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Review

Analytical Chemistry: Tasks, Resolutions and Future Standpoints of the Quantitative Analyses of Environmental Complex Sample Matrices

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Abstract: Nowadays, the challenges that analytical chemistry has to face are ever greater and more complex both from the point of view of the selectivity of the analytical methods and of the sensitivity. This is especially true in quantitative analysis, where various methods must include the development and validation of new materials, strategies and procedures to meet the growing need for rapid, sensitive, selective and green methods. In this context, given the International Guidelines, which, over time, are updated and which set up increasingly stringent "limits", constant innovation is required both in the pre-treatment procedures and in the instrumental configurations to obtain reliable, accurate and reproducible information. In addition, the environmental field certainly represents the greatest challenge as analytes are often present at trace and ultra-trace levels. These samples containing analytes at ultra-low concentration levels, therefore, require very labour intensive sample preparation procedures and involve the high consumption of organic solvents that may not be considered as "green". In the literature, in recent years, there has been a strong development of increasingly high performing sample preparation techniques, often "solvent free", as well as the development of hyphenated instrumental configurations that allow reaching previously unimaginable levels of sensitivity. This review aims to provide an update of the most recent developments currently in use in sample pre-treatment and instrument configurations in the environmental field, also evaluating the role and future developments of Analytical Chemistry in light of upcoming challenges and new goals yet to be achieved.

Keywords: environmental analysis; instrument configurations; extraction procedures; environmental applications

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1. Introduction

In recent years, the increase in production activities in all industrial sectors has led to an increase in the production and consumption of xenobiotic compounds [1]. Specifically, their extensive use has led to the pollution of the environment as a major consequence [2], a fact that represents a direct threat to human health. In this perspective, the Stockholm Convention aims to protect human health and the environment from all those activities that produce (and often release in an illegal and/or uncontrolled way) persistent organic pollutants (POPs), defined based on four criteria: persistence for a long time, toxicity, bioaccumulation and wide geographical distribution [3].

Along with POPs, another major problem has recently emerged, linked to the widespread use of plastic products. The presence of plastic particles in various environmental compartments (water, soil and air) [4], even of micrometric dimensions (microplastics, MP, with dimensions <1-5 mm) as part of industrial or domestic products (scrub, peelings, toothpastes, make-up), and other products deriving from degradation/fragmentation (secondary microplastics) has reached such a level that considerable concentrations of these compounds have been found even in remote places such as Antarctica [5], the Arctic [6] or the deep ocean [7].

This large diffusion is essentially attributable to the fact that the smaller the particle size, the more these particles spread in the environment [8]. Another fundamental problem related to these MPs is that they are able to retain chemical substances on the surface, especially persistent organic contaminants such as polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), organochloride pesticides (OCPs), and polybrominated diphenyl ethers (PBDE) [9-11]. These MPs, therefore, act as a sort of pre-concentrators and modify their interactions and their toxicity in living organisms [12, 13].

Among the previous classes, PAHs have been well known for some time and have been reported for decades as the main harmful compounds. Since the 1970s, a list of priority pollutants has been drawn up, leading to the identification of 16 PAH Priority Pollutants by the U.S. EPA [14]. This list does not take into account non-polar high molecular weight (HMW) PAHs, alkylated PAHs or polar polycyclic aromatic compounds (PACs) [15]. In the category of polar PACs, is mandatory to consider nitrate PAHs (NPAH) and oxygenated PAHs (OPAH), which, currently, are the most studied [16-18] as their formation can result from reactions between "parent" PAHs and oxidizing agents in the environment. In addition to NPAHs and OPAHs, other polar PACs such as azaarenes (AZA, also referred to as polycyclic aromatic nitrogen heterocycles PANH) and polycyclic aromatic sulfur heterocycles (PASH) should also be considered. These compounds, although similar to PAH, NPAH and OPAH in terms of sources and toxicology [19-21], are mainly related to petrogenic emissions [22, 23]. It should be emphasized that all the compounds reported are being studied by IARC (International Agency for Research on Cancer) and some of them have been classified as possible or probable carcinogens [24]. Regarding this category of pollutants, the very complete review paper by Galmiche *et al* [25] appears to be very interesting.

Heavy metals also deserve particular attention which, as widely reported in the literature [26, 27], not only represent an environmental problem for their presence in soils, superficial, deep, and sea waters, but also food (and food supplements and herbal medicines), especially related to the fact that many of them do not provide for maximum legal limits and/or are not considered as elements to be monitored and quantified.

As reported by McGregor and Zhao [28] trichlorethylene (TCE), cis-1,2-dichloroethene (cis-1,2-DCE) and vinyl chloride together with per - and polyfluoroalkyl substances (PFAS) have recently been identified as a substance of concern in groundwater. Many of these compounds have also been confirmed as carcinogens or suspected carcinogens and therefore of interest at the level of environmental monitoring. Although there is a variety of technologies for the treatment of chlorinated

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ethenes, technologies for treating PFAS in groundwater are not widespread and / or developed.

In particular, the Per- and Polyfluorinated Alkyl Substances (PFAS) are a group of highly stable and degradation-resistant anthropogenic chemicals. These are produced and used in many consumer and industrial products (e.g. food packaging, fire fighting foams and textiles) due to their heat resistant and water repellent properties. PFAS compounds are persistent, toxic and potentially harmful to humans and the leaching and presence of PFAS in our environment have raised serious concerns on a global scale. Exposure to PFAS through drinking water was investigated, leading the European Parliament in December 2020 to adopt the revised Drinking Water Directive (DWD), effective from January 12, 2021, including the "total PFAS" parameter (all per- and polyfluoroalkyl substances with a maximum concentration of 0.5 μg/L).

Regarding their analysis, an application note from Shimadzu is very interesting which provides Direct Injection Analysis of Organofluorine Compounds (PFAS) by Triple-Quadrupole LC-MS/MS [29] although to date the panorama of pre-treatment procedures is still very limited and not very widespread. With regard to this aspect, the recent review by Winchell and collaborators [30] which highlights how much has been developed for the analysis of these analytes and how much still remains to be done , not only at the monitoring level, but also at the level of removal processes. This point highlight that their analysis is very difficult as their advisory limits are in sub ppb to sub ppt levels, showing the emerging challenges to analytical chemists.

In light of what have seen so far and what is reported in **Figure 1**, is clearly highlighted the massive problem inherent in the environmental monitoring of molecules that are harmful (or potentially harmful) both for the environment but also for the life of all organisms.

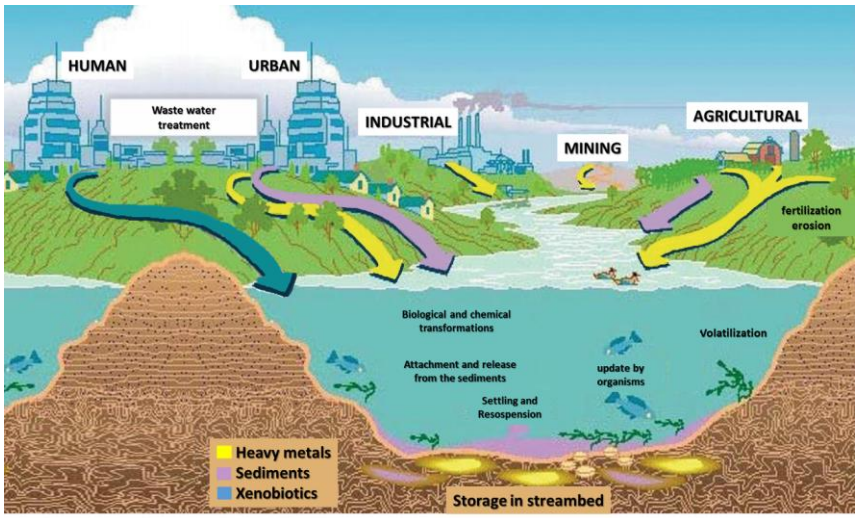

Figure 1. Connections and sources of xenobiotics that pour into the environment as result of human activities.

All these characteristics have been recently reviewed in the literature [31, 32], highlighting the great area of interest for Analytical Chemistry and the challenges that await this discipline in the near future. In this scenario, the main role of the Scientists is to check, follow, and resolve the negative impacts of chemical and biological pollutants on people's health to protect the clean drinking water supply, thereby managing their ef-

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fects on the ecosystems and environment. It should be noted that in recent years different factors have been taken into consideration in the development of new instrumental configurations and/or new analysis procedures, in particular the possibility of performing miniaturized measurements using low-priced and portable sensors for monitoring biological and chemical pollutants in environmental samples, ease of use, low environmental impact (fundamental concept of Green Analytical Chemistry).

The purpose of this review, as a sort of second "act" of a previously published review [33, 34], is to highlight the recent applications developed in the environmental field and aimed at the xenobiotics, POPs, pesticides, heavy metals and other pollutants monitoring, and how these can have positive repercussions on future applications, both from the point of view of pretreatment procedures and instrument configurations (also portable devices).

2. Pre-treatment Procedures

The step following the sampling and relative to the treatment of the sample in order to make it suitable for the instrumental analysis represents a crucial point in practically all analytical methods, especially if the concentration of the analytes of interest is extremely low. Another critical element is represented by the presence of interfering substances often present at high concentrations that can lead to matrix effects and problems related to the correct identification and quantification of the analytes [35]. For an accurate (precise and true) and sensitive determination of the elements present at the level of traces and ultra-traces, a pre-concentration phase is normally required before their detection using different instrumental techniques [36]. In this phase, in addition to having an enormous waste of time, there is the risk of obtaining not only an increase in the analyte signal, but also if the sample treatment procedure is not carried out correctly, an increase in interferents may be encountered with consequent problems in the instrumental analysis phase.

Another very important component in this phase is represented by the use of solvents of various type, especially organic, which can present toxicity and high volatility when used in the classic liquid-liquid extraction (LLE) or solid phase extraction (SPE) techniques for preconcentration of trace elements prior to total or speciation analysis. Modern analytical methods are increasingly focused on the development of simple, fast, sensitive and environmentally friendly practices that follow the principles of Green Chemistry (e.g. replacement of toxic reagents, miniaturization and automation, development of solvent free procedures) [37].

The development of innovative procedures and materials reflect the actual trend in sample preparation field for analytical applications. Specifically, nowadays, the application of nanomaterials has also represented a valuable tool for sample preparation methods, especially in SPE, leading to many advantages especially with regard to their high surface-volume ratio, chemical stability and the possibility of functionalization of the samples surface in order to increase selectivity [38]. In this scenario, certainly, the development of new materials, also based on the molecularly imprinted polymer concept, allow obtaining high performances in terms of sample clean up and interferences removal. Coupled to these materials, often based on polymer technologies, the implementation of alternative solvents supported on solid nanomaterials can be considered a further interesting approach (and development) to provide a high surface area by increasing their extraction efficiency [39], with a reduction in solvents/sample volume consumption.

Recently, Oviedo *et al* [40] report an exhaustive and complete overview of the preconcentration and determination of trace elements using alternative solvent systems such as ionic liquids (IL), surfactants, deep eutectic solvent (DES), as well as their combinations with new nanomaterials, summarizing and underlining the progress observed from 2017 to date in the extraction and clean up procedures with the use of these green solvents.

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In **Table 1** were reported the different and more recent developments related to the extraction methods.

Table 1. Most key developments on extraction methods.

Matrix	Analyte/S	Material	Phase System/fields/technique	Sensitivity (in terms of LOD)	Ref.
Environmental	Pollutants	Engineered enzyme-conjugated materials	Dehalogenating enzymes	Lower than 2 ppt	[32]
Water	Metals	ILs	DLLME	10 - 4.0 x 10^{-4} ppb	
Water	Metals	Surfactants	CPE	0.5 - 1.1 x 10^{-3} ppb	
Water	Metals	DESs	DLLME/LLME	2.9 – 0.12 ppb	
Water	Metals	Nanomaterials combined with alternative solvent system	MSPE/D-µ-SPE	0.11 – 1.1 x 10^{-3} ppb	[40]
Water	Pesticides	Graphene based nanosorbents	MSPE/SPE/DSPE	-	
Water	Fungicides	Graphene based nanosorbents	MSPE/SPE/DSPE	-	
Water	Herbicides	Graphene based nanosorbents	MSPE/SPE/DSPE	-	
Environmental	Pesticides	Carbon nanomaterials	Enzyme based Antibody based Aptamer based MIPs based General	99 – 2.5 x 10^{-5} ppb 8 ppb 1.1 – 4.0 x 10^{-5} ppb 470 - 4.2 x 10^{-3} ppb 905 – 6.5 x 10^{-4} ppb	[41]
Water	Glimepiride	LAY-FOMM 60	SPE sorbent 3D printed	-	[42]
Water	As, Se	BV-007 resin and TiO2 NPs	Column holders 3D printed	-	[43]
Water	Fe	Clear photoactive resin	Disk-based SPE 3D printed	-	[44]
Groundwater and leachate	14 trace metals	Clear photoactive resin	Extraction disks 3D printed	1.3 – 0.03 ppb	[45]
Water	Organophosphate pesticides 4-*n*-nonylphenol 4-*Tert*-octylphenol Bisphenol A Phenol	ILs	[C4MIm][NTf2]	5–16 x 10^{-3} ppb	[46]
Water	4-*n*-nonylphenol 4-*Tert*-octylphenol Bisphenol A Phenol	ILs	DDAC	3 x 10^{3} ppb	[47]
Water	Metals	ILs	$[OPy]^+[BF4]^-$	0.1 ppb	[48]
Wastewater	Fluoxetine and Citalopram	MSPE	Fe_3O_4 @PPy-GO	1.6 ppb	[49]
Water	Pirimicarb and Fenitrothion	FPSE	PCL-PDMS-PCL	3 ppb	[50]
Water	Propoxur and Fenitrothion	MSPE	Decanoic Acid Modified	1.4 ppb	[51]
Water	4-Cyanophenol and 3-Nitrophenol	SPE	MWCN	0.1 µg	[52]
Soil	Epoxiconazole, Fluroxypyr Metribuzin Oxyfluorfen	ILs	(VBHDIM-NTf^2) [ViC_{10}OHIM][Nf^2T])	0.4 ppb	[53]

CPE: cloud point extraction; DES: deep eutectic solvents; DLLME: dispersive liquid-liquid micro extraction; DSPE: dispersive solid phase extraction; FPSE: fabric phase sorptive extraction; ILs: ionic liquids; LLME: liquid-liquid microextraction; MSPE: magnetic solid phase extraction; MWCN: multi-walled carbon nanotubes; SPE: solid phase extraction; SPME: solid phase micro extraction;

As indicated in **Table 1**, it is noted that recent literature and scientific research is directed above all towards pre-treatment systems based on techniques that exploit the interaction between membranes or chemically functionalized particles in order to maximize the selectivity of the method, while still few are the applications that resort to liquid phases with green solvents (ionic liquids) [40, 46-48, 53].

It should be emphasized that among the membrane-based techniques, FPSE has recently proved to be a very promising technique as it allows not only the pre-treatment of the sample, but also its conservation for subsequent confirmatory analyzes. This technique is also very promising as it has shown to have analytical performances that allow the analysis with dated, robust and well-known instrumental configurations (HPLC-PDA) of xenobiotic traces in complex matrix, obtaining quantification limits comparable with well-known configurations respect to more complex and expensive and requiring trained personnel (for example LC interfaced with mass spectrometry).

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These techniques are also easy to perform since once the membrane has been activated it is sufficient to proceed, after optimization of the main parameters (sample volume, extraction and back-extraction time, solvent and back-extraction volume), with sampling and the subsequent instrumental analysis, as highlighted in the literature [54, 55].

Currently, only techniques based on solvents and / or functionalized particles have been applied for the analysis of heavy metals, opening spaces for research in the field of membranes capable of selectively adsorbing these analytes for environmental applications.

3. Instrument Configurations and new materials

Concurrently with the development of new sample treatment procedures, new materials and new solvent systems presented above, there has also been the development of new instrumental configurations and new techniques for quantitative measurements. These elements, often combined in order to minimize the manipulation of the original sample (to minimize errors and analyte losses), have recently improved with the development of new carbon-based nanomaterials such as diamond, graphene, amorphous carbon, C60 fullerene, carbon nanotubes, carbon dots (CD) and materials for organic structures that allowed the simultaneous extraction of the analyte and its fluorimetric detection [56-60]. Such systems could directly or indirectly recognize target analytes by generating fluorescence signals (FRET, IFE, electron transfer mechanism) [61-63] in a single system and simultaneously. At present, however, the structural integrity, chemical/thermal stability and surface microenvironment of carbon nanomaterials) which greatly influence their practical applications and signal intensity still need to be "resolved" and/or standardized in order to have maximum reproducibility of the procedure.

It should be emphasized that in addition to carbon nanomaterials, also other materials for fluorescence (e.g. quantum dots of semiconductors, metallic nanoclusters and luminescent materials of higher conversion) have seen wide application in the analysis of pesticides through integration with recognition units in the benchtop or portable configuration [64, 65] that exploit the use of new sensors [41]. Metal-organic frameworks are a versatile and remarkable class of crystalline functional materials with many unique features and huge potential for numerous applications. There are four main categories of luminescent MOFs: lanthanide-based MOFs, transition metal-based MOFs, heterometalorganic frameworks, and main group metal-organic frameworks. In the field of environmental pollutant analysis, LMOFs have shown their potential as suitable candidates for detecting temperature, pH, nitroaromatic explosives, small molecules, metallic cations, as well as the inorganic anion.

Currently in this scenario, luminescent metal-organic structures (LMOFs) represent an important sub-category of MOF in which photon emission occurs following absorption of radiative excitation energy with great potential for practical applications [66, 67]. In fact, LMOFs have proven to be a unique basis for chemical detection thanks to their characteristics of size, shape, chemical composition, and surface specifications of the pores, which can be finely controlled [68, 69]. These elements are reflected in the fact that porosity allows the adsorption of molecules and increases interactions, preconcentrate the target molecule [69, 70], and consequently an increase in sensitivity is observed.

The possibility of monitoring the level of environmental pollution in real time using selective and sensitive techniques is today the main objective, in the light of a growing introduction of polluting compounds due to anthropogenic activity. There are indeed a large number of organic pollutants and metal ions in water and soil, and there are many volatile organic chemicals in the atmosphere, which pose a serious threat not only to the environment but also especially to human health. Many organic molecules show high toxicity values and are able to influence physiological and pathophysiological functions [71, 72] to such an extent that their rapid and sensitive detection is of great importance.

At present, the main pollutant detection methods include ultraviolet (UV) spectrophotometry techniques and methods [73], high performance liquid chromatography

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(HPLC) [74] coupled with various types of detectors (especially mass spectrometry , MS), Fourier Transform Infrared Spectroscopy (FTIR) [75], Near Infrared Spectroscopy (NIR) [76], and Surface Enhanced Raman Spectroscopy (SERS) [77]. All the configurations indicated show high sensitivity and accuracy, but often the high purchase/maintenance cost and the lack of the "portability" feature limit their practical application.

Surely the optical detection method, thanks to its high sensitivity, portability, short response times and low cost, represents the most used configuration in the field of environmental pollutants detection, especially through procedures to increase the luminescence ("ignition"), switch off the luminescence ("switching off") and measurement of the luminescence ratio [69, 78].

With regard to the development of new devices, nowadays Analytical Chemistry increasingly uses three-dimensional (3D) printing [79], especially for the production of microfluidic systems, electrochemical sensors and biosensors, as well as the production of instruments applications in the field of separation sciences, sample pretreatment, wearable sensors [80, 81]. Compared to traditional techniques, microfluidic techniques have many advantages, including the low cost and small footprint that allow their portability and a high analysis speed, in addition to a reduced consumption of sample and solvents and the integration of the various components [82, 83].

Regarding microfluidic systems, the application proposed by Li *et al.* is very interesting. Using a system in a Y-shaped configuration with colorimetric detection, they determined the content of iron in the water [84] or nitrates in the soil [85]. Mattio *et al.* developed a similar device, in 3D using poly (methyl methacrylate) (PMMA), improving the portability, simplicity and low cost determination of lead in natural waters [86]. SLA 3D printing has also been employed for the construction of the fourth generation microflow injection analysis system for metal and glucose trace detection in complex samples and other applications [87], while Fornells *et al.* exploited different materials integrated on a 3D printed microfluidic device for the detection of ammonium in ambient water samples [88].

In **Table 2** were reported the different and key developments on instrument configurations applied in environmental analyses.

Table 2. List of key developments on instrument configurations.

Matrix	Analyte/S	Instrument Configuration	Sensitivity	Ref.
Water	Organophosphate pesticides	GC-MS	5–16 x 10^{-3} ppb	[46]
Water	4-n-nonylphenol 4-Tert-octylphenol Bisphenol A Phenol	UV/Vis spectroscopy	3 x 10^{3} ppb	[47]
Water	Metals	ICP-MS or AFS	0.1 ppb	[48]
Wastewater	Fluoxetine and Citalopram	HPLC-PDA	1.6 ppb	[49]
Water	Pirimicarb and Fenitrothion	HPLC-PDA	3 ppb	[50]
Water	Propoxur and Fenitrothion	HPLC-PDA	1.4 ppb	[51]
Water	4-Cyanophenol and 3-Nitrophenol	CE	0.1 µg	[52]
Soil	Epoxiconazole, Fluroxypyr Metribuzin Oxyfluorfen	GC-MS	0.4 ppb	[53]
Water	Metformin	CE	10^{4} ppb	[88]
Water	Heavy metals	Portable sensing - optical	0.5 ppb	[90]
Water	Heavy metals	Portable sensing - colorimetric	3 ppb	[91]
Water	Heavy metals	Portable sensing - electrochemical	0.15 ppb	[92]
Water	Heavy metals	SWASV	0.0096 µM	[93]
River water	Methyl parathion	DPV	0.015 µM	[94]
Water	Nitrite	Amperometry	0.03 µM	[95]

AFS: atomic fluorescence spectrometry; CE: capillary electrophoresis; DPV: differential pulse voltammetry; GC-MS: gas-chromatography-mass spectrometry; HPLC-PDA: high performance liquid chromatography-photodiode array detector; ICP-MS: inductively coupled plasma mass spectrometry; SWASV: square wave anodic stripping voltammetry;

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In this panorama, it should also be highlighted how, in the environmental field, instrumental configurations are increasingly used that resort to electrochemical (bio) sensors based on carbon cloth and carbon paper, combining their characteristics of interesting features, highly efficient, versatile, and disposable designed for biomolecules, biomarkers, and hazardous and chemical compounds detection in environmental samples. The advantage of easy integration in miniaturized and portable devices, envisages their successful application in point-of-care diagnostics and *in-situ* measurements through the development of portable, space-saving and highly performing devices in terms of sensitivity and specificity [96, 97].

The improvement at the level of the analytical parameters related to the detection of various water pollutants in different ecosystems and/or remote locations is strongly correlated to the development of convenient, portable, simple, sensitive systems, easy to use even by untrained personnel. In this context, the possibility of coupling portable devices for measurement (based on sensors) with an efficient and easy-to-use platform such as a Smartphone, have opened a very important line of research for the development of configurations and procedures for in-situ analysis [98, 99] exploiting mobile applications and cameras with very good performance and light sensors, many fascinating biosensors were developed based on smartphones [100-105].

Regarding the techniques/processes based on (bio)sensors, fundamental points in their study and development are based on: *(i)* evaluating the different analytical signals that can be used for quantitative purposes by means of different electrochemical and optical sensors, *(ii)* developing different molecularly imprinted probes to increase the selectivity of the procedure, *(iii)* exploit the possibility of nanomaterials to be incorporated and used in portable sensors.

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4. Conclusions

In this article, only the most recent developments in the field of environmental analysis have been reported that have led to a rapid increase in the application potential of analytical techniques in this sector. It should be noted that many developments observed in a specific application field are however used as ideas for other sectors and this leads to a greater choice of procedures that can be applied to analytical problems that are often very "distant" from the original intent. Specifically, however, it can be observed that in recent years more and more attention is paid to all those techniques that allow a reduction of the impact of human activities on the environment, to the development of green procedures, of devices for *in-situ* analyzes.

As depicted in **Figure 1**, the close connection between the environment, human activity and health is even more evident. These are sectors that, even if at first glance they could be limited in their "boundaries", in reality involve strong reciprocal influences linked to the life cycle of the molecules and their degradation/metabolism processes. It can be fairly concluded that it is possible to apply, after appropriate verification of the analytical performance (and in the case a new validation process in the new matrix), methods created for different purposes. If we combine this element with the continuous interest in green and high throughput procedures, we can understand how Analytical Chemistry plays a predominant role in all fields where chemical processes are involved.

Eliminato: Metal-organic frameworks are a versatile and remarkable class of crystalline functional materials with many unique features and huge potential for numerous applications. There are four main categories of luminescent MOFs: lanthanide-based MOFs, transition metal-based MOFs, heterometalorganic frameworks, and main group metal-organic frameworks. In the field of environmental pollutant analysis, LMOFs have shown their potential as suitable candidates for detecting temperature, pH, nitroaromatic explosives, small molecules, metallic cations, as well as the inorganic anion.¶

Eliminato: ¶

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