved to be efficient for the GC quantification of the relative PAEs in environmental samples [61–64].

2.2. Analytical Methods

2.2.1. Sample Preparation

In sample preparation, the steps of extraction, preconcentration, and cleanup are important to improve the sensitivity during the analytical determination of PAEs. Due to the threat of background contamination, this stage should be as fast and simple as possible. Additionally, the recent literature has focused on the reduction in the polluting character of this analytical phase, by developing green and sustainable processes.

There is a large variety of sample pretreatment techniques because the best strategy of extraction concentration and cleanup, as well as their best combination, primarily depend on the characteristics of the sample and the physicochemical properties of the target PAEs.

For water samples, liquid–liquid extraction (LLE) and solid phase extraction (SPE) have always been considered the most suitable sample preparation methods.

LLE consists of adding an organic solvent to the aqueous sample, shaking it vigorously to promote PAE extraction, and decanting the organic phase containing PAEs. These steps are repeated in a sequence up to three times and recovery rates >80% are generally obtained [65–68]. Propanol is considered a good solvent for PAE extraction. However, it is miscible with water, so ammonium sulfate should be added to the mixture to separate the two phases [69]. The water-immiscible solvents that do not require the addition of salt are hexane and/or dichloromethane (DCM) [68,70,71]. In this respect, the use of DCM is contemplated in EPA Method 8061 [72], one of the most considered methods of PAE extraction from water samples [65,68,70]. However, the addition of an organic modifier, such as methanol (MeOH), can improve the extraction yield of apolar PAEs, such as DEHP and DnOP [73].

Overall, the LLE technique is easy to implement and minimizes the sources of cross-contamination by requiring only a few steps. However, it is time-consuming and requires the use of large volumes of organic solvents, making it expensive.

This has led to the development of alternative techniques to LLE with a clear "green" character. Solid supported LLE (SLE), for example, consists of passing the water sample through a cartridge packed with high purity, inert, diatomaceous earth and then, eluting the PAEs with a water-immiscible organic solvent. SLE is considered to be a hybrid procedure between SPE and LLE and allows the reduction in the volume of solvent and sample used, but also the matrix interference [24].

Dispersion liquid–liquid microextraction (DLLME) has also been employed for PAE extraction [74,75]. In this case, a dispersive organic modifier (e.g., acetonitrile [ACN] or MeOH) is added to the extraction solvent (e.g., chlorobenzene, chloroform, etc.) and the mixture is injected rapidly into the sample to form a cloudy solution characterized by an increased contact surface between the sample and the extractant, which allows the

equilibrium state to be reached rapidly, thus significantly reducing the extraction time. After the centrifugation of the cloudy solution, the phase containing the PAEs is settled at the bottom of the tube and is ready for analysis. The main advantages of DLLME include easy implementation, rapidity, a low cost, high recovery yields and enrichment factors, and, not least, environmental friendliness [76].

However, to further improve the efficiency, DDLME variants have been developed and used for PAE extraction, such as ultrasound-assisted dispersive liquid–liquid extraction (UA-DLLME), ultrasound vortex-assisted dispersive liquid–liquid microextraction (USVA-DLLME), and magnetic stirring-assisted dispersive liquid–liquid microextraction (MSA-DLLME) [45,74].

SPE relies on the interaction of analytes of the aqueous sample with a solid phase (i.e., sorbent or filler), usually packed in a cartridge. This process consists of four steps to be performed by the cartridge, namely conditioning (or equilibration), sample loading, washing, and analyte elution [45].

Since low PAE concentrations are expected in water samples, the main strength of SPE is that it can extract large sample volumes with high enrichment/concentration factors. In addition, SPE can benefit from the ease of implementation, the ability to save time and solvent, and the possibility of semi- or full automation [77,78]. However, SPE has a major constraint, as most commercial sorbents are only available in plastic cartridges, which can leach PAEs into the extract and interfere with subsequent PAE analysis [79]. Therefore, if glass cartridges are not available, a procedural blank should be prepared to correct for this cross-contamination.

Since PAEs have a wide range of polarity, the choice of the most appropriate sorbent and solvent is critical. Generally, hydrophilic–lipophilic balanced (HLB) sorbents, such as Oasis HLB (Waters^{TM}, Milford, MA, USA) or mixed LiChrolut RP18 and LiChrolut EN (Merck, Darmstadt, Germany), and C18 fillers are preferred [80–82]. Diverse elution solvents with varying polarity were tested in SPE, such as acetone, DCM, ethyl acetate (EtOAc), MeOH, and *n*-hexane, to optimize the analyte recovery. When extracting large volumes of seawater, for example, medium polar solvents, such as DCM and EtOAc, generally provide the best results, with recoveries >90% for most common PAEs (i.e., DMP, DEP, DPP, DIBP, DBP, BBP, DEHP, and DnOP). On the other hand, more polar solvents, such as acetone and MeOH, yield lower but still acceptable recoveries for DMP, DEP, DPP, DiBP, DBP, and BBP, while *n*-hexane is useful only for the extraction of less polar PAEs (i.e, DEHP and DnOP) [83]. Interestingly, the addition of a small amount of MeOH to the aqueous sample prior to SPE increases the recovery rate of the less polar PAEs due to a greater solubility of their alkyl chain in water, which prevents their adsorption onto glassware. In addition, the parameters, such as the sample volume and the flow rate of the elution solvent, need to be optimized for further improving the PAE recoveries.

Dispersive SPE (dSPE) is a variant of SPE that can be used to extract PAEs from water samples. dSPE can avoid some of the difficulties typical of SPE, such as sample loading, cartridge clogging, or the need for a controlled and constant flow rate [84]. In addition, dSPE is less time-consuming and does not involve the use of plastic cartridges, thus minimizing the risk of cross-contamination. Magnetic nanoparticle (MNP) solutions can be used as green dispersive sorbents for extracting PAEs with very good recovery rates and instrumental sensitivities [85,86]. Several studies encourage the utilization of environmentally friendly MNP materials based on characteristics, such as the reusability and the low cytotoxicity of MNPs, the minimal sorbent quantity needed, and the minimal waste generation [87].

The most analyzed solid samples for PAEs are aquatic sediments and biota. Although there is evidence that the extraction of PAE can be carried out on these matrices as such, it is strongly recommended that the prior steps of freeze-drying, homogenization, and sieving are carried out prior to extraction.

In this case, the sample preparation generally includes steps of extraction and cleanup. The extraction is typically conducted with diverse organic solvents, such as acetone, ACN,

DCM, EtOAc, and *n*-hexane, and by exploiting technologies, such as sonication (USAE), microwave-assisted extraction (MAE), and pressurized liquid extraction (PLE), also known as accelerated solvent extraction (ASE) [88–96]. These techniques already have a clear green character due to their ease of implementation and reduced solvent volumes and extraction times, and they are also characterized by higher recovery yields than traditional methods, such as Soxhlet, which require long extraction times and large solvent volumes, and cause PAE cross-contamination [97,98].

Due to the complexity of the solid matrix, the obtained extract is then subjected to a cleanup procedure, generally based on SPE and its variants, to remove any co-extracted compound that may interfere with analyses of PAEs and, thus, increase the selectivity of the method [85,89].

Among innovative and green sample preparation protocols, the Quick Easy Cheap Effective Rugged Safe (QuEChERS) technique has always been the mainstream approach to sample preparation in pesticide analysis [98,99]. However, due to its great versatility and flexibility, it has extended to the analysis of other organic contaminants, such as PAEs, in a variety of solid samples, including the environmental ones [100–104]. The QuEChERS protocol involves the extraction of a sample with a certain water content followed by a cleanup step. Initially, the extraction is carried out with an organic solvent, such as ACN, or a mixture of DCM/*n*-hexane or DCM/EtOAc, and a salting-out step with anhydrous NaCl and $MgSO_4$, helps the partitioning of PAEs into the separated solvent phase. Then, the organic phase is subjected to a cleanup step by a dSPE, usually using a primary secondary amine (PSA) as a sorbent [94,104–106]. Although all the extraction techniques discussed for solid samples show similar method sensitivities, QuEChERS has demonstrated itself to be the simplest and fastest procedure because it is conducted without laboratory equipment, such as an ultrasonic bath, a microwave digestion system, or PLE. However, it can more easily lead to the cross-contamination of samples, as it requires more manipulation than the other techniques [80].

2.2.2. Analysis

In environmental samples, the identification and quantification of PAEs typically occur by separation techniques, such as high-pressure liquid chromatography (HPLC) or gas chromatography (GC), coupled with a sophisticated detection system, such as mass spectrometry (MS).

Due to its low polarity and scarce water solubility, GC is the election technique for the analysis of PAEs. The most used capillary column is a fused silica column coated with (5%-phenyl)-methylpolysiloxane (e.g., DB-5MS and HP-5MS) [94,103,105,106], since it offers good resolution, higher operating temperature, and lower bleeding than higher polar columns (e.g., wax or cyanopropyl columns). However, 100% dimethylpolysiloxane columns [89,107], (35%-phenyl)-methylpolysiloxane columns [108] and low-polarity polymeric columns [109,110] have also been reported to be successful. After GC separation, PAEs are identified and quantified over time with diverse detection systems, including electron capture (ECD) and photoionization (PID) detectors [111,112]. However, MS, in the form of quadrupole, triple quadrupole, ion trap, and magnetic sector, along with single, tandem, or hybrid arrangements, is generally considered the most efficient tool for the simultaneous identification and quantification of targeted PAEs [17,45,81]. By using a MS detector, PAEs are first ionized thanks to electronic impact (EI) or chemical ionization (CI) and subsequently detected in full-scan, single-ion monitoring (SIM), or even the multiple reaction monitoring (MRM) mode in the case of tandem MS. The use of tandem MS implies the achievement of a greater method sensitivity and specificity and, therefore, the determination of PAEs at very low levels (e.g., ng/L or ng/g) [45].

PAE can also be analyzed via LC-MS. In this case, PAEs are first dissolved in a mobile phase and, subsequently, chromatographically separated through a column packed with a stationary phase. The most common MS detectors coupled to LC systems are the triple quadrupole, the ion trap, and the orbitrap analyzers, and, depending on the

detector type, they can be used in single, tandem, or hybrid MS configurations. These MS systems are equipped with electrospray (ESI) or atmospheric pressure chemical (APCI) interfaces, generally exploiting ionization in positive mode. In LC, PAE separation is commonly obtained on a C18 analytical column, using a mobile phase consisting of organic modifiers, such as MeOH and CAN, and ultrapure water. Also, additives (i.e., acetic or formic acid) are usually added in a concentration range 0.01–1% to improve the following analyte ionization [17,45,81].

When comparing GC and LC approaches, the latter has been demonstrated to suffer from a lower sensitivity for many PAEs. However, HPLC, and more recently, ultra-HPLC (UHPLC), may be more suitable for the analyses of PAE degradation products and for certain isomeric mixtures (e.g., DINP and DIDP) [17,77].

3. Occurrence, Spatial, and Seasonal Distribution of PAEs in the Mediterranean Area

According to the reviewed studies, the most investigated PAEs in the Mediterranean marine ecosystems were those regulated by the Regulation (EC) No.1907/2006 [35], namely DEP, DBP, DIBP, BBP, and DEHP. In this section, we analyze the occurrence of these compounds in marine abiotic and biotic matrices, discuss the sources of PAE contamination, and detail their spatial and temporal variations. Finally, we critically evaluate the effectiveness of PAEs as indicators of microplastic pollution.

3.1. Seawater

Table 3 reports the occurrence of main PAEs in the seawater samples collected from the Mediterranean region over the past 20 years. A few works focused on the investigation of plastic additives in seawater [82,112,113], often among other organic contaminants [114–116]. In addition, some of these studies did not report numerical data, but rather graphics, and they were therefore not included in the table [117–119]. In these studies, DEHP and DBP had the highest concentrations and detection frequencies, thus confirming that they are the main PAEs polluting the Mediterranean seawaters, and the main study areas were the Marseille Bay [82,113] and the Catalan coast [114,115]. Both Marseille Bay and the Catalan coast are well known for their intense coastal tourism, for their high level of maritime traffic, and for their numerous ports, which host a wide range of urban, commercial, touristic, and fishing activities. In addition, many water rivers and effluents from wastewater treatment plants (WWTP) are routinely discharged into these coastal waters. Other investigated areas were the Spanish Valencian coast, which is an economical and industrial developed area populated by many WWTP effluents [117], and the portion of the Tunisian coast belonging to the Mahdia governorate, which is known for the intense recreational coastal activity and fishing, and the elevated maritime traffic, reaching their maximum from spring to autumn [112].

Table 3. Occurrence of main PAEs (ng/L) in the seawater from several Mediterranean areas recorded over the past 20 years.

Study Area	Sampling Year	DMP	DEP	DBP	DIBP	BBP	DEHP	Ref.
Mahdia coast (TN)	2018–2019	n.d.	n.d.–0.017 × 10^6	n.d.–0.0305 × 10^6	n.d.–0.106 × 10^6	n.d.	n.d.–0.168 × 10^6	[112]
Marseille Bay (FR)	2013–2014	0.8–11.9	3.3–50	12.0–596.0	27.5–383.4	2.6–6.1	15.8–923.8	[113]
	2014	1.4–7.3	6.9–50	28.8–466.0	56.5–383.4	3.2–5.1	56.2–296.5	[82]
Catalan coast (SP)	2005	-	-	110–4620	-	80–460	n.d.–12,740	[114]
	2009	2.8–142	24–143	-	-	1.3–104	31–617	[115]
Valencian coast (SP)	2008–2009	n.d.	n.d.–20 × 10^6	n.d.–0.3 × 10^6	-	-	n.d.–15 × 10^6	[116]

n.d.: below the limit of detection; -: not investigated.

As shown in Table 3, the highest concentrations of both DEHP and DBP were recorded along the Valencian (up to 15 mg/L and 0.3 mg/L, respectively) [116] and Tunisian (up to 0.168 mg/L and 0.0305 mg/L, respectively) [112] coastlines. In addition, the Mahdia coast was also characterized by the highest levels of DIBP (0.106 mg/L) [112]. Lower but still significant levels of both plasticizers were reported in the Catalan coast (DEHP: up

to 12.74 μg/L; DBP: up to 4.62 μg/L). The comparison of PAE contamination investigated in the same coastal area but in different years highlighted that both the levels of BBP and DEHP were remarkably lower between 2005 and 2009 [114,115]. This finding could be related to the limitations imposed by current legislation in the production and use of these legacy PAEs in favor of alternative plasticizers, as will be discussed for sediments (Section 3.2). Marseille Bay was the least contaminated area, since DEHP and DBP were up to 923 ng/L and 596.0 ng/L, respectively [82,113]. Moreover, the different studies conducted during two consecutive years in this area reported comparable concentrations for almost all the investigated PAEs, except for DEPH, which significantly decreased its maximum levels in seawater (from 923.8 ng/L to 296.6 ng/L) [82,113].

DEHP and DBP are the most widely used plasticizers in the manufacture of soft PVC, rubber and, hence, derived items. DBP is also advantageously exploited in non-PVC mixtures for its viscosity reducing properties and good compatibility with other polymers. The high log K_{OW} and, therefore, the high hydrophobicity of both plasticizers (Table 1) also makes their degradation by photolysis, hydrolysis, or biological processes more difficult, which can facilitate their accumulation [120]. Schmidt and colleagues demonstrated through a regression analysis that the waterborne PAEs at Marseille Bay were not correlated with the corresponding microplastic abundances [119]. However, recent studies conducted in heavily polluted areas outside the Mediterranean basin revealed a significant positive correlation between microplastics and PAEs in surface water, as they tend to adsorb waterborne contaminants, including PAEs, while simultaneously leaching their own plasticizers into the seawater [120,121]. In any case, the plasticizer contamination of coastal systems is certainly indicative of the wider plastic pollution issue and, as such, it may originate from many sources, such as household greywater, plastic leakage (e.g., leaching from WWTPs and municipal sewage systems), industrial, tourism, and commercial inputs, as well as from plastic litter, including microplastics.

In the reviewed studies (Table 3), the spatial (i.e., horizontal and vertical) and seasonal distribution of PAEs have been studied. Concerning its horizontal distribution, Paluselli and colleagues [82] pointed out that the total concentration of PAEs is significantly lower in offshore water than in coastal sites, which are generally more impacted by anthropogenic activities. Clearly, coastal currents can greatly affect the final plasticizer distribution along the coastline: it is enough to think of the hotspots of floating plastic litter created in specific areas by peculiar currents [122]. In Marseille Bay and the Catalan and Valencian coasts, the PAEs determined in the seawater were generally also present in WWTP effluents, thus highlighting that WWTPs are a significant source for plasticizers in coastal waters [82,115,116]. In these areas, major rivers, such as the Spanish Ebro River and the Rhone River crossing Switzerland and France, were also identified as main sources of plasticizers [82,116]. However, agricultural runoff, the direct discharge of untreated urban or industrial waters, the pollutant sources, and even the atmospheric deposition, could significantly contribute to the plasticizer contamination of the northwestern Mediterranean Sea. Considering the Tunisian coast, other types of pollution sources were hypothesized, mainly related to shipping and industrial inputs. Indeed, the sampling areas considered in the governorate of Mahdia, were in the proximity of fishing ports and industrial activities, particularly textile companies, that satisfy most of the industrial segment in the region [113]. Among the reviewed studies, only Paluselli and colleagues analyzed the vertical distribution of PAEs in Marseille Bay [82,113]. In general terms, the superficial seawater showed the highest levels of PAEs, followed by a slight decrease at the greater depths, and then, again, an increase in the PAE concentrations close to the bottom. This gradient concentration could be either due to the photochemical and/or prokaryotic degradation preferentially present in the surface water column than in deeper seawater. However, while photodegradation is more effective in the first meters of the water column, prokaryotic degradation is likely to act above the sediment. On the other hand, the high concentrations of PAEs observed at the bottom could be related to direct plasticizer inputs from SPM and sediments. In this respect, more specifically, under 500 m, DEHP, DIBP, and DBP were the most abundant

PAEs, followed by DMP and DEP. A possible explanation may be that DMP and DEP are more easily distributed in superficial seawater due to a relatively high solubility, while DEHP, DIBP, and DBP with higher Log K_{OW} values are preferentially adsorbed to the SPM and sediment phase [82,113].

With respect to the seasonal distribution, Paluselli and colleagues pointed out that elevated concentration of PAEs were revealed in the summer seawater of Marseille Bay due to intense recreational and tourist activities and elevated maritime traffic. Additionally, the vertical distribution just described may also be affected by seasonality, since PAE gradient is more evident by the end of winter/spring, while more similar concentrations were observed along the water column in the winter period, probably because of a more homogenous water mixing under the action of the strong Mistral wind [82,113]. Similarly, higher levels of PAEs, especially DEHP, were recorded during the period of May–October along the coast of the Mahdia governorate due to the many human activities of the tourist season. It is also likely that tourism preferentially generates DEHP inputs, due to the abundance of such plasticizers in surfing, swimming, and diving articles, as well as food packaging, bags, and sunscreen containers left "accidentally" on the beaches. However, similarly to the geographic distribution, climatic factors such as rainfall, urban stormwater, and agricultural runoff and atmospheric deposition may affect the seasonal distribution of such pollutants to a different extent [112].

Overall, the quality of Mediterranean seawaters in terms of PAE contamination, could be evaluated by considering (i) the EU guideline for environmental quality, which establishes a limit of 1.3 µg/L for DEHP in marine waters [123], and (ii) a study by Van Wezel et al., which calculated the environmental risk limits (ERLs) for DEHP and DBP in marine waters based on (eco)toxicology and environmental chemistry data, by fixing the respective limits of 10 µg/L and 0.19 µg/L [124]. On this basis, the concentrations of DBP were much higher than the respective ERL in the Valencian coast (300 µg/L), the Mahdia region (30.5 µg/L), the Catalan coast (4.62 µg/L) and even Marseille Bay (up to 0.59 µg/L). Similarly, the DEHP levels were considerably higher than the allowance values in the seawater of the Valencian (15,000 µg/L), Tunisian (168 µg/L), and Catalan (up to 12.74 µg/L) coasts.

3.2. Sediments

Table 4 illustrates the concentrations of the main PAEs revealed in the sediments from the Mediterranean region. Despite the literature period covered in this review (20 years), we only found studies from the last 10 years, thus suggesting that the investigation of PAEs in sediments from the Mediterranean area is a relatively recent topic. Similarly to seawater, a few works focused on the investigation of plasticizers in sediments [105,112,125–127] together with other environmental toxicants [128]. Moreover, one study was not listed in Table 4 due to the absence of numerical data [119].

Table 4. Occurrence of main PAEs (mg/kg, dw) monitored in the sediments of diverse Mediterranean areas over the past 20 years.

Study Area	Sampling Year	DMP	DEP	DBP	DIBP	BBP	DEHP	Ref.
Mahdia coast (TN)	2018–2019	n.d.	0.0644–0.142	0.0423–0.0824	0.152–0.394	n.d.–0.0425	4.15–5.24	[112]
	2020	-	0.016–0.047	0.130–0.326	0.379–1.734	-	0.314–1.773	[125]
Gulf of Lyon (FR)	2018	0.00001–0.0122	n.d.–0.0008	n.d.–0.6877	n.d.– 0.0129	n.d.–0.0236	n.d.–0.6397	[126]
Marseille Bay (FR)	2018	n.d.–0.0002	n.d.–0.0021	0.0003–0.0031	0.0019–0.0057	0.0008–0.0019	0.0042–0.3195	[105]
Maltese shoreline (Malta)	Not reported	-	0.0092–0.0704	-	-	-	<LOQ–0.0977	[127]
Abruzzo coast (IT)	2013	n.d.–0.20	n.d.–2.18	n.d.–1.56	0.16–5.17	n.d.–4.86	0.02–12	[128]

n.d.: below the limit of detection; -: not investigated; LOQ of DEHP: 0.0084 mg/kg according to [127].

Similarly to the seawater, DEHP, DIBP and DBP generally result in congeners with the highest detection rates and concentrations. To follow, lower frequencies and concentrations of other plasticizers, including DMP and DEP, were determined in the investigated coastal areas. Alongside the already discussed Marseille Bay [105,119] and the Tunisian coast of Mahdia [112,125], other Mediterranean sites studied for the contamination of sediments were the larger area of the Gulf of Lyon, which includes Marseille Bay [126] and the Maltese coastline, characterized by diverse beaches with a high tourism pressure [127], and the portion of the coast of the Italian region of Abruzzo, which includes the major coastal city of Pescara, one of the most densely populated in Abruzzo, as well as several river mouths and local ports [128].

As highlighted in Table 4, the most contaminated sediments were found on the Abruzzo coast. In this study case, DEHP, DIBP and BBP were the PAE congeners revealed at the highest concentrations (i.e., up to 12 mg/kg, 5.17 mg/kg, and 4.86 mg/kg, respectively). Interestingly, DMP and DEP were also present at very high levels (i.e., up to 0.20 mg/kg and 2.18 mg/kg) [128]. To follow, the coast of Mahdia was also confirmed to be an important hotspot of PAE pollution with respect to sediments (DEHP: up to 5.24 mg/kg; DIBP: up to 1.734 mg/kg; DBP: up to 0.326 mg/kg). In this area, increasing concentrations of DIBP (from 0.152 mg/kg to 1.734 mg/kg) and DBP (from 0.0423 mg/kg to 0.326 mg/kg), and decreasing levels of DEHP (from 5.24 mg/Kg to 0.314 mg/kg) were found in two consecutive years of study [112,125]. Similarly to seawater, the decrease in the DEHP pollution in the sediments could be related to a concomitant increase in the production and use of other plasticizers, such as the bis (2-ethylhexyl) terephthalate (DEHT) [data shown in 112 and 125], an isomer of DEHP that is increasingly employed as a replacement to conventional PAEs in PVC items, including toys, childcare articles, and consumer products [129]. Mediterranean sites with less contaminated sediments were consequently the Gulf of Lyon and the Marseille Bay, although DEHP, DBP, and DIBP were more abundant in the Gulf of Lyon (up to 0.6397 mg/kg, 0.06877 mg/kg and 0.0129 mg/kg, respectively) than the Marseille Bay (up to 0.3195 mg/kg, 0.0031 mg/kg, and 0.0057 mg/kg, respectively), probably due to the larger study area and the higher number of PAE inputs considered [105,126]. Sediments from the Maltese coast were only analyzed for DEP (range: 0.0092–0.0704 mg/kg) and DEHP (range: <LOQ−0.0977 mg/kg), the latter being at the lowest level among the areas investigated [127].

A comparison of Tables 3 and 4 shows that PAE concentrations are significantly higher in sediments than in seawater because of the lipophilic nature of PAEs, which allows them to be adsorbed on carbon-rich particles and surfaces. Indeed, Wang and coworkers [130] suggested that the partitioning of PAEs between sediments and seawater depends on their physicochemical characters: while low molecular weight PAEs diffuse from sediment to seawater and high molecular weight PAEs migrate from seawater to sediment, medium molecular weight PAEs are in a dynamic equilibrium distribution between these phases. As a result, DEHP, along with DBP and DIBP, tend to concentrate more easily in sediments, while DMP and DEP tend to concentrate in the overlaying water [130].

Similarly to seawater, the spatial distribution of the PAEs in sediments was confirmed to be strictly related to a variety of anthropogenic sources. In the Gulf of Lyon, the PAE concentrations were higher in the coastal areas, owing to the inputs of ports, river mouths, and WWTPs, than in more remote sites, such as marine protected areas, and offshore. In particular, the total PAEs in the sediments from the sampling stations near the Rhône estuary indicated that (i) plasticizers associated with sediments are transported by this river and (ii) PAEs are efficiently diluted from the river mouth area to offshore [126]. Castro-Jiménez and Ratola focused on Marseille Bay within the Gulf of Lyon and confirmed that the sediments most contaminated were generally found near the Cortiou WWTP [105]. In the Tunisian coast, plasticizers in sediments had a similar concentration trend to that previously discussed for the overlaying seawater. Overall, the total PAEs and the predominant DEHP gradually decreased from the inner to the outer areas of the investigated coastline. In general, high pollution levels were recorded in correspondence with Chebba, a coastal

city with an active coastal port and many seafood and textile industries [112], and Rejiche, a touristic town hosting a WWTP and many industrial companies [125]. The spatial distribution across the Abruzzo coastline displayed a high geographical heterogeneity. High PAE concentrations were predominantly associated with the mouths of the Saline, Foro, and Pescara rivers, thus confirming that the river transport of sediments represents a continuous source of replenishment of PAEs in coastal areas. On the island of Malta, the sediments from Riviera Bay were characterized by the highest DBP concentration, but not DEHP. Owing to its esthetic value, Riviera Beach is a highly popular and frequented place, thus being subjected to an intense tourism pressure. Despite being a secluded beach, Ghar Ahmar bay was characterized by sediments with the highest DEHP levels, probably due to the intense activity of a power plant installed in a nearby location [127].

Among the reviewed studies, only the Mahdia coast was investigated for the seasonal distribution of PAEs in sediments. The total PAEs and the congeners DEP, DIBP, and DEHP showed similar seasonal trends, as their highest concentrations were detected in April–May, slowly decreased during June–August, and then dropped down in September–November. Similarly to seawater, the seasonal trends of such pollutants in sediments could be explained by the combination of both anthropogenic sources with "seasonal" activity (e.g., tourism activities), and the seasonal variation in the weather (e.g., monthly rainfall) [112].

Similarly to seawater, the quality of Mediterranean sediments can be assessed by considering the ERLs for PAEs, such as DEHP and DBP, for marine sediments equal to 7 mg/kg and 1 mg/kg, respectively [125]. Only sediments from the Abruzzo coast exceeded the limit value set for both DEHP and DBP, thus, resulting in being heavily polluted by these plasticizers.

3.3. Biota

Table 5 reports the occurrence of the most investigated PAEs in marine biota from different Mediterranean areas, according to the literature of the last 20 years. As can be readily observed, a greater number of studies have been devoted to the investigation of PAEs in biota [105,112,119,125,131–140] than in seawater (Table 3) and sediments (Table 4). The greater focus on biota is due to the fact that, given a known set of environmental parameters, the study of PAE concentrations in marine specimens could help to predict changes in ecosystem structure and function, and organism health as well, with the final goal being to avoid losses in ecosystem composition before they occur, as opposed to conducting a retrospective analysis once a species has declined. A wide range of species—from simple plants and invertebrates to complex organisms like cetaceans—were considered and, among them, ascidians [140], holothurians [132], mollusks [105,125], and amphipods [139] were demonstrated to be suitable as sentinel species of plastic additives in ecotoxicological studies.

Table 5. Occurrence of main PAEs in biota at various trophic levels sampled in the Mediterranean basin over the past 20 years. PAE concentrations are expressed as mg/kg on a dry, fresh (*), or lipid (**) weight basis.

Study Area	Sampling Year	Biota Sample	DMP	DEP	DBP	DIBP	BBP	DEHP	Ref.
Mahdia coast (TN)	2018–2019	Plant	n.d.	0.0323–0.0809	0.307–0.491	n.d.–0.120	n.d.–0.171	0.465–0.845	[112]
		Fish (muscle)	n.d.	0.561–2.70	n.d.–0.299	0.434–1.480	n.d.–0.739	0.772–1.46	
	2020	Plant	-	0.016–0.046	0.027–0.054	0.050–1.216	-	0.082–0.150	[125]
		Mussel	-	0.071–0.169	0.119–0.219	0.363–1.961	-	0.454–1.223	
Marseille Bay (FR)	2017–2018	Zooplankton	0.052–0.1409	0.0186–0.0337	0.1302–0.3771	0.0461–0.1104	0.715–0.811	2.982–6.656	[119]
	2018	Plant	n.d.–0.0012	0.0027–0.0089	0.0121–0.1667	0.0154–0.0158	n.d.–0.0056	0.1495–0.6996	[105]

Table 5. *Cont.*

Study Area	Sampling Year	Biota Sample	DMP	DEP	DBP	DIBP	BBP	DEHP	Ref.
		Mussel	n.d.–0.0003	0.0024–0.0031	n.d.–0.0176	0.0048–0.0228	n.d.–0.0175	0.0535–0.6384	
		Fish (muscle)	n.d.–0.0003	0.0016–0.007	0.0026–0.0369	0.0034–0.0229	n.d.–0.0036	0.0114–0.0123	
Catalan coast (SP)	1990–2018	Striped dolphin (muscle) **	n.d.–1.38	n.d.–8.04	n.d.–26.59	-	-	n.d.–48.9	[131]
The Cabrera Maritime–Terrestrial National Park (SP)	2019–2020	Bivalve Mollusk *	-	0.540	0.780	-	-	2.580	[132]
		Fish (muscle) *	-	0.170	0.720	-	-	0.880	
		Holothurians (muscle) *	-	0.490	1.240	-	-	1.480	
Pelagos Sanctuary (IT)	2007–2011	Neuston/plankton *	-	-	-	-	-	0.005–0.172	[133]
	2016	Neuston/plankton	-	-	-	-	n.d.–0.475	n.d.–2.699	[134]
		Cetaceans (skin)	-	-	-	-	n.d.–1.629	1.130–26.068	
	2022	Zooplankton *	n.d.	n.d.	n.d.	-	n.d.	0.104–5.091	[135]
		Bivalve mollusk *	n.d.	n.d.	<LOQ	-	n.d.	<LOQ–0.050	
		Fish (muscle) *	n.d.	n.d.	<LOQ	-	n.d.	<LOQ−0.641	
Western Sardinia coast (IT)	2020	Sea urchin (gonads) *	-	n.d.–0.0139	n.d.–0.0105	-	n.d.–0.0035	n.d.–0.0726	[136]
Tyrrhenian sea (IT)	2019	Loggerhead turtles * (blood)	0.009–0.014	0.008–0.074	0.006–0.057	0.007–0.041	-	0.012–0.073	[137]
Campania coast (IT)	2020–2021	Fish (muscle)	0.178–0.453	0.041–0.224	0.054–0.289	-	-	0.018–6.739	[138]
		Fish (gills)	0.179–1.293	0.057–1.221	0.054–3.737	-	-	0.011–4.107	
Stagnone Nature reserve (IT)	2013–2014	Amphipods	-	n.d.–0.230	0.009–0.046	n.d.–0.240	-	0.006–0.086	[139]
Israeli Mediter-ranean coast (IL)	2017	Ascidians	-	-	1.643–5.064	-	-	4.851–9.095	[140]

n.d.: below the limit of detection; -: not investigated; LOQ of 0.010 mg/Kg for DMP, BBP, and DEHP; LOQ of 0.020 mg/kg for DEP and DBP according to [139].

The highest detection frequencies and concentrations were recorded for DBP and DEHP, followed by DMP, DEP, and DIBP. The matrices with the most abundant PAEs were generally edible fish [112,138] and cetaceans [131,134], while the least contaminated samples were marine plants (i.e., *Posidiona oceanica*) [112,125].

Considering the study areas, special attention was again paid to the Mahdia coast [112,125], Marseille Bay [105,119], and the Catalan coast for the reasons previously discussed. In addition, many marine protected areas, such as the Cabrera Maritime–Terrestrial National Park in the Balearic Sea [132], the area of the Pelagos Sanctuary delimited by the Ligurian and North Tyrrhenian seas [133–135], and the Stagnone Nature Reserve of the Western Sicily coast [139], were investigated. Factors, such as the oceanographic processes and marine currents and the disturbance from intense maritime traffic, along with tourist, industrial, and agricultural inputs in correspondence with urban agglomerations and river mouths, may be responsible for the plasticizer exposure of the inhabiting species and may threaten the "conservation status" of these areas. Coastal areas with many sources of anthropogenic pollution (i.e., WTTPs,

municipal sewage, and massive littering of beaches during the summer season) were also considered in the review process [136–138,140].

On these premises, it is difficult to compare the degree of contamination of the biota in the different study areas because, as shown in Table 4, the PAE concentrations were calculated based on dry weight (dw), fresh weight (fw), and even lipid weight (lw). Accordingly, the highest plasticizer contamination was determined on a lw basis in the muscle of striped dolphins (*Stenella coeruleoalba*) found stranded along the Spanish Catalan coast (DMP: up to 1.38 mg/kg; DEP: up to 8.04 mg/kg; DBP: up to 26.59 mg/kg; DEHP: up to 48.9 mg/kg) [131]. To follow, high PAE concentrations were recorded on a dw basis. In this respect, the Mahdia coast was home to fish (*Sparus aurata*) with high levels of DEP (up to 2.70 mg/kg, dw) and DIBP (up to 1.480 mg/kg, dw) in their muscle [112]. Considerable levels of DMP (up to 1.293 mg/kg, dw), DEP (up to 1.221 mg/kg), and DBP (up to 3.737 mg, dw) were also revealed in various fish species (i.e., *Mugil cephalus*, *Diplodus annularis*, and *Mullus barbatus*) from the Campania coast [138]. The skin and underlying blubber biopsies of the free-ranging cetaceans (i.e., *Balaenoptera physalus*, *Tursiops truncatus*, *Grampus griseus*, and *Stenella coeruleoalba*) from the Pelagos Sanctuary were the most contaminated with DEHP. The detection of plastic additives in the superficial tissues, combined with the long lifespan of the species, indicates that cetaceans are chronically exposed to such persistent and emerging contaminants [134].

Interestingly, one of the reviewed studies addressed the PAE distribution in different fish tissues and highlighted that the gills had a higher plasticizer load than muscle (Table 4) [138]. Specifically, the gills were more contaminated by low-molecular weight PAEs, such as DMP, DEP, and DBP, while muscle had higher concentration of longer-chain PAEs, such as DINP. Overall, the tissue distribution of plasticizers in marine organisms is primarily affected by the hydrophobicity of PAEs —and consequently, by fat content of the organ—and reflects a balance between their metabolism and bioaccumulation. On this basis, Hu and coworkers observed higher concentrations of PAEs and their monoesters in gills (DMP and DBP) and kidneys (DMP, DEP and DBP) than in liver and muscle due to relatively low hydrophobicity (Log K_{OW} = ≤4.50). Conversely, the liver and muscle had higher levels of DNOP and its monoester (Log K_{OW} = ≤7.33). Hence, it may be argued that kidneys and gills, for their anatomical structure and function, are the potential main routes for relatively low hydrophobic PAEs, whereas the liver is likely the main route of accumulation and metabolism for the most hydrophobic PAEs [141].

Among the reviewed studies, the changes in the distribution of plasticizers across the food web were often addressed [105,112,125,132,134,135]. Some authors reported an increase in PAE concentrations as the trophic level increased, probably due to the bioaccumulation phenomenon [112,125,134]. In this respect, Jebara et al. [112] calculated the bioaccumulation factors (BAFs) of every investigated plasticizer in relation to the studied marine species and compared the obtained values with the criteria fixed by the REACH program for predicting the accumulation ability of aquatic organisms, according to which a BAF equal to 2000 or 5000 indicates, respectively, a "bioaccumulative" or a "highly bioaccumulative" compound [142]. According to the obtained BAFs, both *P. oceanica* and *S. aurata* showed a low capacity to accumulate plasticizers in the Mahdia coast [112]. Similarly, Schmidt and colleagues explored the bioaccumulation potential of the base of the food web in Marseille Bay and they pointed out that DMP and BBP can be considered bioaccumulative pollutants in zooplankton [119]. Indeed, zooplankton are thought to accumulate a significant fraction of organic contaminants from the water column [143]. In the study of Baini et al. [134], increasing levels of BBP and DEHP were observed, moving from planktonic samples to cetaceans, thus suggesting that these organisms are potentially exposed to PAEs, not only via direct microplastic ingestion (see below), but also via the ingestion of "contaminated" zooplankton. Blasi et al. assessed the stable isotopic ratios of $^{13}C/^{12}C$ ($\delta^{13}C$) and $^{15}N/^{14}N$ ($\delta^{15}N$) along with the PAE concentrations in the blood of loggerhead turtles to trace chemicals assimilation from a given trophic habitat. They found out a significant correlation between $\delta^{13}C$ and four PAEs, namely DMP, DEP, DIBP, and

DBP, thus suggesting that marine species at high trophic levels may be particularly exposed to PAEs, despite their different dietary habits and levels of exposure [137].

Contrary to what has been discussed so far, other studies reported some kind of "trophic dilution" by moving to higher trophic levels [105,132,135]. This may be caused by a more rapid metabolization/excretion of the pollutants or a more selective feeding strategy of higher species. For example, in the Cabrera Maritime–Terrestrial National Park, mollusks (i.e., *Arca noae*) and holothurians (i.e., *Holothuria forskalii, Holothuria poli*, and *Holothuria tubulosa*) showed a higher contaminant load than fish (i.e., *Oblada melanura*, *Diplodus vulgaris*, *Serranus cabrilla*, and *Serranus scriba)*, probably due to the non-selective feeding behavior of selected invertebrates, which directly exposed them to plastic additives [132]. In the Pelagos Sanctuary, fish species (i.e., *M. cephalus*, *Merluccius merluccius*, *S. aurata*, *Umbrina cirrose,* etc.) had an intermediate PAE accumulation with respect to zooplankton and bivalve mollusks (i.e., *Magallana gigas*, *Ostrea edulis,* and *Mytilus galloprovincialis*). In this study, fish that consume benthic organisms or demersal species with higher bioaccumulation factors were selected [135]. Overall, these studies highlighted that the distribution pattern of plasticizers in a given food web results from the complex interaction of many factors, including the feeding strategy, the living habits, and the metabolic characteristics of each marine species.

Conflicting opinions exist on the hypothesis that the PAE contamination of marine biota may occur via the direct ingestion of microplastics suspended in the water column or deposited in sediments. Rios-Fuster et al. highlighted a positive correlation between microplastics and PAE concentrations in the soft tissues of the mollusk *A. noae*, as well as between the microplastics of the gastrointestinal tract of *H. forskalii, H. poli,* and *H. tubulosa,* and DEP and DEHP in their muscle. However, no significant correlation was outlined between ingested microplastics and plasticizers in the muscle of diverse fish species [133]. These results suggest that factors, such as the feeding strategy and type of tissue, may affect the complex relation between microplastics and plasticizers within the organism. In two reviewed studies, a positive correlation between microplastics and PAEs was observed in planktonic samples [133,134]. Furthermore, Baini and colleagues found a significant correlation between PAE levels and microplastic size, rather than color and shape, in the same zooplankton samples [134]. On the other hand, the lack of correlation between the abundance of microplastics in the digestive tract and the concentrations of DEP, BBP, and DBP in the gonads of sea urchins did not confirm the attribution of microplastics to the PAE contamination of the sea urchins themselves, although a correlation between the microfibers and DEHP was highlighted. This indicates that the contamination of sea urchins by PAEs may be affected by the concentration of PAE congeners in the marine environment, which in turn may be differentially transported by microplastics [136]. Similarly, no significant correlation was highlighted between microplastics and PAE contamination in ascidians. Nonetheless, the authors referred that this result may be misrepresentative, as it is derived from the visual detection method used to count microplastics, which is known to underestimate their number in samples [140]. Overall, the complex interaction between microplastics and PAEs in marine biota still requires exploration of many factors that may be involved, and therefore more research is needed before PAEs can be considered as markers of the exposure of marine biota to microplastics.

4. Conclusions

In the present review, we stressed the concept that PAEs are ubiquitous pollutants of the Mediterranean basin, as proven by the contamination of the coastal ecosystems of southern France, Eastern Spain, Italy, and North Africa. This statement is clearly supported by the reliable study of abiotic and biotic marine matrices analyzed by validated and QC/QA-controlled analytical workflows. In fact, over the last few decades, there has been considerable focus on PAE extraction and analysis techniques to improve the determination of such contaminants at very low levels in a variety of liquid and solid matrices (i.e., seawater, sediments, and biota), while embracing the principles of green chemistry. In this respect, common techniques of extraction (e.g., LLE, SLE, SPE, ASE, USAE, QuEChERS,

etc.) and analysis (e.g., GC or LC coupled to a MS detector used in single, tandem, or hybrid MS configurations) have been made increasingly environmentally friendly by reducing the required amount of sample, solvent, analysis time, etc. Overall, the best strategy of extraction and analysis, as well as their best combination, should be chosen by primarily studying the characteristics of the matrix and the physicochemical properties of the target PAEs as well.

The literature reviewed over the last 20 years showed that a few studies have determined the occurrence of PAEs in seawater and marine sediments, while a greater effort has been devoted to studying PAEs in marine biota. PAEs such as, DEP, DBP, DIBP, BBP, and DEHP, were the plasticizers that came under the scientific magnifying glass, since they are strictly regulated in their manufacture and placing on the market according to Regulation (EC) No.1907/2006. Among them, DBP, DIBP, and DEHP were generally characterized by the highest detection frequencies and concentrations in both abiotic and biotic matrices, most likely because they are still the most used plasticizers in the manufacture of soft PVC and rubber and, hence, all their derived items. Considering the abiotic compartment of coastal ecosystem (i.e., seawater and sediments) sites in the proximity of WWTPs, river mouths, maritime ports, industrial zones, and touristic areas represented hotspots of PAE pollution allowed to outline a geographical distribution of such contaminants. Similarly, a seasonal trend of PAEs could be defined, as higher pollution levels coincided with the summer season or, in any case, with the periods when anthropogenic activities were most intense, although weather conditions also play a role in such distribution. However, distribution patterns may be considerably affected by many dynamic, complex, and often interacting variables: on the one hand, oceanographic processes related to the nearby Atlantic Ocean, marine currents, rainfall, runoff, and atmospheric deposition may exert a diluting or concentrating effect on PAEs in specific areas rather than others; on the other, physicochemical and biological processes, such as hydrolysis, photolysis, photooxidation, and prokaryotic degradation, may cause the degradation of PAEs into specific metabolites. If not properly considered, all these factors may lead to misleading interpretations of the pollution pattern. The ubiquitous presence of PAEs in the abiotic compartment inevitably leads to the contamination of the marine biota. In the reviewed studies, the PAE contamination of simple and complex marine species was investigated, even at tissue level, and the diverse organisms were suitable sentinels of PAE pollution. A special focus was devoted also to the distribution of plasticizers across the organisms of the marine food web. In this respect, the bioaccumulation process may cause the concentration of these pollutants as trophic level increases. However, other factors, including the feeding strategy, the living habits, and the metabolic characteristics of the marine species involved, may cause a kind of "trophic dilution", rather than a biomagnification, at higher levels of the web.

Finally, conflicting opinions exist on the potential use of PAEs as indicators of microplastic pollution in seawater, sediments, and biota. Although a correlation between microplastic abundance and PAEs may exist, since microplastics themselves are a PAE source, there is no scientific evidence that PAEs positively correlate with microplastics, and this is the main reason why they cannot be considered as reliable tracers of microplastic pollution. The lack of a bidirectional relationship is due to (a) the complex interaction between microplastics and PAEs and (b) the character of PAEs as "stand-alone" environmental pollutants. In fact, on the one hand, the interaction between the microplastics and PAEs in each marine compartment was highly complex and affected by many factors (e.g., the type of microplastic, the physicochemical properties of PAEs and their degradation pathways, the physicochemical properties of the surrounding environment, the presence of co-pollutants [i.e., PAHs and heavy metals], the type of tissue and metabolism of the living organism, etc.) which may undermine the role of PAEs as tracers of microplastics; on the other hand, PAEs are toxicants not necessarily related to plastic fragments because they may contaminate the marine environment from a variety of non-plastic products, as well as wastewater and industrial discharges.

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