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Recent achievements of greenness metrics on paper-based electrochemical (bio) sensors for environmental and clinical analysis

Habdias A. Silva-Neto [a], Lucas F. de Lima [b], Danielly S. Rocha [a], Vanessa N. Ataide [c], Gabriel N. Meloni [c], Giulia Moro [d], Ada Raucci [d], Stefano Cinti [d,e,f], Thiago R.L.C. Paixão [c,g], William R. de Araujo [b], Wendell K.T. Coltro [a,g,*]

[a] Instituto de Química, Universidade Federal de Goiás, Goiânia, GO, 74690-900, Brazil
[b] Departamento de Química Analítica, Instituto de Química, Universidade Estadual de Campinas, Campinas, SP, 13083-970, Brazil
[c] Departamento de Química Fundamental, Instituto de Química, Universidade de São Paulo, São Paulo, SP, 05508-000, Brazil
[d] Department of Pharmacy, University of Naples Federico II, 80131, Naples, Italy
[e] BAT Center- Interuniversity Center for Studies on Bioinspired Agro-Environmental Technology, University of Napoli Federico II, 80055, Naples, Italy
[f] Bioelectronics Task Force at University of Naples Federico II, Italy
[g] Instituto Nacional de Ciência e Tecnologia de Bioanalítica, Campinas, SP, 13084-971, Brazil

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ABSTRACT

This review proposes, for the first time, a recent overview of ecological information involving electrochemical paper-based analytical devices (ePADs) dedicated to sensing environmental and clinical situations. The options of manufacturing methods are screen printing, stencil printing, pencil drawing, laser scribing, inject-printing, and additive printing. We have covered ecological aspects such as resource efficiency, safety, and toxicity regarding using paper-based (bio) electrodes. To see the ecological impact of testing methods by using ePADs, the Analytical GREEnness (AGREE) approach was utilized as a greenness metric calculator model since the tool makes use of 12 principles of Green Analytical Chemistry. Positive and negative concepts from the revised values of AGREE metric of clinical and environmental analysis were introduced and discussed. Also, we finalize the present review informing the life cycle of ePAD and some challenges that can impact the next generation of disposable electrodes.

1. Introduction

In the last year, the global market involving analytical instrumentation was estimated to be ca. USD 53.42 billion, and it is expected that this field increases by an annual growth rate of ~3.53% by 2030 [1]. Some day-to-day services very common in the chemistry field justify the above-mentioned positive market indexes as separation, purification, identification, and quantification of organic, inorganic, and artificial materials. Also, the manufacturing, sales, and distribution of laboratory tools and equipment such as standard reagents, day-to-day glass utensils, HPLC-MS, ICP-MS, spectrophotometer, ELISA reader, electrochemical detectors, and so on [1–5].

Another key point to mention is that the analytical tools and testing methods need to be also sustainable in terms of materials and energy consumption to keep a circular economy active. It is possible to see role examples of initiatives that have impacted the eco-friendly profile of analytical chemistry positively [6–8]. Some efforts include the development of flow injection analysis, purge-and-trap approaches, micro total analysis system, microextraction system, and portable analytical devices, for example. These strategies have drastically reduced the consumption of samples, reagents, energy, and analysis time. In addition, the combinative use of sampling and analytical tools has also generated minimal quantities of waste [6].

The above-mentioned trends have started the concept of Green Analytical Chemistry (GAC) and its concern has emerged as one pivotal way to keep popular analytical instrumentation [9–11]. Nowadays, the GAC concept has 12 important principles that think about from ecological and safety to economic aspects to the use of analytical methodologies [6,12]. There is also the utilization of the term White Analytical Chemistry (WAC) that has been employed as an extension of GAC [7]. WAC makes use of ecological aspects like CAG, however, in association with its functionality such as the scope of application and

* Corresponding author. Instituto de Química, Universidade Federal de Goiás, Campus Samambaia, 74690-900, Goiânia, GO, Brazil.
E-mail address: wendell@ufg.br (W.K.T. Coltro).

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cost-efficiency, for example. Some reports have introduced specific models of metric software (e.g., NEMI, Analytical Eco-Scale, GAPI, Hexagon and AGREE) [12–14]. These examples have explored the key concerns of GAC's to measure how eco-friendly is one analytical platform and its testing methods, and the desired achievements can be represented as an ecological score by using colored pictograms in some cases.

From that perspective, one suitable example of analytical instrumentation that has been demonstrated to be a thankful option of the green tool refers to paper-based sensors [15–17]. That device makes cover two important analytical trends as ASSURED criteria (affordable, sensitive, specific, user-friendly, rapid, robust, equipment-free, and deliverable to end-users) and suitability for using in the point-of-care testing (POCT) [18,19]. Its protagonist can also be explained due to its association with portable analytical detectors, including distance-based, colorimetric, and electrochemical readouts [20–22]. If there is a need to find analytical responses with more selectivity and sensitivity, the models of electronic detectors are preferable, and these devices are called paper-based electrochemical sensors (PES) or electrochemical paper-based analytical devices (ePADs) [23–25]. A milestone associated with the above-informed fields is illustrated in Fig. 1A.

Another suitable aspect of the sensing mentioned above materials is the possibility to anchor distinct biostructures such as enzymes, antigens, aptamers, and mimicking materials to create (bio)sensors [25, 26]. Examples of applications using ePADs for forensics, pharmaceutical, food, environmental, and clinical studies have been successfully reported [27]. However, the literature has presented minimal or unknown information demonstrating how much greenness is those electrodes when used for sensing applications. In the last four years, it is possible to observe that the GAC, greenness metrics, and ePADs have demonstrated appreciable progress (Fig. 1B–C), and introducing initiatives to popularize the ecological profile of disposable electrodes can be positive.

The next section of this review will introduce and discuss green contributions involving the use of paper-based (bio) electrodes reported in the past four years. The main strategies used for constructing those sensors as well as their safety, toxicity, and life cycle will be presented. Through the AGREE approach, the ecological achievements associated with using ePADs for environmental and clinical applications will be covered as sensing target fields. Lastly, future challenges involving the use of paper-based devices and their greenness metrics will be also discussed.

2. Resource efficiency of paper-based electrodes

Disposable (bio)electrodes can be fabricated through different

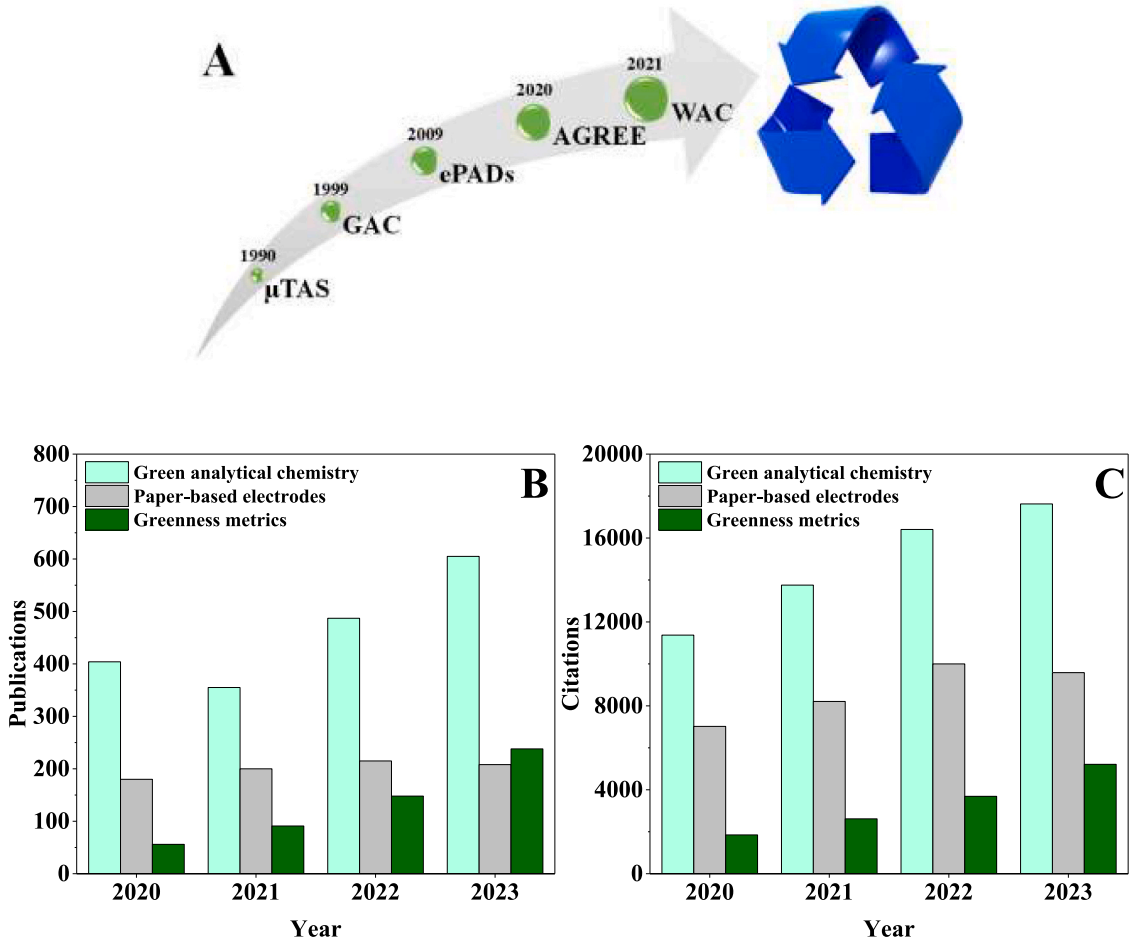

Fig. 1. (A) Some milestones of paper-based electrodes, green analytical chemistry (GAC) and AGREE tool. Micro total analysis system (µTAS). (B) Number of scientific documents per year searching the keywords "GAC*" (blue bars), "paper-based electrodes*" (grey bars) and "greenness metrics*" (green bars) and (C) the number of citations utilizing the above-mentioned criteria. The database selected was the Web of Science® core collection from 2020 to 2023.

strategies, including screen printing, stencil printing, pencil drawing, laser scribing, inject-printing, and more recently, by using the additive printing method [28]. These distinct alternative manufacturing methods offer advantages that justify their increasing popularity, such as minimal consumption of consumables and energy saving. Sometimes, these emerging protocols do not employ toxic solvents, and the resulting electrochemical sensors may be designed and fabricated without sophisticated instrumentation requirements or outside cleanroom facilities. It is possible to see below some prospects from ePADs regarding morphology, resource efficiency, and ecology.

2.1. Screen-printing

Screen-printing is one of the most used approaches to manufacturing paper-based (bio)electrodes [29]. To obtain screen-printed electrodes, a few components are necessary: a substrate (in this case, paper-based substrates), conductive inks (generally carbon, silver, and gold-based), an insulator (it is usually a natural or synthetic polymer), an option of solvent (acetone and ethanol, e.g.) a mask (with the shape/size of the desired electrode to produce), a spatula (to diffuse the conductive ink through the mask) and an oven or UV-lamp (to cure the conductive inks).

The major strengths of screen-printing, or thick film technology, are represented by the limited cost, simplicity, and scalability. Even if the use of semi-automatic screen-printers (up to 50k USD) allows obtaining electrodes with a repeatability of 1–2%, the main drawback of this technique is characterized by the requirement of specific masks for all the electrodes that one needs to print, e.g., specific size and shape. However, this is a minor issue considering the cost of a mask is *ca.* 50–100 USD depending on the materials (e.g., polyester, mesh, stainless steel).

Although traditional screen-printing is often employed to create electrochemical sensors on plastic-based, alumina, and ceramic substrates, as confirmed by most of the commercially available screen-printed electrodes (Metrohm, Zensors, Micrux, OG, e.g.) the use of paper-based substrates has been highlighted [25]. Paper-based are generally of two types: high-adsorption and low-adsorption substrates [30] (Fig. 2). The former is characterized by chromatographic and filter papers, which have the advantages of storing reagents and blocking gross interferences, ideal for realizing reagent-free devices [31]. Instead, the low-adsorption cellulose-based substrates include office and waterproof papers: they are not the best choice to realize a reagent-free devices, but they have mechanical strength similar to plastic-based ones with a reduced cost of *ca.* 40% [32]. The selection of the appropriate paper-based substrate also affects the electrochemical cell and the modification of the working electrode (WE).

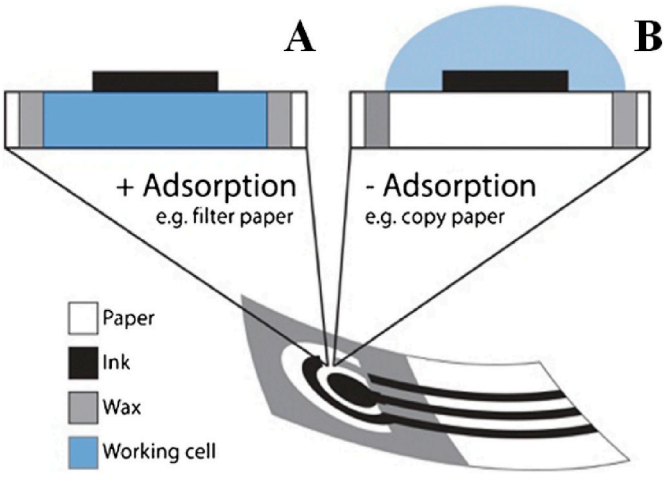

Fig. 2. Examples of electrochemical-paper based sensors developed on high-adsorption substrates (A) and low-adsorption ones (B). Reproduced with permission from Ref. [30].

In fact, if chromatographic paper is used to screen-print the electrodes, the resulting electrochemical cell is represented by the porosity itself of the paper, consequently the solution is not going to be in contact with the electrodes at the air interface, Fig. 2A. This implies the modification should be inside the ink, avoiding drop-casting. Instead, when office paper is used, the electrochemical cell is characterized by a drop of solution that is at the air interface. Thus, a drop-casting modification of the WE is effective, Fig. 2B. The efficacy of paper-based substrates depends on the possibility of merging these features: the porosity of chromatographic paper to obtain pre-concentration of the analyte and the mechanical stability of the office paper. This synergy has been applied to detect metals in complex matrices, e.g. mercury in drinking water, nickel in cosmetics, and copper in serum, and the combined effect of the different papers has brought to superior electrochemical platforms [30,33,34].

2.2. Stencil-printing

The stencil-printing approach has emerged from the screen-printing technology, and the manufacturing option has been popularized in the last few years, mainly in developing countries where resources are limited. Some aspects of the stencil approach can be explained by its usability, such as the simplicity of obtaining the stencil tools, easy to use of the machines, low energy consumption, and minimal waste generation. The necessary components for manufacturing the ePADs are similar to those informed in section 2.1 (screen-printing). However, one suitable option of stencil printers can be obtained for *ca.* 300 USD [35].

Stencil-printed electrodes on paper have manual handling steps such as preparing stencil kits and deposing conductive ink in the desired mold. In addition, the painting of reference electrode and delimitation of the detection cell using Ag ink and insulating options of polymers, respectively, are also required to obtain a stencil-printed electrochemical cell. The effective cost of stencil-printed electrodes ranges from 0.01 to 0.5 USD, and satisfactory prototypes with repeatability of ca. 10% have been reported [23,36,37].

Other key points in choosing the stencil-printing technique are scalability, fast time to obtain the device (5–30 min), and utilization of different options of conductive ink formulations [38]. Some manufacturing limitations can be also observed in some cases, such as the need to use masks and time to dry the desired ink. In addition, some production of residues can be polymers, acetone, ethanol, and carbon-based particles [28,39]. In terms of positive ecological aspects, different reports have explored suitable options for materials, including eco-friendly binders [40,41], biodegradable substrates [38,42] and recyclable materials [41,43].

2.3. Pencil-drawing

The pencil drawing technique can be considered the most inexpensive manufacturing protocol for constructing paper-based electrodes [28] due to the direct way of depositing graphite flakes onto desired porous paper by mechanical friction of pencil. It is worth mentioning that the pencil models grade 6B or higher can promote better results in terms of electrical resistivity (50–1000 Ω cm) [23,36]. This attractive protocol has enabled the creation of disposable sensors in different paper sheets, including office [44], chromatographic [45], vegetal [46], and sandpaper [47] materials. Some advantages inherent to the pencil-drawing method are an equipment-free, sub-minute time for manufacturing electrodes, and, most importantly, it does not require energy power and additional liquid materials such as polymers and solvents. Another ecological benefit is that there is no/or minimal waste generation [38]. However, some drawbacks are also observed in that approach, including direct dependence on the manual handling process, reduced large-scale production, and inferior reproducibility [28,47–49].

2.4. Laser-scribing graphene

The laser-scribed graphene (LSG) technique is a powerful tool for patterning in-situ 3D porous graphene electrodes on several polymeric substrates using a CO_2 or UV laser systems [50,51]. The convenience of this technique is mainly based on the use of polymeric materials that support the photo-thermal process of laser irradiation causing superficial graphitization and by simple optimization of the laser-scribing parameters, such as laser power, speed, focal distance (distance between the laser tip and substrate), and the number of lasing steps in an open and non-controlled environment [52,53].

It is well known that the electrochemical performance of carbonaceous materials is strongly dependent on structural defects, functional groups, and impurities or doping species present in the graphene-based material [54]. The presence of oxygenated functional groups on graphene derivatives like graphene oxide (GO) and reduced graphene oxide (rGO) can provide enhanced electroanalytical performance for the analysis of some surface-sensitive redox species [55] and active sites for (bio)molecule immobilization towards (bio)sensors development. These aspects are in line with the LSG method since the localized and controlled graphitization of the substrate is commonly performed without atmospheric control (noninert environment), maintaining oxidizing properties and thus, generating graphene-based nanomaterials rich in oxygenated functional groups and defects, which can produce devices with high electrocatalytic performance [53,56].

The first mention of the CO_2 laser-scribing method was reported by Kaner et al. to convert GO to graphene using CO_2 laser radiation [57]. Subsequently, Tour's research group reported the laser-induced 3D porous graphene by direct conversion of polyimide (PI) substrate, opening a new avenue to the development of LSG devices in nonconductive polymeric substrates [58]. Over the years, recent efforts have been carried out to manufacture LSG devices in a plethora of convenient platform materials, including synthetic polymers, wood, cloth, xylan, leaves, mushroom biomass, cork, food, biopolymers based on lignin and cellulose, phenolic resins, paper, among others, with a special interest in bio-based substrates as cellulose, *i.e.*, development of paper-based LSG devices (Fig. 3).

Kim et al. [61] reported, in 2014, the production of a hydrophobic and asymmetrically laser-scribed reduced GO paper electrode. For this purpose, the authors manufactured a graphene oxide paper (GOP) by vacuum filtration of GO suspension through an anodic aluminum oxide filter, followed by HI acid treatment and laser scribing of the GOP device. De Araujo et al. [56] developed the first LSG sensor on a paper-based substrate by direct and localized carbonization of the paperboard surface induced by CO_2 radiation, resulting in a highly porous 3D graphene nanomaterial with versatile electroanalytical applications in clinical, pharmaceutical, food, and forensic fields. Exploring the versatility of the LSG technique, Ataide et al. [62] described the use of laser scribing as a simple method to fabricate high-performance ePADs by CO_2 laser treatment of pencil-drawn office paper (A4) surface. The authors hand-drawn commercial graphite lead onto office paper and used the CO_2 laser radiation to treat/activate the

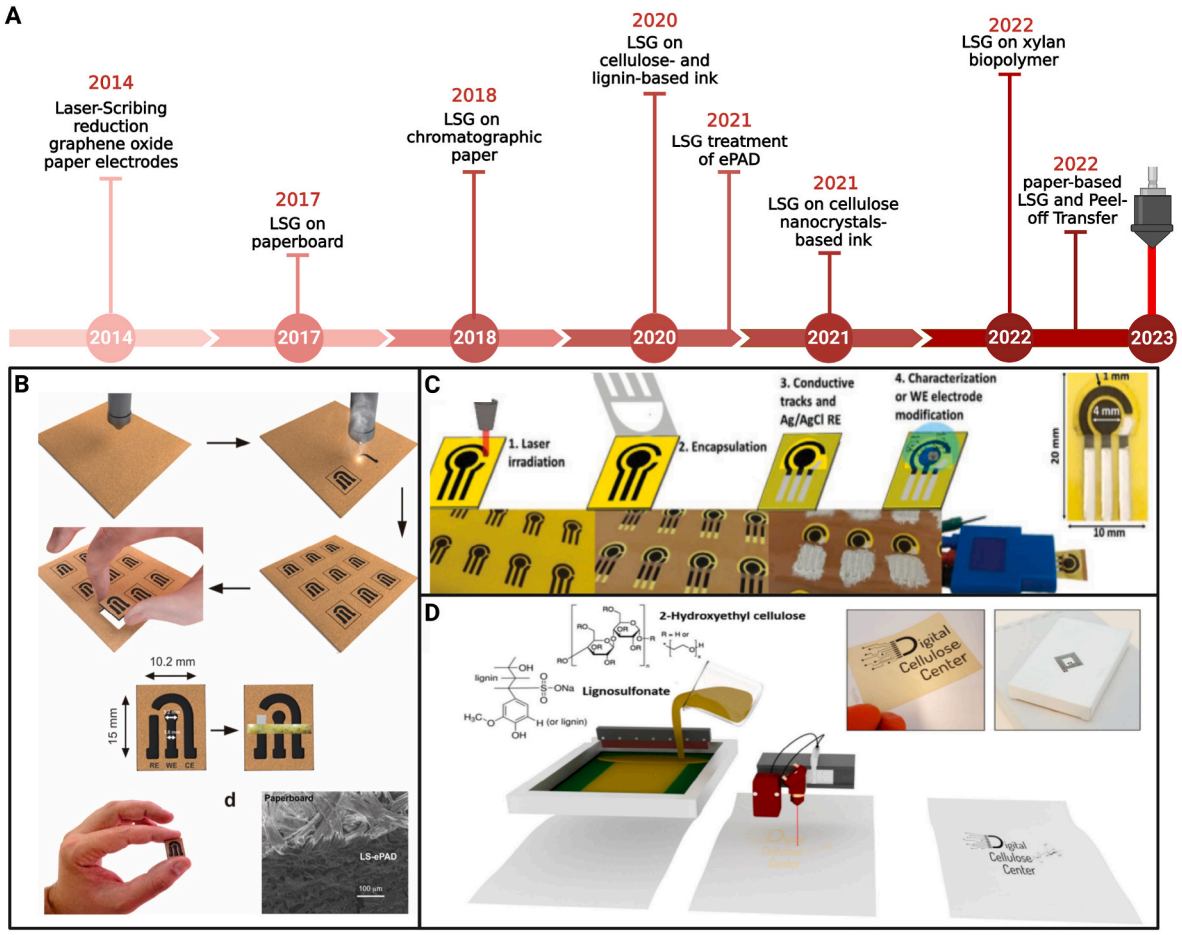

Fig. 3. (A) Timeline of progress in the fabrication of green LSG devices on novel precursor cellulosic-based substrate materials, with mentions of the first work reporting the laser-scribed graphene from GO nanomaterial to recent studies using the direct conversion of paper or cellulosic-based substrates to graphene derivatives electrodes. (B) Schematics of the LSG electrochemical sensor fabrication on paperboard and images of the device. (C) Electrochemical paper-based LSG sensor employing a chemical-treated chromatographic paper with a fire-retardant agent. (D) LSG on cellulose and lignin-based ink. Reproduced with permission from Refs. [56,59,60]. This figure was created in BioRender.com.

graphite layer and pattern the electrode layout. The proposed sensor presented an excellent analytical performance for the detection of furosemide drug in synthetic urine samples, obtaining a limit of detection (LOD) of 2.4 × 10^{-7} mol L^{-1}.

Instead of direct patterning LSG conductive tracks on paper substrates, Edberg et al. [60] developed an ink based on cellulose and lignin precursors and used it to screen-printing the bio-based material on flexible polyethylene terephthalate (PET) and cardboard (lignographic patterning). Following this, they used the laser-scribing technique to convert this carbon-rich precursor into a highly conductive graphite-like carbon. The cellulosic and lignin-based LSG presented a high degree of graphitization and lower sheet resistance of 3.8 Ω sq^{-1}, demonstrating great performance to be used as an electrical/electrochemical device. Similarly, Claro et al. [63] used a nanocellulose-based material to produce an LSG material and formulate a conductive ink. The carbon-based powder material produced by the LSG technique was mixed with a formulation containing carboxymethyl cellulose as a binder and was used to print electroconductive material onto a tracing paper substrate. Another interesting approach was described by Kulyk et al. [64], where they synthesized a produced paper-LSG on different types of filter papers and xylan biopolymer for potential applicability in the sensors field, reporting a material with reduced cost and low environmental impact.

To obtain adherent, stable, and reproducible conductive tracks on thin or porous paper-based substrates using the LSG technique, the treatment of the paper substrate using a flame-retardant species is a crucial step to enable the localized and superficial graphitization without the complete burning of the substrate. Using flame retardant as a treatment step improves the fiber resistance to heat caused by the laser engraving process, reducing their thermal degradation [65]. This behavior was noted in the studies reported by Pinheiro et al. [59] and Reynolds et al. [66], where they used paper substrate chemically treated with sodium tetraborate such as a fire-retardant agent to direct photoconversion of paper to 3D porous laser-scribed graphene. Also, other types of flame retardants can be used, such as halogens, phosphorous, metal hydroxides, carbonates, intumescent, and nanocomposites, among others [61,65]. For example, Pinheiro et al. [67] reported a chemically treated Whatman paper grade 1 with sodium tetraborate followed by a wax-printing step to make a skin-worn wearable electrochemical planar cell. The colored wax printing layer on paper substrates introduces aromatic chemical structures that boost the graphitization potential of paper, allowing the production of LSG structures with sheet resistances as low as 5 Ω sq^{-1}. They demonstrate multiple potential applications in wearable electronics using a simple transfer method based on a water-induced peel-off process to separate the patterned LSG structures from the paper substrate. Collectively, the use of the LSG technique on paper and cellulosic-based substrates enables the fabrication of sustainable ePADs for (bio)analytical applications using simple laser irradiation on thick or high grammage paper-based materials, like cardboard, or by previous treatment of cellulosic fibers with flame-retardant agents, which in general are non-toxic and non-hazardous species providing low-toxicity and greener devices.

2.5. Inkjet-printing

Inkjet printing is a non-template method widely used for the fabrication of flexible electronic devices, enabling the printing of several (nano)materials such as graphene, carbon nanotubes, nanoparticles, graphite, and conductive inks onto flexible substrates [68]. This non-contact, additive patterning and maskless technique enable the manufacturing of reproducible electrochemical devices with high resolution and using a low quantity of materials (typically microliter range), which contributes to reducing the impact of solvent and chemicals used in the ink formulation and thus, to greenness metrics of devices produced. However, it is important to note that inkjet printing usually requires several printed layers to generate devices with adequate electrical conductivity for electrochemical applications, which can compromise the device's resolution and manufacturing speed [23]. This fact occurs because the need to use liquid phase materials, commonly diluted inks. These commonly diluted inks lead to a low conductive material phase in the ink composition. The control of the rheological properties (surface tension and viscosity) of the ink used is imperative to better printability and avoid nozzle clogging [23]. There are two major types of inkjet printing methods reported in the literature, which can be divided into continuous inkjet (CIJ) and drop-on-demand (DOD) [69]. In the first case, an electric field generates a constant stream of conductive droplets onto a substrate. However, due to the continuous production of droplets, there is a need to deal with unused droplets generated. The second type (DOD) has this name due to the droplets generated only when required, which enables a more efficient method with minimal contamination generated in the process since recycling unused droplets is avoided. However, solvent evaporation, velocity, the volume of ejected droplets (depending on the viscosity of the ink), and pressure pulse, among others, may result in nozzle clogging, being a limitation of this method [69].

Kant et al. [70] reported an inkjet-printed paper-based electrode for glucose detection. For this purpose, the authors used an AuNP/starch suspension dispersed in organic solvent and printed onto Kodak photo paper, Whatman filter paper (n°1), and bond paper. The quantification of glucose was performed in the interval concentration ranging from 0.05 to 35.0 mmol L^{-1} using the cyclic voltammetry (CV) technique and resulted in a LOD of 10.0 μmol L^{-1}. Also, excellent analytical performance was obtained when the device was applied to the analysis of serum samples. Boonkaew et al. [71] presented a label-free electrochemical immunosensor for human Ferritin protein detection. For the ePAD manufacturing, a Whatman paper (n°1) was hydrophobized by a wax printing technique, followed by a three-electrode system fabricated by inkjet printing using graphene ink. The WE was modified with anti-Ferrin and bovine serum albumin (BSA) to detect Ferrin by differential pulse voltammetry (DPV) in an interval range from 1.0 × 10^{-9} to 1.0 × 10^{-6} g mL^{-1}, resulting in a LOD of 0.19 × 10^{-9} g mL^{-1} and presenting adequate performance when applied in human serum samples. Deroco et al. [72] developed an electrochemical sensor on Whatman paper (n°1) using silver ink for paraquat pesticide detection. The authors obtained a LOD of 0.80 μmol L^{-1} in an interval ranging from 3.0 to 100.0 μmol L^{-1} using the square wave voltammetry (SWV) technique and good performance of the sensor when applied to analyses of water, human serum, and orange juice spiked with paraquat. Pokpas et al. [73] used the inkjet method to manufacture an electrochemical sensor on photographic paper using graphene-coated silver nanoparticles (AgNP) ink for quantitative analysis of Ni^{2+} by square wave adsorptive cathodic stripping voltammetry (SWAdCSV). Also, the authors obtained a LOD of 32.19 × 10^{-6} g mL^{-1} in a concentration ranging from 50.0 × 10^{-6} to 500.0 × 10^{-6} g mL^{-1} Ni^{2+}. Lastly, Mohan et al. [74] reported an electrochemical sensor on Whatman paper (n°113) manufactured with carbon ink and modified with ZnO nanoparticles for picric acid detection by SWV. The authors obtained a LOD of 4.0 μmol L^{-1} in an interval ranging from 4.0 to 60.0 μmol L^{-1} and good performance when the device was tested in a spiked lake water sample.

2.6. Additive printing

Additive printing, more commonly referred to as 3D printing, is often used to fabricate paper-based devices. 3D printed parts are used as either structural parts that support the paper matrix, allowing efficient contact with the sensing electrode [75,76], or employed in the fabrication process to define the paper device geometry (hydrophobic barriers) [77–80]. Since some 3D printing technologies can print conductive materials [81], 3D printing technology has the potential to be used to fabricate complete paper-based devices, including mechanical parts and electrodes. Although this strategy has not been explored quite yet for paper-based devices, with 3D printing only used to assist in the fabrication of the electrodes by producing stencils for stencil-printing (*vide*

supra) [82], a clear parallel would be with the use of thermoplastic electrodes in paper-based microfluidic devices [83].

3D printed electrodes are also manufactured from a conductive thermoplastic layered into a precise shape, defining the electrode geometry, by the printer [84]. Significant advances in the fabrication of 3D printed electrodes have been seen in the past years, mainly focusing on improving the electrochemical response of the electrodes by changing printing parameters [85], or employing chemical treatments to the electrode surface [86–88]. Such treatments usually employ strongly alkaline media [89], or organic solvents [90], producing harmful waste which has to be properly disposed of. New alternatives have been developed which are more environmentally conscious, relying on less harmful chemicals. One such approach is using ascorbic acid or sodium borohydride, both reducing agents, for surface treatment [91]. In both cases, it was reported that a significant increase in the electrochemical performance of the printed electrodes with the sodium borohydride treatment presenting results comparable in performance to treatments with dimethylformamide. This represents a big milestone towards greener 3D-printed electrodes, as surface treatments are almost always used for analytical applications.

It is important to mention that 3D printing is a very energy-expensive technique, more so than subtractive manufacturing techniques if we compare the specific energy consumption and the energy used per mass of object produced [92]. The use of recycled materials can severely offset this energy cost, as has been done recently for the sustainable development of a circular electrochemistry economy [41,93]. 3D printing is still considered an environmentally friendly technique for electrode and paper-based device fabrication as it produces very little residue and can produce entire complex geometries, including functional and structural parts, in a single fabrication step. Bringing most fabrication procedures for an electrochemical paper-based device to a 3D printer could significantly reduce the environmental footprint of the device fabrication, by completing the entire device in a single and efficient fabrication process.

3. Environmental, health, and safety aspects of electrodes

In the era of microplastic pollution and electronic waste (e-waste), ePADs are considered valuable examples of sustainable, climate-neutral, and safe analytics. Paper substrates represent a green alternative to plastic ones that are difficult to degrade and, contribute to plastic pollution which harms animal and human health. The ePADs are mostly coupled with portable and miniaturized potentiostats, allowing limiting the usage of non-renewable resources, such as precious and valuable metals, and the growing of e-waste.

By enabling rapid, sensitive, and accurate measurements in organic-solvent-free conditions with low-energy instrumentation and minimal waste production, ePADs fulfill the 12 principles of White Analytical Chemistry, which considers not only the ecological impact (as for the GAC) but also its performance and easiness. Recent advances in treating lignocellulose biomasses, synthesizing sustainable nanomaterials, and manufacturing paper-based electrodes will contribute to making ePADs a net-zero technology, as discussed by Mishra et al. [94]. These gains are contributing to the large-scale production and commercialization of ePADs. Envisaging the massive use of ePADs, it is worth asking if the manufacturing, use, and disposal of ePADs have no environmental and safety impact. Not really, because the lack of government regulatory frameworks leaves unaddressed the sustainable and safe waste management of these devices.

Considering the approaches based on screen and stencil printing, it should be considered that the conductive inks can be made with organic solvents, polymers, and metals, for example. Even if several examples of low environmental footprint ePADs have been reported [95], their disposal is still an open challenge. Many ePADs, particularly POCT, have been designed to improve life quality, food safety, and environmental monitoring plans in low- and middle-income countries: finding new solutions for ePADs disposal is even more urgent if we consider that the massive use of these devices will be carried out in countries with poor waste management resources [96].

From this perspective, it is worth noting that the zero-waste treatment of paper-based materials is not technically feasible with the current technologies [97]. Despite these limitations, alternative ways to dispose of ePADs have been reported, ranging from reuse to biodegradation. For instance, Su et al. [98] have described how to recycle ePADs as substrates for developing hybrid supercapacitors with good energy density and excellent stability. Liu et al. [99] have reported a strain sensor to be applied as flexible electronic devices which can be easily degraded under rubbing in a wet state. So far, these alternative paths are limited to a few examples, but implementing ePADs waste management is instrumental in addressing these environmental, health, and safety issues.

Another important aspect is related to the use of modifiers, such as nanomaterials. In the last decade, the ground-breaking applications of nanomaterials as raised attention to their impact on the ecosystem, especially on living organisms. In general, the dispersion or detachment of nanomaterials for ePADs might result in harmful effects on the exposed subjects. Among nanomaterials, carbon-based ones (CBNs) are of paramount importance in ePADs. Their toxicity *in vivo* and *in vitro* was investigated showing that small-size CBNs can even pass through biological barriers with important consequences in terms of neurotoxicity as well as genotoxicity [100]. Although the use of paper-based electrodes represents a promising sustainable alternative to traditional plastic-based substrates, many aspects need still to be evaluated including the effect on health. For instance, the development of wearable devices represents a hot topic; however, a limited number of studies have yet to focus on the release of toxic species at the skin interface.

4. Analytical greenness metric

In recent years, some mathematical approaches have been introduced based on the GAC information, and special tools are employed to infer how ecological is one analytical procedure [13]. The principles of GAC are (1) direct analytical techniques should be applied to avoid sample treatment; (2) minimal sample size and a minimal number of samples are goals; (3) *in-situ* measurements should be performed; (4) integration of analytical processes and operations saves energy and reduces the use of reagents; (5) automated and miniaturized methods should be selected; (6) derivatization should be avoided; (7) generation of a large volume of analytical waste should be avoided, and proper management of analytical waste should be provided; (8) multianalyte or multiparameter methods are preferred versus methods using one analyte at a time; (9) the use of energy should be minimized; (10) reagents obtained from renewable source should be preferred; (11) toxic reagents should be eliminated or replaced and (12) the safety of the operator should be increased [6].

To make an ecological analysis more representative, the metric score needs to be interconnected with GAC trends, however, converting those principles into one green profile is not trivial way due multivariate and complex parameters [6]. It is important to emphasize that the use of this metric calculator is still unknown or scarcely explored by many research groups and, for this reason, its usability must be widely boosted in the literature to promote a worldwide popularization of greenness metric software, mainly in developing countries where the development of disposable and sustainable paper-based sensors has received noticeable attention. Two different greenness tools are considered pioneered and have been identified as (i) National Environmental Methods Index (NEMI) and (ii) Analytical Eco-Scale [11]. The approach (i) uses pictogram obtained from information associated with the used reagents and generated waste. (ii) There is a metric score based on penalty points involving the utilization of toxic reagents, waste, and consumable energy.

In another report, Pena-Pereira et al. [14] demonstrated a

free-available metric tool that can also be utilized infer the ecological impact of one analytical method, named as AGREE. Unlike the previously mentioned pioneering studies, the AGREE calculator uses all principles of GAC, which can increase its greenness sensitivity. The AGREE diagnostic is based on a circular pictogram with scores ranging from 0 to 1. Green, yellow, and red colors are also generated to inform visually the overall perspective of the desired methodology (Fig. 4). From GAC principles, the AGREE points are 1 sample treatment; 2 sample amount; 3 device positioning; 4 sample preparation stages; 5 automation and miniaturization; 6 derivatization; 7 waste; 8 analysis throughout; 9 energy consumption; 10 sources of reagents; 11 toxicity and 12 operator's safety [14].

As mentioned above, the resulting profile generated in the AGREE calculator is derived from an overall result associated to 12 inputs. For the sample pretreatment (principle 1), there are ten possible scores in the AGREE software. For example, if the sample treatment procedure uses a large number of steps, the obtained score is close to number zero, while remoting sensing without sample damage has a score of 1. To get a green color from principle 2, the type of analysis must consume a sample size $\leq$100 (μL or mg). Suitable results using principle 3 can be obtained by in-line or on-line measurements. However, sample analysis at-line and off-line have exhibited numerical scores 0.33 and 0.00, respectively.

The input 4 that is associated to integration of analytical procedure there is appreciable greenness responses when employed the desired analysis using three or fewer steps. Other principles like 5, 6 and 7 are interconnected to automation, derivatization and quantity of generated waste, respectively, and they can also impact the score seen in the pictogram. Principle 8 must be close to a full score when multiple analytes are measured in a desired testing method. For obtaining the scores 0.0, 0.5, 0.9 and 1.0, it is necessary to record 1, 10, 50 and 70 detections per hour, respectively. Principles 9, 10 and 11 may be positively impacted when minimal consumption of energy, reagents, and toxic materials are employed, respectively. Lastly, the input 12 can reach score 1.0 for cases when the laboratory environment is free of potential hazardous materials like toxic, high inflammable, oxidable, corrosive or explosive compounds [14]. In this way, the use of the AGREE calculator for estimating how ecological are the paper-based (bio)electrodes as well as environmental and clinical sensing applications are discussed in the next subheadings.

5. Greenness metrics of environmental analysis

Modern analytical instrumentation is one pivotal way to support the ecological system due to its capacity for identifying and monitoring distinct environmental pollutants. Some testing methods using ePADs have been successfully reported for detecting pollutants. However, the ecological profile of those devices has yet to be explored or discovered, making pivotal to introducing strategies aiming to popularize its greenness achievements, mainly in developing regions. The section below will focus on informing and discussing the greenness metrics involving ePADs to analyze heavy metals, pesticides/herbicides, and phenolic compounds.

5.1. Heavy metals

Potential toxic metals have represented as one of the main classes of pollutants that can negatively impact all ecological systems due to their nonbiodegradable ability [101]. For example, the main commerce that needs to use metals for day-to-day activities includes mining, fertilizer, batteries, and pesticides. Believed that wastewater from the above-mentioned industries must be the pivotal source of heavy metals in the environmental compartment, mainly in developing countries [101]. Examples of heavy metals that have received particular attention due to high carcinogenic are copper (Cu), mercury (Hg), cadmium (Cd), chromium VI (Cr), and lead (Pb). According to the WHO ~1 million people die every year due to the toxicity of Pb and millions more are exposed to the long-term chronic effects of heavy metals poisoning [102]. It must be crucial to keep on increasing the advancements in treatments of remotion, stringent regulations, greenness criteria, and monitoring of heavy metals.

Pungjunun et al. [103] successfully demonstrated that the combination of paper-based graphene electrodes and bismuth nanoparticle (Bi-NPs) could be utilized for increasing the voltammetric responses of Sn and Pb. Due to the sample nature, one additional step based on acid digestion (2% HNO_3, v/v) have required to extract the metals from solid-liquid phases (principle 1). The authors have informed values of LOD ~0.26 ng mL^{-1} for Sn, 0.44 ng mL^{-1} for Pb, and an ecological metric ~0.76 (Fig. 5A). Eco-friendly benefits of the reported method, including the utilization of a portable detector, *on-site* analyses, and sample aliquot ~100 μL, which have influenced to increase the AGREE assessment.

Silva-Neto et al. [104] reported using ePAD modified with Bi for SWV detecting Zn, Cd, and Pb. They have demonstrated a suitable range of LOD 0.9–10.5 μg L^{-1} for sensing Zn, Cd, and Pb in river water samples. In terms of ecological profile, the reported method exhibited a metric score of ~0.82 due to acceptable aspects such as minimal quantities of sample, energy, and short analysis time (Fig. 5B). Before performing the analysis, the desired sample was pre-concentrated by using a hot plate at ~100°C for 1 h and filtered (∅ = 0.22 μm). That additional procedure reduced the score (principles 1 and 4), however, that strategy was important to make possible the determination of metals in real river samples, and the reported concentration of metals ranged from 16 to 110 μg L^{-1}.

Soulis et al. [105] proposed the utilization of Bi-NPs/ePAD aimed for electrochemical sensing of metals Pb and Cd in drinking water, and the proposed method exhibited LOD of 3.1 μg L^{-1} for Cd, 4.5 μg L^{-1} for Pb,

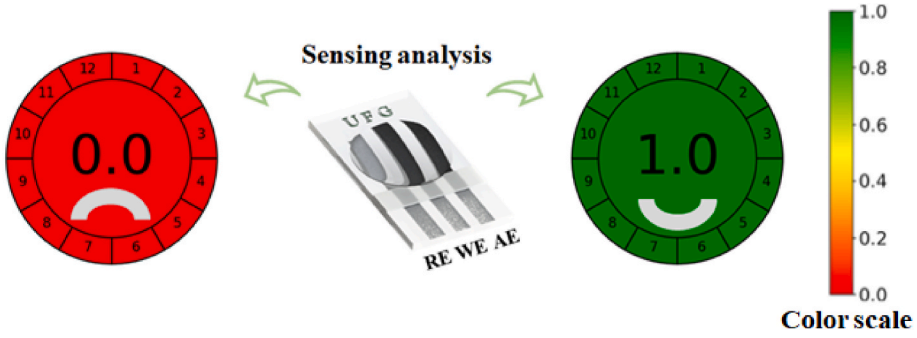

Fig. 4. Schematic representation of the use of AGREE tool for estimating how much ecological one is one target sensing analysis. In the sensor device image, the labels RE, WE and AE mean reference, working and auxiliary electrodes, respectively. In the pictograms, the numbers are associated to the Green Analytical Chemistry principles, as follows: 1, sample treatment; 2, sample amount; 3, device positioning; 4, sample preparation stages; 5, automation and miniaturization; 6, derivatizations; 7, waste; 8, analysis throughout; 9, energy consumption; 10, source of reagents; 11, toxicity; and 12, operator's safety.

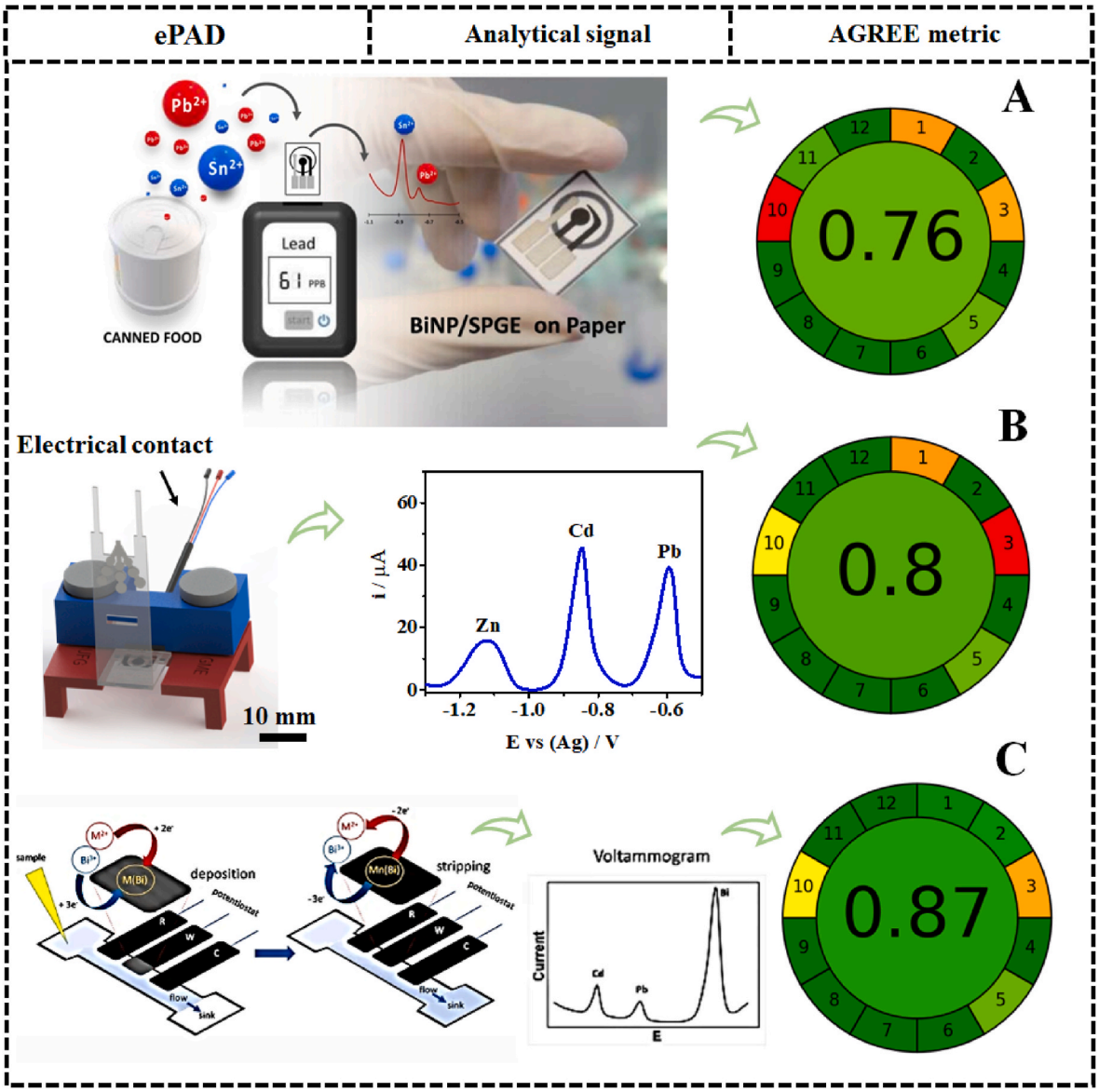

Fig. 5. (A) Schematic representation of the use of ePADs for sensing metals and its AGREE result. (B) Plug-and-play assembling to perform analysis of metals in river samples and obtained value of the ecological score. (C) The utilization of ePADs for performing electrochemical analysis of metals and the estimated value of AGREE response. Reproduced with permission from Refs. [103–105].

and an AGREE response ~ 0.87 (Fig. 5C). The reported analytical method showed an acceptable capacity for detecting those metals in fortified water samples without using additional pre-treatment (principle 4) or toxic reagents (principle 11), making possible the desired analysis *on-site*.

5.2. Pesticides/herbicides

Believed that existing ~1000 different types of pesticides/herbicides commercially available aiming to ensure that food is not destroyed by pests [106]. Many of the older models and/or high toxicity of pesticides have been banned in developed countries, however, some chemicals keep on active to use in developing regions [106]. The awareness of the toxicity of ubiquitous chemicals, such as pesticides and herbicides, has led to an increasing interest in the development of portable screening kits and on their ecological impact on environmental monitoring, biomonitoring, and food quality assessment.

In the advances of inhibition-based enzymatic sensors, using paper substrates has played a crucial role in designing user-friendly platforms. The porous structure of paper allows to pre-loaded reagents (i.e., enzyme, substrate), control of their release, shorten the test procedure, and limit the waste production requiring just a few microliters of sample [25]. In this frame, the possibility of using different types of paper enhanced the analytical performances of inhibition-based sensors. Cioffi et al. [107] developed a sustainable and portable paper-based biosensor for quantifying the levels of organophosphorus pesticides, taking paraoxon as the model compound. The platform produced on office paper enabled measuring paraoxon in soils, fruits, and vegetables and demonstrated a suitable value of AGREE profile ~0.83, as depicted in Fig. 6A. Although this approach was effective in replacing the use of the plastic-based substrate, the platform cannot be considered fully user-friendly because of the complexity of the analytical procedure requiring external sample preparation (principle 1) and the fact that has used 2% ethanol solution (principle 11). In this field of application, the possibility of limiting the tasks and having simple procedures is essential to allow non-experts to perform *in-situ* analysis contributing to large scale monitoring.

Ulteriorly, by combining office paper and chromatographic one, a

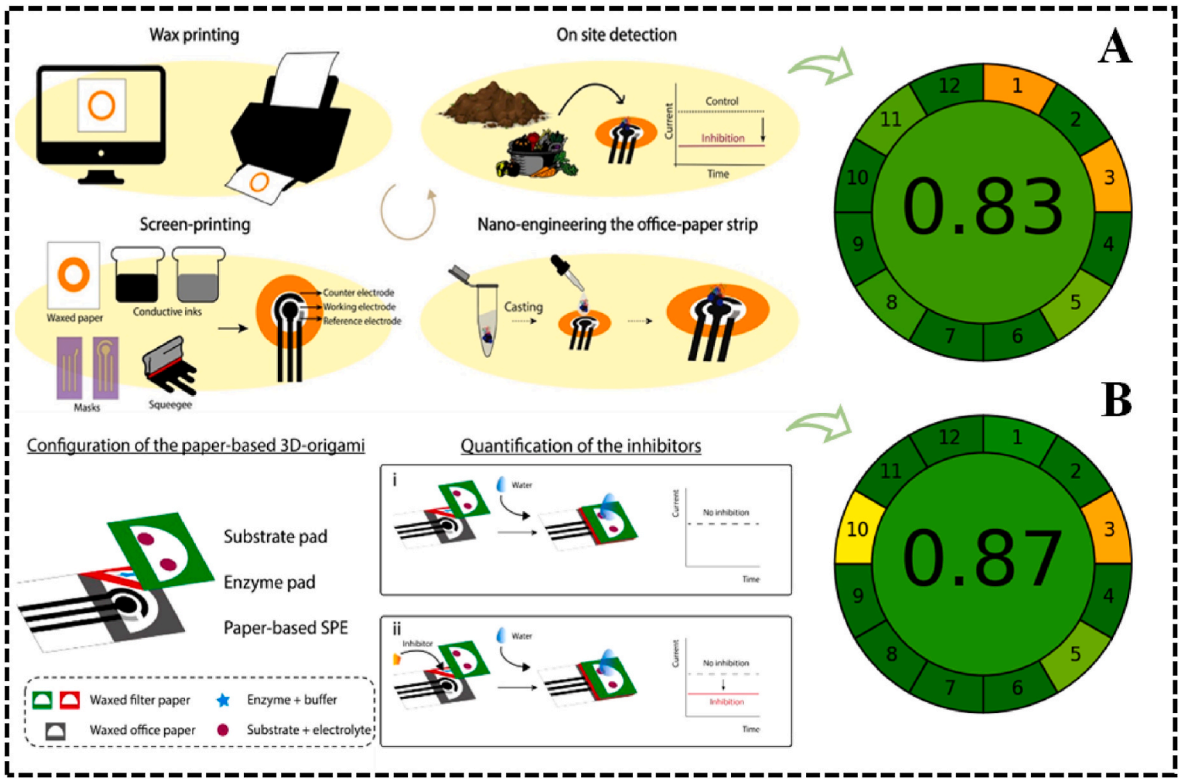

Fig. 6. Schematic representations of: (A) the manufacturing, application of screen-printed office paper-based electrochemical strips and AGREE score for the enzymatic detection of organophosphate; (B) the assembly procedure of a 3D multi-pad system to measure the enzymatic activity and the estimated value of ecological score. Reproduced with permission from Refs. [107,108].

first prototype of 3D origami biosensor for multi-pesticides detection has been developed, Fig. 6B [108]. The reported device has been applied to the detection of paraoxon, 2,4-dichlorophenoxyacetic acid, and atrazine at part per million level in both standard solutions and river water samples. This approach appeared to go beyond the state of the art, paving the way for pesticides and herbicides multiplexing based on different inhibition reactions occurring at different spots of the same origami-based device and that sensing approach has received a positive value of ecological score ~0.87. Future efforts can be focused on exploring better principles 3 and 10 that have associated with the positioning of the analytical device and the nature of reagents, respectively.

5.3. Phenolic compounds

Phenolic compounds are extracted from petroleum and is expected that its global market increase leveraged by the industrial production of some important products such as epoxy resins, polycarbonates, nylon, bakelite, detergents, phenolic resins, pharmaceutical drugs, and herbicides [109]. It is also important to mention that phenolic substances make up part of the hazardous material class. In the atmosphere, those photochemical reactions to dihydroxybenzenes and nitrophenols can degrade compounds. Abiotic and microbial activities can convert its chemicals into carbon dioxide and methane in the water and soil [110]. In this way, the AGREE software was also used to evaluate the greenness of ePADs for phenolic compound detection in different matrices.

Gomez et al. [111] reported the development of a microfluidic device coupled with electrochemical detection based on commercial carbon tapes modified with carbon nanotubes (CNTs) and enzymes. The samples analyzed in this work were five types of beer and one 1cider, representing a complex matrix. The device was applied to detect glucose, ethanol, and phenol. Focusing our discussion on the latter analyte, detecting phenolic compounds in these samples is essential because they are used as antioxidants and colloidal stability agents, impacting the beer's shelf life. Besides that, the phenolic compounds, in addition to other compounds, can give a bitter taste to some beers. In terms of greenness, its approximation was 0.8 (Fig. 7A). This means that the analysis procedure can be assessed as environmentally friendly, safe for operators, and without negative impacts on health. The colored pictogram showed that the main criteria that impacted the analytical procedure of this work were not closer to 1: probably due to the principles 5 and 10 [14]. Principle 5 had a moderate impact, as the paper-based

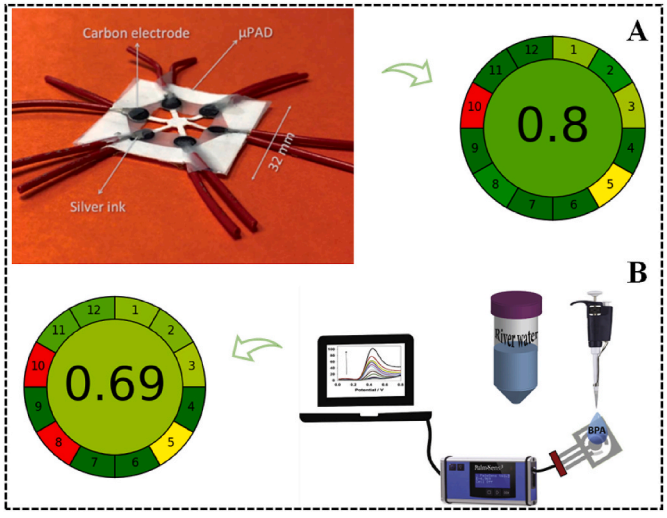

Fig. 7. Schematic representations of: (A) the µPAD and AGREE score for the electrochemical detection of glucose, ethanol, and phenols; (B) the reported electrodes to detect the bisphenol A and the calculated value of ecological score. Bisphenol A (BPA). Reproduced with permission from Refs. [111,112].

device used is miniaturized and uses the microfluidic properties of paper, which allows delivery of reagents without the analyst having contact with the samples. This point is very positive for this analytical method, as it ensures the analyst's safety. Principle 10, however, had a negative impact, as none of the reagents used in the analyses were from a renewable source; all were commercial, although they are not considered highly toxic.

Jemmeli et al. [112] developed an analytical method to detect bisphenol A (BPA) in water samples (river and drinking water) using an ePAD fabricated with filter paper and screen-printed carbon electrodes. BPA is used in the industrial production of plastics, and its presence in the environment is toxic, an endocrine-disrupting compound, and considered an emergent pollutant. The greenness analysis of the analytical procedure reported in this work was 0.69 (Fig. 7B). The most critical principles were 5, 8, and 10. Principle 5 contributed moderately to the final classification since the analysis is not automated, with manual sample introduction steps, despite the miniaturized device. Principles 8 and 10 significantly impacted the greenness rating. In the case of principle 8, the analytical method only analyzed the BPA, and the analysis time was not reported, which affected the sample throughout. For principle 10, as in the discussion of the previous work, the reagents used were commercial, and none were from a renewable source. Acetonitrile as a solvent for dissolving BPA, a toxic and flammable reagent, was a weakness in this analytical method. Regarding the other principles, the strong points that can be highlighted are the small number of samples (principle 2), which in this case was 600 μL, the minimum number of steps (principle 4), and low energy consumption (less than 0.1 kWh) (principle 8), because he did not use any energy-intensive equipment.

6. Greenness metrics of clinical analysis

In recent years, it is possible to see the utilization of ePADs for distinct clinical applications and believed that its popularity can be attributed to the possibility to use of globally affordable materials, low consumption of samples, and suitable sensing aspects at POCT [39,113,114]. Examples of clinical fields that can be covered by using ePADs include metabolic syndrome [115], microorganism [17], cancer [116] and neurological [117]. However, the recent reports does not have its ecological metrics. In this context, the AGREE software was used to inform the sensing platform's greenness level by using the reported information in some examples of paper-based (bio)electrodes as carefully discussed below.

6.1. Metabolic syndrome

Metabolic syndrome (MetS) is a condition caused by the dysfunction of different metabolic pathways, which may increase an individual's predisposition to develop a chronic (or non-communicable) disease, such as diabetes, cardiovascular disease, cancer, neurodegenerative disorders, among others [17,118]. The development of analytical methods for detecting metabolites related to these diseases is critical since, according to data from the WHO, non-communicable diseases kill 41 million people per year, equivalent to 74% of deaths globally [119]. As the development of paper-based (bio)electrodes for detecting these diseases has been extensively developed and reported in the literature, we will cover in this section the greenness of analytical methods for detecting metabolites related to cancer and cardiovascular diseases.

Wang et al. [120] described an analytical method for the detection of two lung cancer biomarkers, carcinoembryonic antigen (CEA) and neuron-specific enolase (NSE), in clinical serum samples with reported values of LOD ~ 2 pg mL^{-1} and 10 pg mL^{-1}, respectively. Considering the ecological score, this method presented a classification of 0.81, which the value expresses that, in general, the developed analytical method has several strengths in greenness. Inputs 8 and 10 were the principles that had a moderate impact. Principle 8 greatly impacted the classification of this method, as the article does not describe the total analysis time, although the positive point is the multiplexed analysis. Principle 10 had a moderate contribution since only some reagents were used from renewable sources. Electrodes were made in several steps with many reagents and probably with waste generation. These factors are described in principle 7 but were not considered here because they concern the previous analysis step.

Regarding cardiovascular diseases (CVDs), Boonkaew et al. [121] developed a label-free immunoassay on an electrochemical paper to detect simultaneously three CVD biomarkers: C-reactive protein, troponin I, and procalcitonin in serum samples, informing values of LOD ranging from 0.16 to 0.38 ng mL^{-1}. The greenness rating for this analytical method was 0.87. One of the most interesting features is that the analysis is multiplexed, and the analytes are delivered from the device inlet to the detection zone in approximately 3 s, allowing a high analysis frequency (around 20 analyzes per minute). This time should have considered the time of the electrochemical measurement, which may reduce the analytical frequency, leading to the analysis being performed in the order of minutes. This item is described in principle 8. The points that moderately affected the analytical method were principles 5 and 11. In the case of principle 5, although the analysis is multiplexed, as already mentioned, and the delivery of reagents is done semi-automatically, there is still the need to add samples and solutions to the device. For principle 11, the surface pretreatment of the graphene oxide-modified graphene screen-printed electrode was performed using a concentrated NaOH solution (0.5 mol L^{-1}), which adds not only one more step in the total analysis time but also makes use of a corrosive reagent that generates waste.

6.2. Microorganism

Microorganisms are infectious agents of microscopic or submicroscopic size and can be divided into viruses, fungi, bacteria, and protozoans [122]. According to the WHO, there is contamination by microorganisms during the healthcare-associated process at hospitals when each 10 patients infected one died [123]. Also, since the COVID-19 pandemic caused by the SARS-CoV-2 virus, the rising interest to monitor and detect pathogenic microorganisms for clinical diagnosis has intensified.

Based on this context, modern medicine has adopted some medical devices capable of generating significant results in a short time, accurately and that has potential to be an environmental option [124]. Table 1 presents a compilation of some paper-based (bio)electrodes, target evaluated, LOD, and the AGREE score of ePADs dedicated to the monitoring of microorganisms.

Contributing to this approach, Ehsan et al. [128] developed a screen-printed graphene-based electrode on paper pads from Millipore® for impedimetric detection of spike protein (SP) from SARS-CoV-2. The authors used a WE modified with SARS-CoV-2 SP IgG antibody for SP biosensing, resulting in a LOD ~0.25×10^{-15} g mL^{-1}, suitable performance when the device was tested in 5 clinical samples, and the analysis presented an ecological score ~0.76. Similarly, Pusomjit et al. [130] reported an option of ePAD modified with Pt-decored single-walled carbon nanotubes (Pt-SWCNTs) and anti-HCV-aAg antibody for voltammetric detection of hepatitis C virus. The author obtained a LOD of 0.015×10^{-15} g mL^{-1}, good accuracy when the device was tested in 15 clinical samples and an AGREE score ~0.76. As above-informed, both sensing analyses have exhibited similar AGREE results that can be associated with the observed similarity in the principles 1, 8, and 10.

Exploring the same theme of virus sensing, Lee et al. [129] reported a multiplex electrochemical immunosensor for multiple avian influenza virus antigen detection. The WEs were modified with multiwalled carbon nanotubes (MWCNTs) and the polyclonal antibody of influenzas A (H_5N_1, H_7N_9, and H_9N_2). They obtained a LOD of 55.7×10^{-12} g mL^{-1} for H_5N_1, 99.6×10^{-12} g mL^{-1} for H_7N_9, and 54.0×10^{-12} g mL^{-1} for H_9N_2 hemagglutinin antigens in phosphate buffer saline. In terms of

Table 1
Comparison of examples of ePADs employed for microorganism sensing and the estimated AGREE metrics.

SENSOR	TARGET	APPLICATION	LOD	AGREE ON SCORE	REF.
CLIG	Bacterial phenazine	Clinical	3.4 μmol L^{-1} for PYO, 23.4 μmol L^{-1} for PCA and 21.7 μmol L^{-1} for PCN		[125]
EPAD/SNAP-25	Botulinum neurotoxin serotype A and C	Clinical	10.0 pmol L^{-1}		[126]
IDE	*Pseudomonas aeruginosa* and *Staphylococcus aureus*	Clinical	$<1.5 \times 10^2$ CFU mL^{-1}		[127]
SPGCE	SARS-CoV-2 spike protein	Clinical	0.25 fg mL^{-1}		[128]
SPE	Hemagglutinin from H_5N_1, H_7N_9 and H_9N_2	Clinical	55.7 pg mL^{-1} for H_5N_1, 99.6 pg mL^{-1} for H_7N_9, and 54.0 pg mL^{-1} for H_9N_2		[129]
SPE/PTSWCNT	HCV-cAg	Clinical	0.015 pg mL^{-1}		[130]
NAFION-MODIFIED GRAPHITE LEADS EPAD	Pyocyanin from *Pseudomonas aeruginosa*	Clinical and environmental	10 nmol L^{-1} PYO and ~100 bacterial cells		[131]
BC/G-PEG/ACE2/BSA/ Nafion®	SARS-CoV-2 spike proteins	Clinical	4.26×10^{-18} g mL^{-1} SP and 0.05 copies μL^{-1} SARS-CoV-2		[132]
LSG/AuNS/Ab-MPXV	A29 protein and MPXV	Clinical	3.0×10^{-16} g mL^{-1} A29 and 7.8×10^{-3} PFU mL^{-1} MPXV		[133]

Legend: cLIG**:** cellulose-based laser-scribed graphene; ePAD: paper-based electrochemical device; SNAP-25**:** synthetic peptide able to mimic the natural substrate; IDE: interdigitated electrode; SPGCE: Screen-Printed Graphene/Carbon Electrodes; SPE: screen-printing electrode; HA: hemagglutinin; CFP: carbon fibers paper; CoMOF: 3-dimensional cobalt-dimethylimidazole framework; AuNPs: gold nanoparticles; GSH: glutathione; PtSWCNT: Pt nanoparticles deposited on single-walled carbon nanotubes; HCV-cAg: hepatitis C virus core antigen; PYO: pyocyanin; PCA: Phenazine-1-carboxylic acid; PCN: phenazine-1-carboxamide; BC: bacterial cellulose; ACE2: angiotensin-converting enzyme-2; G-PEG: graphene oxide conjugated with polyethylene glycol; BSA: bovine serum albumin; AuNPs: gold nanoparticles; AuNS: gold nanostructures; Ab-MPXV: monkeypox virus monoclonal antibody.

ecological result, the reported analytical method has presented a suitable value of greenness metric (~0.79) when the AGREE inputs 3, 7, and 10 are the key points to overcome.

The detection of other microorganisms has been extensively addressed by using ePADs. For example, Caratelli et al. [126] developed an electrochemical paper-based peptide sensor for *on-site* detection of botulinum neurotoxins generated by *Clostridium botulinum* bacteria that causes botulism. The authors used (bio)modified materials gold nanoparticles (AuNP), and a peptide sequence for voltammetric detection of botulinum neurotoxin serotypes A and C. They obtained a LOD lower of 10.0×10^{-12} mol L^{-1}, good recoveries in orange juice samples spiked with the neurotoxins studied, and an AGREE response of ~0.86. Key facts such as the absence of laborious sample preparation (principles 1 and 4) and the use of smartphones (principle 3) have positively impacted the ecological results.

Butler et al. [125] employed a Whatman paper (n°1), sprayed with FireGuard flame suppressant, followed by two wax printed steps, and submitted to CO_2 laser radiation to manufacture a paper-based LSG electrochemical sensor for voltammetric detection of bacterial phenazines (pyocyanin (PYO), phenazine-1-carboxamide (PCN) and phenazine-1-carboxylic acid (PCA). The authors obtained LOD of 3.4 μmol L^{-1} for PYO, 23.4 μmol L^{-1} for PCA and 21.7 μmol L^{-1} for PCN, with excellent performance of the device in spiked samples containing the bacterium metabolites and an ecological profile ~0.75.

Simic et al. [127] developed an ePAD by inkjet method for impedimetric detection of *Pseudomonas aeruginosa* (PA) *and Staphylococcus aureus.* The authors obtained a LOD $<1.5 \times 10^2$ CFU mL^{-1} for both bacteria, great performance when the device was applied to clinical samples with a good result of AGREE ~0.71. Also aiming at the detection of *P. aeruginosa,* Silva et al. [131] reported a simple ePAD for detection of PYO biomarker in human saliva and contaminated surfaces, without any sample preparation or separation steps. The WE was modified with Nafion semipermeable anionic resin to preconcentrate PYO species and thus improve the detectability of the method. The authors obtained a LOD of 10 nmol L^{-1}. Importantly, two virulent PA strains, PA14 and PAO1, were analyzed. The electrochemical data presented a high correlation between the PYO levels detected and the optical density values of PA colony-forming units (CFU). This simple analytical approach provides a green score ~0.83 which was increased due to the simple sample preparation (principles 1 and 4) and the presence of bio-based reagents (input 10).

As above-informed and discussed, it is possible to highlight the excellent greenness metrics (>0.7) provided by ePAD fabricated and modified using different (bio)materials, which stand out the importance of the development and use of paper-based electrodes technology that makes part of some aspects of GAC for routine clinical analysis.

6.3. Cancer

It is estimated that there are 20 million new cases of cancer globally and it will increase by ~60% over the next two decades, raising the cases pronouncedly in developing countries [134]. Early cancer screening, through the analysis and rapid detection of cancer-specific biomarkers, plays a key role in reducing cancer mortality. Tumour biomarkers are extremely important diagnostic and prognostic tools in cancer diagnosis. The integration of electrochemical detection techniques with ePADs has greatly facilitated the detection of cancer biomarkers [135]. Indeed, the microfluidic properties of paper allow to limit time-consuming pre--treatment steps, especially towards blood and urine, or even to run the analysis directly on untreated samples. The high performance of these platforms and their capability to screen various classes of oncomarkers, ranging from cells to DNA, relies on the possibility of functionalizing the paper substrate with highly selective biorecognition elements.

For instance, nucleic acid detection is mainly based on target/probe hybridization performed on paper strip electrodes through 'signal-on' and 'signal-off' strategies [136]. These devices are characterized by a simple architecture where the thiolated recognition probes are anchored at the surface of screen-printed electrodes using AuNP. In case of "*signal off*", a redox mediator (i.e., methylene blue) is covalently attached to the recognition probe, while the "*signal on*" devices exploited the use of external redox mediators, usually ruthenium examination, which resulted electrostatically attached to the probe-target more than probe alone. However, even if both the methods allowed a detection limit down to a low nanomolar range, the "*signal off*" only resulted to be suitable for whole blood measurements.

On the other hand, the "*signal on*" strategy was successfully applied to the detection of miRNA-492 associated to pancreatic cancer in undiluted serum samples. Regarding ecological profile, Moccia et al. [137] have reported using a suitable option of ePADs for sensing peptide nucleic acid (PNA) in blood serum samples. The authors reported a value of LOD ~6 nmol L^{-1} and an AGREE score ~0.75 for detecting PNA (Fig. 8A). Some eco-friendly benefits include minimal consumes of the sample (principle 2), desired analysis in undiluted invasive fluid (principles 1 and 4), and absence of toxic solvent (principle 11).

The "*signal off*" strategy has been adopted also for the detection of breast cancer CTCs (MCF-7) using a paper-based aptasensor [138]. In spiked serum samples, the "*signal off*" tool enabled to detect CTCs with an optimal recovery range (from 95 to 104%) and a greenness assessment ~ 0.79 (Fig. 8B). These types of paper-based aptasensors are characterized by a simple manufacturing process (manual screen-printing) and can be potentially applied to the detection of circulating free DNAs, micro-RNAs as well as CTCs, extra-cellular vesicles (EVs) and exosomes. Apart from aptasensors, also paper-based immunosensors showed promising advances. Regarding the AGREE result, it is possible to see that the principles 2, 4, 7 and 12 have increased the ecological aspects of the reported sensing method.

Ortega et al. [139] designed a dual sandwich-type assay for the detection of EVs epithelial protein associated with breast cancer, such as Claudin 7 and CD81. It is reported that values of LOD ~3 pg mL^{-1} and 0.4 pg mL^{-1} for CD81 and Claudin 7, respectively. The sensing platform shows better analytical performance when compared with the ELISA kit and exhibited an AGREE metric of ~0.77 (Fig. 8C). Principles 2, 4, 7, 11 and 12 are the key ecological achievements.

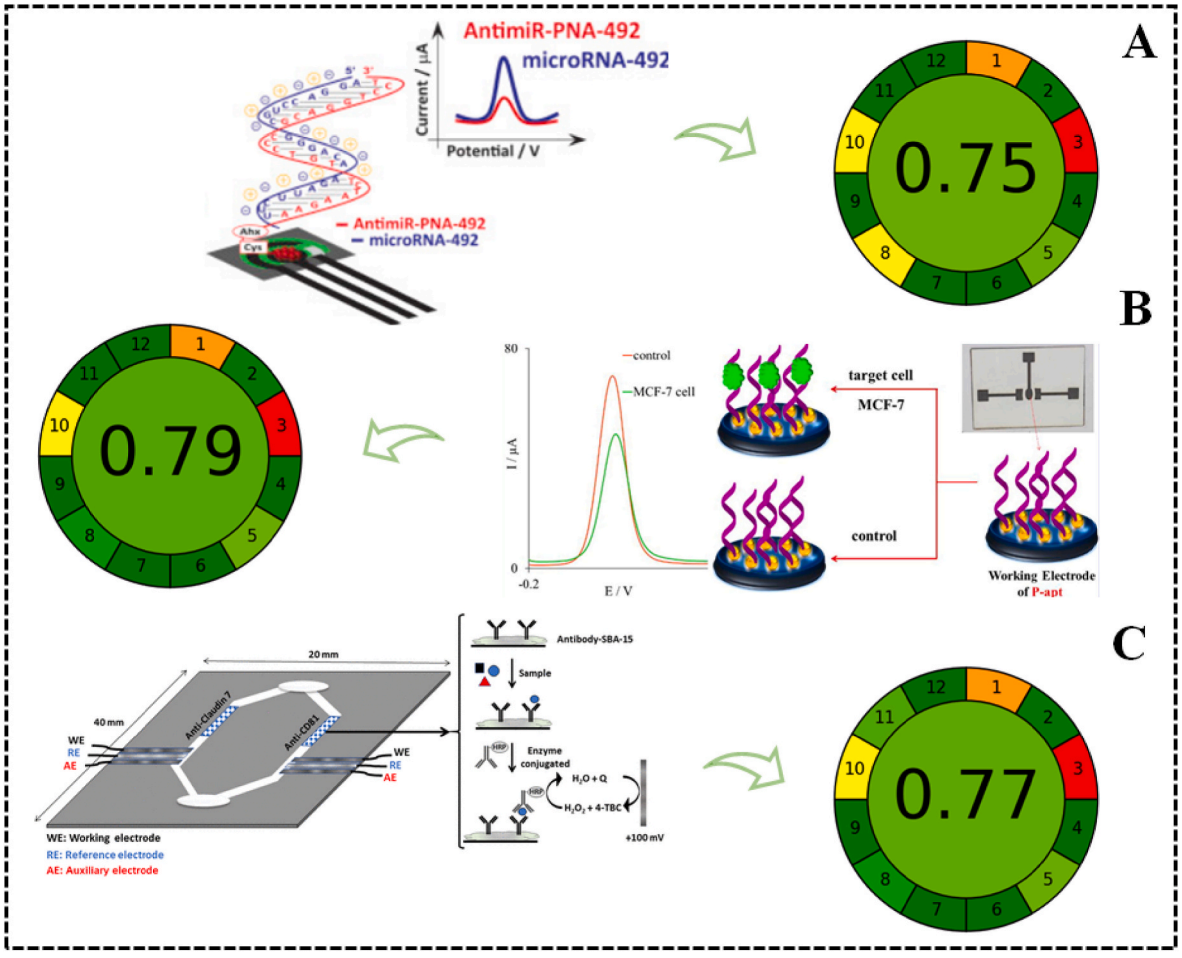

Fig. 8. Schematic representations of: (A) the ePAD and AGREE score for the electrochemical detection of peptide nucleic acid; (B) the reported ePADs to measure the breast cancer circulating tumor cells and the obtained value of AGREE score. Reproduced with permission from Refs. [137–139].

By combining paper-based immunosensors with nanocomposite materials, Sahraei et al. [140] have designed a rapid and inexpensive test to monitor cancer-related exosomes. The nanostructured modifiers provided an enhanced electron transfer improving the platform sensibility, while the antibodies assured a selective recognition of the target exosomes. Apart from the outstanding performance and their affordability, paper-based (bio)sensors have the potential of being extremely customizable, easily coupled within biosensor arrays for multiplexing, and a suitable value AGREE score ~ 0.77. Nowadays, the open-challenges for analytical tools in cancer management are not related to biomarkers detection but to the possibility of performing therapeutic drug monitoring (TDM), which is essential for the therapeutic dosage. The lack of ePADs for TDM can be ascribed to the poor water solubility of most cancer drugs requiring organic solvents not compatible with paper substrates. However, the perspective to integrate biomarkers screening with TDM within one portable and low-cost device is of pivotal importance for the advance in precision oncology and the life quality of cancer patients. With their rapidity, user-friendliness, and agreement with the GAC principles, these devices are fulfilling the requirements of ideal diagnostic tests to be applied in resource-limited areas, highlighting the potential of paper-based application in cancer management [141].

6.4. Neurological

Neurological disorders are diseases that interfere with the central and peripheral nervous system. The brain, spinal cord, autonomic nervous system, neuromuscular junction, and muscles can be affected, for example [142]. Some diseases classified as neurological are dementia, epilepsy, headache disorders, multiple sclerosis, neuroinfectious, Parkinson's disease, Alzheimer's disease, stroke, brain tumors, and traumatic disorders of the nervous system due to head trauma [142]. From the WHO database, it is estimated that hundreds of millions of people are affected globally by neurological diseases [142]. In this way, it is crucial to inform early about some clinical aspects involving neurological diseases aiming to promote/support medical treatment [143,144]. In the last years, some sensing efforts by using ePADs have been reported for monitoring biomarkers associated with neurological disturbance.

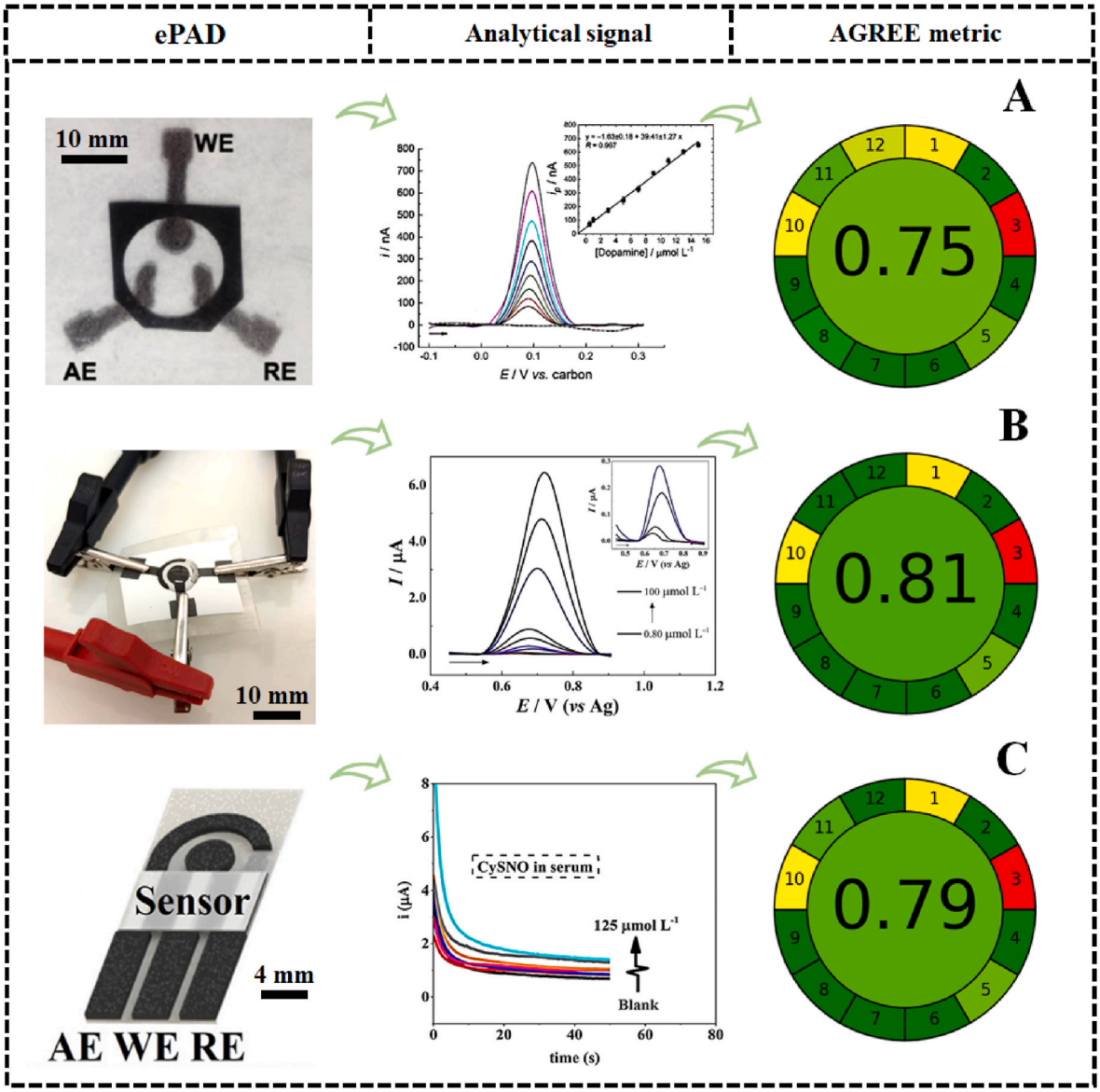

Fig. 9. (A) Captured image of ePAD used for detecting dopamine with respective ecological score. (B) A disposable sensor utilized to measure melatonin and the AGREE score. (C) A schematic representation of ePAD aimed at detection of S-nitrosocysteine and obtained AGREE metric. Reproduced with permission from Refs. [41,145,146].

França et al. [145] demonstrated that ePADs modified with CdSe/CdS magic-sized quantum dots can be used for monitoring dopamine due to direct association with diseases such as schizophrenia and Parkinson's. From analytical aspects, the authors reported a value of LOD ~96 nmol L^{-1} and acceptable recovery rates of dopamine (95.2–102.6%) in human blood samples. In terms of ecological impact, the AGREE analysis showed a value of 0.75 which makes part of the green method range (Fig. 9A). The AGREE inputs that have reduced the greenness level can be associated with principles 1, 3, 10, and 11.

Camargo et al. [146] reported an ePAD that uses waterproof paper as a substrate and carbon-based ink mixing nail polish and graphite powder. That device in association with SWV readout was used for detecting melatonin in synthetic saliva and urine samples, which exhibited LOD value ~32.5 nmol L^{-1} an AGREE score ~0.81 (Fig. 9B). Believed that the above-mentioned green aspect could be linked to the principles 1, 2, 4, 7 and 11 that impacted the AGREE analysis positively. However, ecological metric from prospects of real biological samples is a key point to solve. Also, other ecological aspects such as *off-line* analysis (input 3) and the fact that few used reagents are bio-based (input 10) remain as key challenges.

Silva-Neto et al. [41] proposed a recycled strategy using 3D-printed residues and graphite flakes to manufacture ePAD. As an electrochemical sensing demonstration, the authors have detected S-nitrosocysteine (CySNO) in artificial serum samples as model analysis. For making the analysis possible, the WE surface was modified with a combination of MWCNTs, GO, and Cu. The reported sensing platform exhibited a suitable value of LOD ~4.1 μmol L^{-1} for CySNO and an ecological score ~0.79 (Fig. 9C). Green benefits include the low consumption of sample (principle 2), minimal steps in sample preparation (principle 4), reduced production of waste (principle 7), analysis throughput (principle 8) and operator safety (principle 12). Some penalty point is also observed in principles 3 and 10, influencing the metric score negatively.

7. Paper obtention and life cycle of paper-based devices

Cellulosic-based paper material can be produced from different sources such as bacteria bioprocess (bacterial cellulose), cotton stalks, and trees. Cotton stalks contain around ~39% cellulose, ~24% hemicellulose, and ~26% lignin, an interesting material for paper production. Also, the paper manufactured from cotton presents excellent mechanical properties such as flexibility and high resistance due to the presence of fibrous with a length of 0.75–0.91 mm and diameter of 16.4–22.8 μm [147]. Meanwhile, the main components of paper from trees are around ~30% cellulose, ~30% lignin, and ~19% hemicellulose. These proportions may change depending on the wood tree used for paper manufacturing. Another interesting characteristic presented in paper manufacturing from trees is the fibers, presenting typical lengths of 435–467 nm and diameters of 5.2–5.7 nm [148], which is lower when compared to the cotton stalks paper. Lastly, paper sheet from bacteria cellulose (BC) production presents only cellulose in its composition, since hemicellulose and lignin are originally from plants [149], which decrease the steps of the treatment used for removing hemicellulose and lignin fibers to obtain a paper with a high purity degree. Also, the paper from BC presents fibrous with a length of ~20 μm and a diameter of 50–70 nm, thus affording higher mechanical resistance and purity for this material [150].

The different raw sources and manufacturing steps need to fabricate the paper-based materials impact the fibers type and their orientation, the chemical purity, and the mechanical and physicochemical features, whose aspects can influence the performance of ePADs, like the porosity and microfluidic properties [151]. Thus, these aspects should be considered in selecting the cellulosic substrate used to fabricate ePADs. As mentioned, using papers as substrates for sensor development is attractive since this material is available worldwide, renewable, and can be easily (bio)degraded or recycled, being a greener option for eco-friendly and sustainable sensor development [152].

The life cycle of ePADs can be summarized in up to seven ideal steps, which start with the paper production up to the disposal and (bio) degradation of entire sensor materials, as shown in Fig. 10. Briefly, after obtaining the cellulosic material from several renewable sources (i) and submitting them to physical and chemical processes; it is possible to manufacture paper sheets (ii), which can be used for ePAD fabrication (iii) by different manufacturing techniques, as described in this review. The ePAD can be properly modified and applied in the clinical, environmental, forensic, and food fields (iv). After practical use, the ePAD will be discarded. However, an important issue to avoid environmental pollution is removing metal content such as metallic tracks used as electrodes, metallic nanoparticles, silver ink commonly used in reference electrode fabrication or improving electrical connections. These metals should be removed for processing or recycled to reuse in novel devices (v) or other [153]. Despite the usual low content of metallic species, the massive use of these ePAD as rapid and frequent tests will lead to the accumulation of these species in the environment, causing severe adverse effects on the ecosystem and human health [154]. Depending on the application of the ePAD, a device sterilization process may be needed to eliminate potential biological hazards.

The remaining materials after metal removal (paper substrate and other carbonaceous materials) can be disposed of by three different methods (vi). The simplest and fastest approach is the incineration of the device if no material presents explosive features or toxic gas generation. Alternatively, the paper substrate can be processed and industrially recycled [155]. Also, the third possibility for paper-based disposal and the most common is in a landfill, where the cellulosic paper is consumed by microbial activity over a period of ~12–15 weeks for the complete biodegradation of the paper substrate (vii) [156], serving as a raw material for plant growth, *i.e.*, leading to bioregeneration process [157].

8. Challenges

Paper-based electrochemical (bio)sensors offer numerous benefits in terms of cost and accessibility; however, there are several challenges that need to be addressed to fully realize their potential. Firstly, these devices often exhibit lower sensitivity and specificity in comparison to traditional sensors, which can limit their utility in some contexts. A potential solution lies in the exploration of modification with advanced materials, one example could be nanocomposites. These could enhance the sensor's sensitivity by providing a larger surface area for reactions, while innovative biorecognition elements could be employed to heighten specificity.

Secondly, the longevity and stability of paper-based sensors can be compromised due to their vulnerability to environmental conditions. The introduction of encapsulation technologies or optimizing storage conditions could be potential solutions to increase their shelf-life, maintaining their performance over extended periods.

The ecological footprint of these devices is another critical aspect that influences their adoption and usage. Traditional methods of sample preparation often involve labor-intensive processes and generate considerable waste, impacting the overall greenness metric of these sensors negatively. Therefore, there's a growing need for more sustainable practices and materials in sample preparation. For instance, employing green solvents or implementing microextraction techniques could substantially reduce the environmental impact, or decreasing the number of sample preparation steps.

The lack of automation in both the manufacturing and testing process of these sensors also contributes to a higher ecological score. Manual processes are generally slower, less efficient, and produce more waste. However, the integration of automation in these areas could increase throughput and accuracy, reducing waste generation significantly and, in turn, the ecological footprint of these devices.

The life cycle of paper-based devices—from material extraction, through production, use, and ultimately to end-of-life

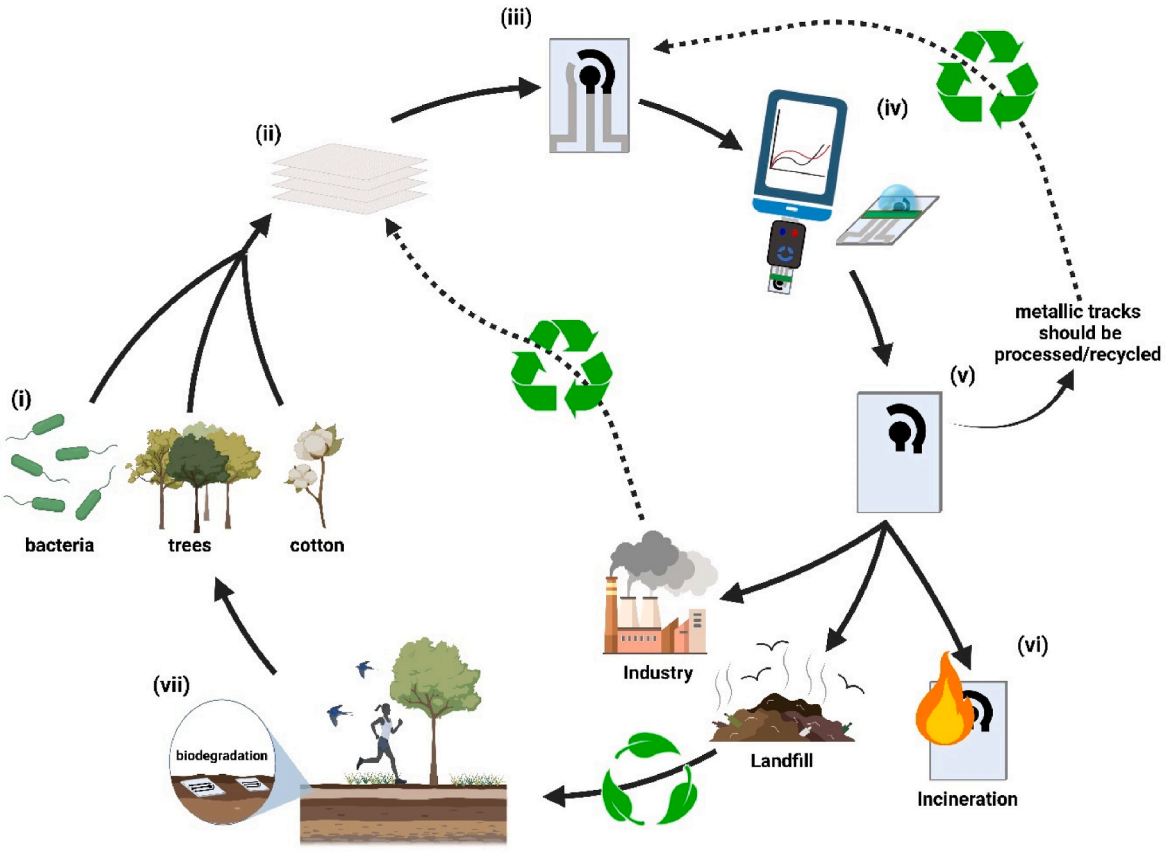

Fig. 10. Life cycle of paper-based devices (i) The life cycle of paper starts in raw material processing, which can be obtained from trees, cotton, or bacteria; (ii) After chemical, physical and/or biological steps, the paper sheets can be used for to fabricate ePADs sensors; (iii) The ePAD sensors can be manufactured by different techniques (LSG, inkjet printing, screen-printing, stencil-printing, pencil drawing, etc) and materials; (iv) The sensor can be applied for several applications including clinical and environmental; (v) Subsequently, the sterilization of the sensor may be required to eliminate microbial or biological infectant species and the metallic tracks should be removed for processing or recycling; (vi) The possible destine for paper substrate and carbon materials may be incineration, industry (the material can be recycled for reuse), or landfill (due to the disposable and degradation features of the paper-based materials); (vii) The disposed cellulosic substrate can be biodegradaded, serving as a raw materials for the soil and trees growing (bioregeneration). This Figure was created in BioRender.com.

management—also offers multiple areas for improvement. The utilization of renewable or recycled materials in the manufacturing process can reduce the depletion of natural resources, marking a significant step towards sustainability. Likewise, developing biodegradable paper-based sensors or devising efficient recycling methods could considerably mitigate the environmental impact at the end of their life cycle.

When considering the commercialization of paper-based electrodes, it's essential to balance environmental friendliness with performance. Reducing the production cost while enhancing efficiency could broaden their application scope, making these devices more economically viable. Moreover, compliance with safety and environmental regulations is paramount, ensuring not only the devices' market acceptance but also their positive environmental impact.

Other challenges, such as the need for more sophisticated equipment for large-scale manufacturing, maintaining quality control during high-speed production, and user education about these devices' benefits and limitations, need to be tackled head-on. However, these challenges shouldn't be viewed solely as hurdles. Instead, they present numerous opportunities for growth and innovation in the field of paper-based electrochemical (bio)sensors, pushing the boundaries of what's achievable while respecting our shared environment.

9. Conclusion

In this review, we have summarized and discussed the key ecological achievements of paper-based (bio)electrodes and their testing methods for environmental and clinical analysis. The AGREE tool was successfully employed and demonstrated to be one suitable option for estimating the greenness metrics for point-of-care testing. To the best of our knowledge, this review is the first report that overviews the 12 principles of Green Analytical Chemistry (GAC) and sensing perspectives of paper-based devices.

The recent data from some special reported papers showed that the observed AGREE scores of clinical and environmental analyses ranged from 0.7 to 0.87, resulting in suitable ecological responses. Some principles of GAC such as the amount of sample, integration of analytical procedures, amount of waste, sample throughput, consumable energy, bio-based reagents, and operator's safety have positively impacted the AGREE responses. Aspects involving principles 1 (sampling procedure), 3 (positioning of the analytical device), and 5 (degree of automation) are the key challenges to overcome in the next generation of paper-based devices for clinical and environmental measurements.

Some examples of solvents such as ethanol, acetonitrile, and acetone are the main classes of toxic chemicals used for creating electrodes and performing sample pre-treatment. Also, carbon-based particles and insulating polymers are examples of solid waste that can be generated using emergent paper-based manufacturing techniques. Considering the life cycle of paper devices, seven different situations were successfully presented at supporting research centers and laboratories, mainly in developing countries. That review can be useful to popularize the use of greenness tools for paper-based (bio) electrodes aimed to keep on active the trends of GAC in the reign of portable analytical instrumentation.

CRediT authorship contribution statement

Habdias A. Silva-Neto: Conceptualization, Investigation, Methodology, Visualization, Data Curation, Project administration, Writing – original draft. **Lucas F. de Lima:** Conceptualization, Investigation, Writing – original draft, Project administration, Writing – review & editing, Methodology. **Danielly S. Rocha:** Methodology, Conceptualization, Investigation, Writing – original draft. **Vanessa N. Ataide:** Conceptualization, Investigation, Writing – original draft, Methodology. **Gabriel N. Meloni:** Conceptualization, Investigation, Methodology, Writing – original draft. **Giulia Moro:** Conceptualization, Investigation, Methodology, Writing – original draft. **Ada Raucci:** Writing – original draft, Conceptualization, Investigation, Methodology. **Stefano Cinti:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision. **Thiago R.L.C. Paixão:** Writing – review & editing, Funding acquisition, Project administration, Resources, Writing – original draft. **William R. de Araujo:** Writing – review & editing, Conceptualization, Funding acquisition, Project administration, Supervision, Writing – original draft. **Wendell K.T. Coltro:** Conceptualization, Funding acquisition, Project administration, Resources, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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