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Green profile tools: Current status and future perspectives

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ABSTRACT

The idea of Green Chemistry began to take shape in an increasingly important way starting in the 90 s when the impact of chemical products and processes began to be critically evaluated.

In the analytical chemistry field, green chemistry represents an essential factor to consider whenever a laboratory procedure is planned. Therefore, from the start it is necessary examine not only green chemistry (GC) but also green analytical chemistry (GAC). The impact of the GAC on publications shows how the trend has seen an exponential increase from 1995 to 2018. From here, it is evident how the GAC is increasingly essential in the analytical chemist work who needs uniform, impartial, and standardized tools and elements to evaluate the "*green profile*" of the procedures, also in order to perform a direct comparison between methods and procedures.

The purpose of this review is to report, compare, and critically evaluate the tools available today, such as Life Cycle Assessment (LCA), National Environmental Methods Index (NEMI), Analytical Eco-Scale, Green Analytical Procedure Index (GAPI) and ComplexGAPI, RGB (Red Green Blue) and White Analytical Chemistry (WAC) models, hexagon-CALIFICAMET, and finally Analytical GREEnness Metric approach (AGREE) and AGREEprep. This comparison was performed in the text after a short introduction to the concepts and principles related explicitly to GC, GAC, and Green Sample Preparation (GSP).

1. Introduction

The idea of Green Chemistry (GC) began to take shape in an increasingly important way starting from the 90 s, when the impact of chemical products and processes began to be critically evaluated. In particular, GC is "*the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances. Green chemistry applies across the life cycle of a chemical product, including its design, manufacture, use, and ultimate disposal*" [1]. It is immediately evident how the fields of intervention are extremely varied, complex, and with problems often very different. Nowadays, green chemistry is applied in any process that involves the use of chemistry to minimize the environmental impact and, for this reason, it is also often mistaken to as "*sustainable chemistry*". As reported by the Organization for Economic Co-operation and Development (OECD), in fact sustainable chemistry is "*a scientific concept that seek to improve the efficiency with which natural resources are used to meet human needs for chemical products and services. Sustainable chemistry encompasses the design, manufacture and use of efficient, effective, safe and more environmentally benign chemical products and processes*" [2].

In the analytical chemistry field, GC represents an important factor to consider whenever a laboratory procedure is planned (from sampling to extraction and purification processes to instrumental analysis) and for this reason, from the start is necessary examine not only GC, but also green analytical chemistry (GAC) [3].

The paper by de la Guardia and Garrigues also reports an interesting assessment of the impact of the GAC on publications showing how the trend has seen an exponential increase from 1995 to 2018 [3]. From here, it is evident how the GAC is increasingly important in the analytical chemist work who needs uniformed, impartial, and standardized tools and elements to correctly evaluate the "*green profile*" of the procedures, also to perform a direct comparison between methods and procedures.

The purpose of this review is to report, compare, and critically evaluate the tools available today such as Life Cycle assessment (LCA) [4], National Environmental Methods Index (NEMI) [5], Analytical Eco-scale [6], Green Analytical Procedure Index (GAPI) and ComplexGAPI [7,8], RGB (Red Green Blue) and White Analytical Chemistry (WAC) models [9,10], hexagon-CALIFICAMET [11], and finally Analytical GREEnness

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Abbreviations

AGREE	Analytical GREEnness Metric approach
AGREEprep	Preparative Analytical GREEnness Metric approach
ComplexGAPI	Complex Green Analytical Procedure Index
FPSE	Fabric Phase Sorptive Extraction
GAC	Green Analytical Chemistry
GAPI	Green Analytical Procedure Index
GC	Green Chemistry
GSP	Green Sample Preparation
HPLC-UV	High Performance Liquid Chromatography-Ultraviolet detection
LCA	Life Cycle Assessment
LC-MS/MS	Liquid Chromatography-tandem Mass Spectrometry
LOD	Limit of Detection
MEPS	MicroExtraction by Packed Sorbent
NEMI	National Environmental Methods Index
OECD	Organization for Economic Co-operation and Development
PP	Penalty Point
RGB	Red Green Blue
SPME	Solid Phase MicroExtraction
TDM	Therapeutic Drug Monitoring
WAC	White Analytical Chemistry

Metric approach (AGREE) and AGREEprep [12,13]. In particular, tools such as LCA, NEMI, Analytical Eco-scale, RGB and WAC, and hexagon-CALIFICAMET will be treated here for completeness of information. Deeper evaluation will be done for the GAPI and ComplexGAPI, the AGREE and AGREEprep, as they represent nowadays the main references (and complete tools) for the green profile evaluation of an analytical method and sample preparation, respectively. Before reporting and critically evaluating the different rating methods of the green profile of a procedure, it is necessary to clarify what GC means and how GAC "differentiates" and "specializes" in the specific field of analytical chemistry. Additionally, the most recent advances Green Sample Preparation (GSP) principle is also discussed.

2. "Green …"

In the scientific field, when the term "green" is used, one immediately thinks of the principles of GC, enunciated in the 90 s. After about a decade, in the early 2000s, was developed the GAC (starting from the GC concepts) which is nothing more than the "*tailored suit*" of green chemistry for analytical chemistry. It was immediately observed that this "*dress*" required several revisions and adjustments according to the different methods and procedures applied in the analytical field (from sampling to sample preparation to instrumental analysis), above all until, in 2022, the concept of GSP was coined. In addition, in this case, the principles of GSP are nothing more than a review and adaptation of the concepts of GC and GAC to the specific scope of sample preparation field. Fig. 1 clearly demonstrates this evolution, while Table 1 shows the principles of GC, GAC, and GSP for an immediate comparison.

In the following paragraphs, the principles of GC, GAC, and GSP will be considered because they represent the basis of all the tools considered here for the evaluation of the green profile.

2.1. Green chemistry (GC)

GC, as already reported, "*is the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances. Green chemistry applies across the life cycle of a chemical product, including*

Table 1
Comparison of the principles of green chemistry, green analytical chemistry, and green sample preparation.

Green Chemistry		Green Analytical Chemistry		Green Sample Preparation	
1	Prevent waste	**S**	Select direct analytical techniques	**S**	Favor in situ sample preparation
2	Maximize atom economy	**I**	Integrate analytical processes and operations	**A**	Use safer solvents and reagents
3	Design less hazardous chemical syntheses	**G**	Generate as little waste as possible and treat it properly	**M**	Target sustainable, reusable, and renewable materials
4	Design safer chemicals and products	**N**	Never waste energy	**P**	Minimize waste
5	Use safer solvents and reaction conditions	**I**	Implement automation and miniaturization of methods	**L**	Minimize sample, chemical and material amounts
6	Increase energy efficiency	**F**	Favor reagents obtained from renewable sources	**E**	Maximize sample throughput
7	Use renewable feedstock	**I**	Increase safety for operator	**P**	Integrate steps and promote automation
8	Avoid chemical derivatization	**C**	Carry out in situ measurements	**R**	Minimize energy consumption
9	Use catalyst not stoichiometric reagents	**A**	Avoid derivatization	**E**	Choose the greenest possible post-sample preparation configuration for analysis
10	Design chemicals and products to degrade after use	**N**	Note that the sample number and size should be minimal	**P**	Ensure safe procedures for the operator
11	Analyze in real-time to prevent pollution	**C**	Choose multi-analyte or multi-parameter methods		
12	Minimize the potential for accidents	**E**	Eliminate or replace toxic reagents		

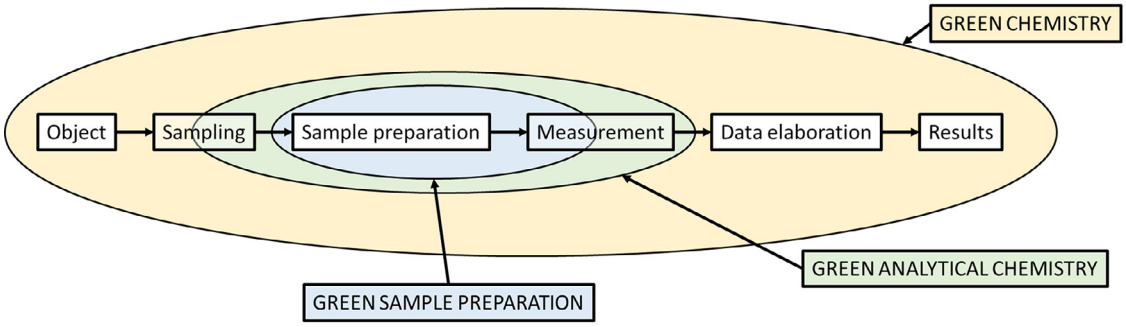

Fig. 1. Evolution from GC to GAC to GSP (the color scale is the same used to highlight the rows in Table 1).

its design, manufacture, use, and ultimate disposal" [1]. It is based on 12 general principles [14], which can be stated as follows:

1 *Prevention.* It is better to prevent waste than to treat or clean up waste after it has been created.
2 *Atom economy*. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3 *Less Hazardous Chemical Syntheses*. Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4 *Designing Safer Chemicals*. Chemical products should be designed to effect their desired function while minimizing their toxicity.
5 *Safer Solvents and Auxiliaries.* The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and harmless when used.
6 *Design for Energy Efficiency.* Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.
7 *Use of Renewable Feedstock.* A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
8 *Reduce Derivatives.* Unnecessary derivatization (use of blocking groups, protection/deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.
9 *Catalysis.* Catalytic reagents (as selective as possible) are superior to stoichiometric reagents
10 *Design for degradation.* Chemical products should be designed so that at the end of their function they break down into harmless degradation products and do not persist in the environment.
11 *Real-time analysis for Pollution Prevention.* Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12 *Inherently Safe Chemistry for Accident Prevention.* Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

As highlighted by these 12 points, GC is applied in all sectors in which the chemical activity (from synthesis to characterization and analysis to the production of materials/substances) is directly addressed. Necessarily these principles, therefore, turn out to be completely general and give a broad indication as to how to develop and proceed in the activities.

GC and its principles therefore generally represent how to be able to use chemical techniques and methodologies that reduce or eliminate the use and/or generation of substances (materials, products, by-products, solvents, reagents) dangerous for human health or for the environment. At present, GC represents a key tool in the field of prevention (as enshrined in the Pollution Prevention Act of 1990) [15,16].

As a result of this increased "green" sense, in recent decades innovative chemical substances have been developed for the treatment of chemical waste, the remediation of hazardous waste sites, new monitoring and analysis tools developed, new procedures developed to minimize exposure to toxic.

However, it should be emphasized that all these actions aim to reduce the risk (therefore once the damage has been done), but do not yet represent the true meaning of "prevention" or "green chemistry". In particular because, as reported by Anastas [17], GC uses chemistry for pollution prevention.

Since its institution, GC has focused on carrying out chemical activities (chemical design, production, analysis, use, disposal) such that all hazardous and/or potentially harmful/toxic substances are not used and generated. Even if this vision seems "simplistic", it gives a good idea of the global intervention of the GC and how the figure of the chemist should be perceived today (as designers of the material). The GC starts from the assumption that any activity involving chemical processes must necessarily contemplate the characteristic of "not-harming human health" and the environment, reducing risks, but at the same time maintaining and increasing the quality of life through chemistry and technological advances. Based on this scenario, GC may appear as a "limiting" element. Actually its aims also include (and above all) the need to further advance the technological results of chemistry in a sustainable way to preserve (and if possible improve) the current scenario [17]. A primary aspect for the GC is therefore the evaluation of the "risk" as the product of the danger of a particular substance and the exposure:

$$Risk = Danger \cdot Exposure$$

It therefore appears evident how the GC works to minimize (or eliminate) the danger. Unfortunately, the real limitation of GC lies in the fact that it is based on a whole series of information now available on factors such as toxicity and environmental impact, but it is clear that this information is continuously updated [17]. Hence the fact that the GC must continue to update itself with new discoveries in order to preserve its function.

From this point of view, another important point should be highlighted. Analytical chemistry is directly involved in the entire process related to GC concepts as the only discipline that allows quantitative analysis (in this case referring to toxic/harmful compounds). Ironically, until a few decades ago, this discipline did not concern the use of potentially "risky" materials (or the generation of products/waste). With the birth and development of the GC, a gradual and growing interest of this discipline has therefore been observed towards a reduction of the impact deriving from the application of "risky" methods and procedures, favoring the development of "green" technologies/methods that could be also in field applied. This has allowed, for example, the development of analytical sensors for the continuous monitoring of processes that can intervene if toxic substances are generated due to excessive heat or

pressure or due to the excessive addition of a reagent in a production process, by regulating the process parameters [17].

In this scenario, as recently reported by Wojnowski et al. [13] it was necessary to develop a further "sub-level" deriving from the principles of GC but more specifically referred to the field of Analytical Chemistry. Gałuszka and coworkers firstly highlighted this concept and necessity about a decade ago, and gave birth to a publication [18] destined to remain the milestone and the true representative of the "birth" of GAC.

2.2. Green analytical chemistry (GAC)

It is interesting to note how from the principles of GC, the specific ones relating to the analytical field have developed. These are enclosed and indicated by the acronym "*SIGNIFICANCE*" and are the "milestones" of GAC [18]. The 12 principles relating to the GAC, as reported by Gałuszka and coworkers [18] can be summarized as follows:

1 Direct analytical techniques should be applied to avoid sample treatment.
2 Integration of analytical processes and operations saves energy and reduces the use of reagents.
3 Generation of a large volume of analytical waste should be avoided and proper management of analytical waste should be provided.
4 Minimal sample size and minimal number of samples are goals.
5 Automated and miniaturized methods should be selected.
6 Reagents obtained from renewable sources should be preferred.
7 The safety of the operator should be increased.
8 *In situ* measurements should be performed.
9 Derivatization should be avoided.
10 The use of energy should be minimized.
11 Multi-analyte or multi-parameter methods are preferred versus methods using one analyte or parameter at a time.
12 Toxic reagents should be eliminated or replaced.

From the enunciation of the GAC principles, it is evident how the general concepts of the GC have been "adapted" and remodeled based on the specific Analytical Chemistry field and procedures. These principles involve all steps of the analytical process and, even if not explicitly, refer to sampling, sample preparation, sample analysis, instrument configuration, and supply [18].

By the definition, analytical chemistry is concerned with providing fundamental data for making decisions about human and environmental health. It follows that the possibility of having rapid, accurate (precise and true) results represent the goal of the analytical chemist. In this context, the GAC adds new challenges to meet the information needs of chemists, industry, and society by reducing the human and environmental impact deriving from the analytical processes.

In this field, due to the nature of the analyte, the matrix and above all the method used to generate the analytical signal are the basis of all evaluations related to the GAC. In fact, for example, methods that do not require pre-treatment, use few reagents or work with aqueous solvents certainly show a huge advantage in terms of "greenness". On the other hand, a method that involve many steps can be divided into 2 macro-categories: the pre-treatment phases (including digestion, extraction, drying and concentration) and the signal acquisition phase.

In principle, therefore, a green analysis will tend to eliminate the pre-concentration phases even if this step remains crucial in the analytical process. As such, recent methodologies developed include intense improvements in reagent and solvent modification, reduction of chemicals used through automation and advanced flow techniques, miniaturization, and even the elimination of sampling by measuring analytes in situ, *on line* or *in field*.

In the last decade, in addition to having witnessed the birth of the GAC, however, it has been observed that, although the principles of the GAC could be applied in the analytical field, they involved the entire process chain without "entering" into the characterizing steps mentioned above. In particular, it can be noted that the steps relating to instrumental analysis and configuration are predominant even if, as experience has shown, the most critical steps are those relating to sampling and sample preparation. This element has been thoroughly discussed in literature [19–22], especially for the field of (Bio)Analytical Sample Treatment Procedures for Clinical Applications (pharmacotoxicological, therapeutic drug monitoring (TDM), and forensic) often coupled to liquid chromatography-tandem mass spectrometry (LC-MS/MS). This is quite apparent as more methods have been published during the last decade, where more attention was paid precisely to these steps.

Nowadays it is increasingly common to see more "green" bioanalytical methods due to the highly selective nature of the reactions, which has usually eliminated the need for further separation or concentration steps, as well as the development of new instrumental configurations that, thanks to their extreme selectivity and sensitivity, allow minimizing the sample manipulation. Examples of these developments and trends are certainly represented by the new electrochemical biosensors [23–26], but also by instrumental configurations that allow the reduction of the sample manipulation by means of the "dilute and shoot" procedure [27], fast multi-analyte LC-MS/MS methods [28,29], or fast procedures for rapid multi-analyte screening [30,31]. These elements highlight how the technological development, the implementation of the automation process through the aid of sample preparers, and integrated systems (even of increasingly smaller dimensions) respond to the principles of the GAC.

2.3. Green sample preparation (GSP)

As previously seen, the so-called "*funnel effect*" which is often observed in many sectors of science has led from the development and consolidation of GC and its principles to GAC, specifically developed for the analytical field, up to the "bottleneck" represented by GSP. The latter considers and originates from both GC and GAC, but applies and enunciates its principles in an extremely specific and detailed way regarding the procedures that are applied during sampling and sample preparation [17]. The 10 principles related to the GSP could be stated as follows [32]:

1 Favor *in situ* sample preparation.
2 Use safer solvents and reagents.
3 Target sustainable, reusable, and renewable materials.
4 Minimize waste.
5 Minimize sample, chemical and material amounts.
6 Maximize sample throughput.
7 Integrate steps and promote automation.
8 Minimize energy consumption.
9 Choose the greenest possible post-sample preparation configuration for analysis.
10 Ensure safe procedures for the operator.

As previously stated, Table 1 shows the principles of GC, GAC, and GSP side by side in order to better evaluate similarities and differences especially at the level of application field (from all sectors related to the chemical activity, to analytical chemistry, to sampling and sample preparation) and in the terminology used to specify the single principle. It should be emphasized that GC, GAC, and GSP represent a sort of evolutionary process that from the general leads to defining characteristic and specific elements of an application field. It is important to note that one does not exclude the other. On the contrary, they integrate in a complementary way to provide (as far as possible) a correct assessment of the green profile of a procedure, reduce the environmental impact, improve and translate the ecology findings in the analytical chemistry laboratories (and operators).

So far we have seen how the succession of events led from GC to GAC and finally to GSP. In all cases we have observed the development of principles starting from the general (GC) to the more specific (GSP)

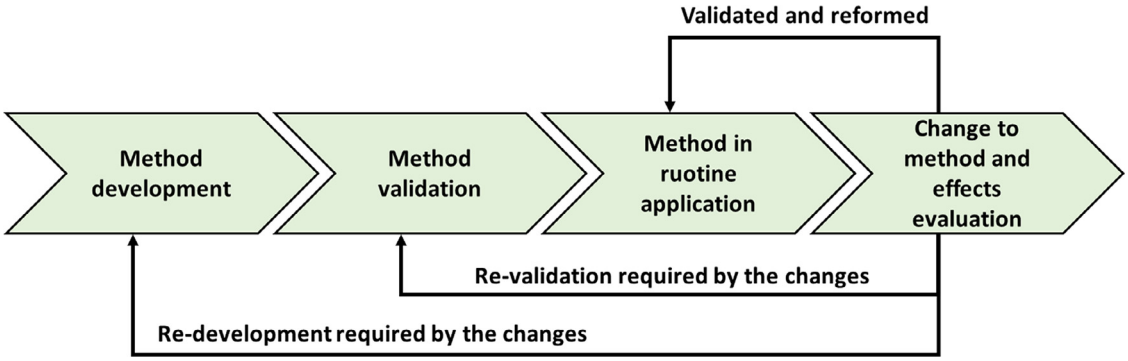

Fig. 2. LCA model.

trying to "adapt" the higher level to the more detailed lower one, sometimes "losing" sight of the objective or items that apparently do not seem related to the "sub-level".

Extremely green methods are often observed from the point of view of sample preparation (SPME, MEPS, FPSE), but which in terms of instrumental analysis or overall impact are "bad" in terms of electricity consumption, use of additives to maximize the analytical signal, reduced reuse or presence of waste that is not easy to manage, the need for a series of surrounding elements that have a strong impact on the environment.

Similarly, green instrumental configurations can be observed (electrochemical sensors for *in field* analysis) which however require the use of reagents or energy sources that have a negative impact on the environment. To optimize and improve the impact of the principles of these 3 elements, the possibility of simultaneously evaluating all these aspects should be considered through an integrated and multi-parameter approach which does not exclude any parameter/principle and which considers them in their totality and how they may involve mutual influences in their evaluation. From what we have seen so far, it should also be considered that GC, GAC, and GSP must deal with Ethics (understood as compromise with the environment and compromise with operators) and with Business (understood as reduction of costs and added value of methods) [33].

It is therefore evident that the scenario and the challenges to be faced are very important and that they necessarily require a multidisciplinary approach, including the economic and ethical one, even if the GC, GAC, and GSP must be made autonomous and independent from other "external" factors which can mislead the results.

The GC, GAC, and GSP seen so far must also be able to "keep up" and be able to evolve according to the continuous change of the scientific landscape, techniques, materials, and knowledge. From this point of view, it could be important to develop a single multidisciplinary sector that incorporates all the elements and all the experts and expertise to serve as an international reference and "speak" a single language. This is to avoid the "*divide et impera*" (divide into several parts in such a way as to provoke rivalry and foment "discord" between them) which is often observed when different types of interests are at stake (especially business) and really generate an idea, a guideline, a set of unique principles, universally accepted and supported by a single working group.

3. Green profile evaluation

After having seen and recalled the principles that "*govern*" GC, GAC, and GSP, let us now see what tools have been developed up to now for green profile evaluation. In this context, is necessary to consider the LCA, NEMI, Analytical Eco-scale, GAPI and ComplexGAPI, the RGB and WAC models, the hexagon-CALIFICAMET, and the AGREE and AGREEprep models.

Before addressing the various protocols proposed for the evaluation of the green profile individually, it would be appropriate to highlight how, in order to be useful and usable, an evaluation scale should be able to:

i) Evaluate and consider all the different elements of a method individually.
ii) Provide some sort of (quantitative) measure of the suitability and potential of the overall method.
iii) Be easy to understand, apply, and fast and intuitive in its execution.
iv) Be flexible so that it can adapt to specific elements of a method (or can adapt to always new procedures/instrument configurations developed).
v) Allow the method to be re-evaluated by other analysts using a standardized approach.
vi) Evaluate the potential of the method from both a qualitative and quantitative point of view.

3.1. Life cycle assessment (LCA)

Analytical processes are currently applied in many fields, and the data obtained from these analyses represent the starting point for making even very important decisions with an impact on the society. These fields can be represented, by way of example, from the forensic, pharmacotoxicological, environmental, food, etc. fields, where Analytical Chemistry and quantitative analysis are the masters as the results of these analyzes can make the difference between subsequent actions/legal decisions at the level of the penal and/or civil code. Precisely for this reason, these processes must be characterized by a high and constant quality. This standard could be guaranteed, among other tools available to the analytical chemist, by the LCA tool, which allows evaluating the potential impacts of products, processes or services through production, use and disposal [4]. This tool serves as a decision support and not as a measurement tool [34] and is adaptable to analytical methodologies only when the analytical protocol is considered as a process and the output of this process in the form of traceable results [35].

The main problem associated with the use of LCA is related to the fact that this tool is based on "*managerial principles*", organizational behavior and cognition, while the analytical field needs standardized guidelines to ensure the high quality of its application. Another element that partially limits the application of the LCA in the field of analytical chemistry consists in the fact that the impact assessment methods must be extended with further indicators of human and ecosystem health. Fig. 2 shows an example of LCA applied to the field of analytical chemistry.

The LCA is an excellent tool applicable in the internal management of a laboratory in order to minimize and streamline the procedures to adapt to new orders and/or regulations regarding specific and new legal limits (or analytes to be monitored), as it allows to speed up (and consequently make more flexible) the revalidation procedures. In this way, the laboratory is faster in responding, for example, to the needs of an increasingly evolving analysis landscape.

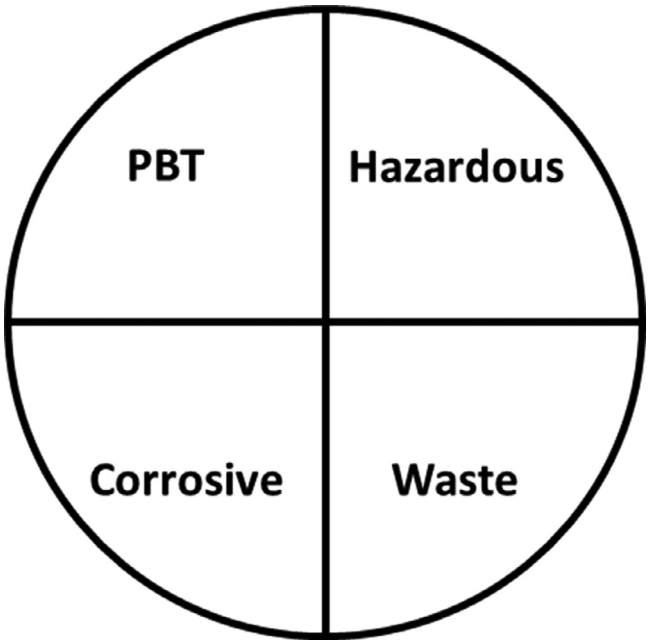

Fig. 3. Pictogram of the NEMI model.

Currently the use of LCA is widely applied in the field of industrial production as a consolidated and structured approach in order to quantify the environmental impacts of production systems by providing a standardized tool to compare different types of raw materials and production technologies. LCA can also be used as a decision-making tool to optimize production systems to understand environmental impacts in terms of e.g. agricultural production, harvesting, transportation, pre-treatment, treatment technology and application. Therefore, LCA of production systems is important for minimizing environmental impacts even though the detailed definitions of functional units and system boundaries (which are often loose) differ between studies and make comparisons difficult. In general, for example to assess climate change, elements such as carbon footprint, greenhouse gas emissions, carbon sequestration, carbon abatement, carbon balance and global warming potential can be considered. Items such as resource depletion and human health, acidification potential, fossil fuel depletion potential, and human toxicity may also be included [36,37]. Other examples of application of the LCA tool have been recently reviewed by Chopra and coworkers [38] regarding the sustainable chemistry for textile waste valorization, by Chordia and coworkers [39] regarding the battery-grade lithium supply from brine and spodumene, and by Zhu and coworkers [40] for sustainable production of biochar from agro-residues.

3.2. National environmental methods index (NEMI)

Following the evaluation of the application limitations of the LCA in the field of analytical chemistry, a new tool for the evaluation of the green profile has been developed, the NEMI. This tool is nothing more than a free database containing freely available environmental methods [41]. The NEMI, even if it overcomes the shortcomings and limitations previously seen for the LCA, and shows some undoubted advantages (easy to read and consult for users and reports a “green” label for the procedure), it also has some disadvantages. First, it is represented by the fact that the NEMI symbol (Fig. 3) shows all the "threats" depending on whether they are above or below a threshold value, but it is not able to provide a "threat scale", thus representing only a purely qualitative tool. Another disadvantage of the NEMI is that it refers to some methods (and not to all of those available). Furthermore, most of them consider water as a matrix, even if the database includes some specific methods for other types of matrix (e.g., air, animal tissue, soils/sediment, and other), and there are a few methods representative of these media.

However, the main limitation of the NEMI is represented by the fact that if the value of the method is below a certain threshold, then the sector of the pictogram is colored green, if above it remains clear (white). This poses a very important limit, even if de la Guardia and Armenta [33] have proposed to improve it with a second pictogram. This second element is divided into 4 sectors to evaluate qualitatively (from red to orange and green for the high, medium, or low risk, respectively) the green profile for operators and the levels of reagent and energy consumption and waste. Another disadvantage is that it needs to consider several critical aspects, especially nowadays, such as energy consumption, chemical products, reagents, and the amount of waste generated. Wanting to highlight other "critical" elements can dwell on the fact that, although it is a free database, the search to be carried out for every single substance that is done by the user in the official lists (EPA TRI list, Resource Conservation and Recovery Act, etc.) takes a long time.

Several articles are beginning to appear in the literature that, during the development of the method and in its application, consider also associating an evaluation of its impact using the tools seen. In particular, NEMI has recently been applied to evaluate the profile of an HPLC–UV method for simultaneous determination of a quaternary mixture used for the treatment of symptoms related to common cold and COVID-19 [42]. Other interesting and very recent application of this tool is related to the evaluation of a new isoindole-based fluoro-probe for feasible tagging and tracking of topiramate in bulk powder and prescribed commercial products [43], to the evaluation of three developed spectrophotometric methods for determination of a mixture of ofloxacin and ornidazole [44], and antihypertensive drug telmisartan with Nebivolol in human plasma [45].

In light of what have seen, and although moving from LCA to NEMI was observed as a step forward in trying to create a "gold standard" for the green profile evaluation, the study and creation of new tools has continued, leading to the development of the Analytical Eco-scale.

3.3. Analytical eco-scale

In the style of NEMI, Gałuszka, and collaborators [6] proposed a new tool for green profile assessment about a decade ago. This tool, the Analytical Eco-scale, is nothing more than a sort of scoreboard. Starting from 100 points, the "penalty points" (PPs) are counted based on the reagents and instrumentation selection, considering also several aspects like amount of reagents, hazards, energy consumption and wastes [6]. At the end of the process, as shown in Fig. 4, a higher score corresponds to a more sustainable analytical procedure. The final score allow to classify the method as “excellent green analysis” (>75 points), acceptable (75–50 points), and inadequate (<50 points).

Compared to its predecessors (LCA and NEMI), the Analytical Eco-scale is characterized by numerous advantages, such as:

- ü Ease to use.
- ü Semi-quantitative calculation.
- ü Information on the environmental impacts of analytical approaches is provided quantitatively.
- ü Different aspects of the environmental impacts are evaluated.

Even if this tool may seem decisive for the evaluation of the green profile, it still has some disadvantages related above all to the lack of additional quantifiers that can discriminate the different "*nuances*" of the analytical procedures (for example, the discrimination between micro and macro scale).

Another disadvantage is represented by the fact that the final result (analytical eco-scale total score) cannot be considered as genuinely informative of the negative environmental impact, and for this reason, it makes difficult the improvement and optimization process (especially as regards environmental impact) during its development and design.

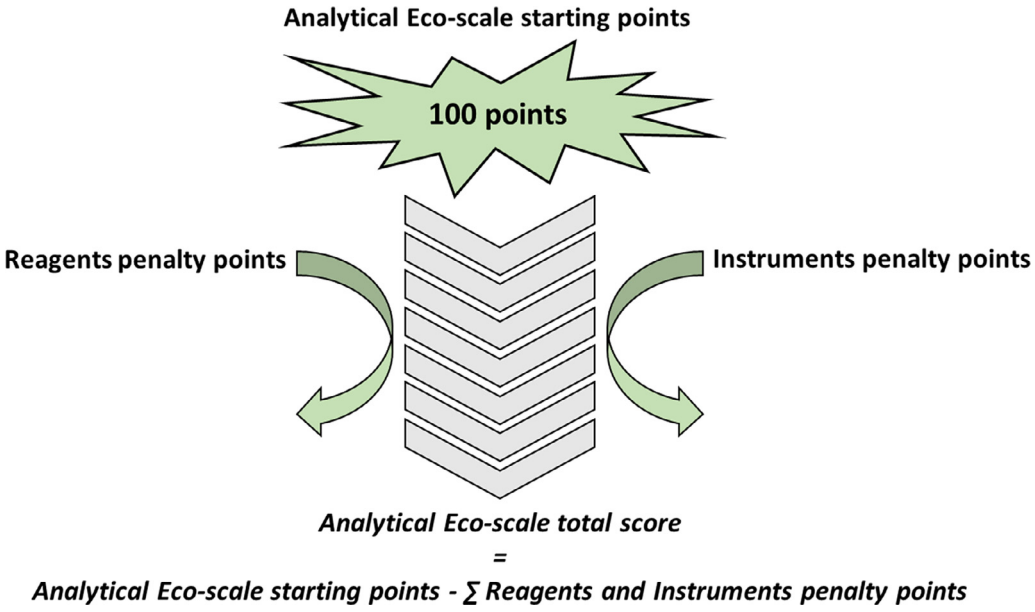

Fig. 4. Analytical Eco-scale model.

Compared to the previous tools, Analytical Eco-Scale represents a significant step forward in the attempt of standardization to obtain a univocal evaluation and to be able to compare the different methods, even if it is limited to a simple score. In fact, from the score, without further information, it is difficult to critically evaluate the procedure and find the critical points on which to intervene (and how). The score does not provide information on the nature of the hazardous components and above all there is little information on the causes of the non-ecological impact on the environment (for example the types of solvents and chemical products involved, the waste produced, their possible reuse, secondary products and their toxicity).

Examples of applications related to the Analytical Eco-scale are reported in the literature for the determination of Dextromethorphan hydrobromide [46], for the simultaneous analysis of combined antihypertensive medications [47], for the analysis of Benzodiazepines [48], Hydrochlorothiazide and Telmisartan [49]. Kanaka [50] recently reviews other interesting examples.

3.4. Green analytical procedure index (GAPI) and ComplexGAPI

Płotka-Wysylka in 2018 [7] proposed a new method for the evaluation of the green profile of an analytical procedure, the GAPI. In this pictogram, 16 characterizing elements (as specified and defined in Table 2) of the method are considered, from collection (1) to waste treatment (15). Furthermore, GAPI gives a quantitative and qualitative result if it has a circle in the center, and only qualitative when it does not have it. These elements, shown in Fig. 5 on the left, highlight by means of three colors (red, yellow and green) inserted in the respective sectors, how "green" the method overall appears to be.

Since its development, the GAPI has been used in the literature with good results in the evaluation of the green profile of an analytical method [28-31,51], although it showed limitations in being able to exhaustively evaluate all the elements necessary for a correct classification of the protocol regarding the environmental impact. In particular, we refer to all the surrounding elements necessary for the method application (preparatory procedures, laboratory-conditioning system, energy consumption linked to the vortex and other accessories, etc.).

For this reason, in Fig. 5, was further highlighted how, in merely three years, the GAPI pictogram was improved and evolved in ComplexGAPI (on the right), as reported by Płotka-Wasylka and Wojnowski [8]. For the specific details relating to GAPI and ComplexGAPI (see Table 2 were parameters of E-factor are shown), beyond the visual pictogram, it is interesting to see the "evolution" of the parameters considered, above all with the addition of the "E-factor" hexagon (Fig. 6), in which were added several parameters related to the pre-analysis process.

In particular, in the ComplexGAPI, the E-factor is an important novelty that introduces the waste generated. The E-factor takes into account not only waste by-products and remaining reactants, but also spent catalysts and catalyst supports, solvent losses, and anything else that could be considered waste. Its calculation is performed through a simple ratio between total mass of waste from process (or even mass of raw materials-mass of product) and total mass of product. In practice, the E-factor is an index related to the amount of waste deriving from the process and the higher it is, the greater the waste generated, the greater its negative and less sustainable environmental impact.

This element can be further highlighted in Table 2, where the description of the GAPI parameters is shown (in practice, it only considers the "component" of sample preparation and analysis). In contrast, the parameters of ComplexGAPI (with the addition of the E-factor), consider the pre-analysis process and sample preparation and analysis.

In the pictogram of GAPI and ComplexGAPI, the assignment of colors (red, yellow, and green) is done by evaluating the individual parameters by assigning them the corresponding color according to Table 1 of the article by Płotka-Wasylka and Wojnowski [8]. Compared to the previous tools, GAPI and ComplexGAPI make it possible to expand the number of parameters considered, allowing for a more precise assessment of the green profile. Furthermore, both provide an immediate "quantitative" pictogram from a visual point of view, in fact the greener it is, the more the method adheres to the principles of the GAC. A limitation of GAPI and ComplexGAPI is that it does not provide a software application that allows to directly entering the method parameters returning the resulting pictogram. In fact, it leaves the individual operator the freedom to process and manage the data and the coloring of the relative sector results only from the comparison with the threshold values (see Table 1 ref. [8]).

3.5. RGB (Red green blue) and white analytical chemistry (WAC) models

There is a growing interest in the literature in reducing the environmental impact and improving the green profile, even if it is often challenging to find the right compromise between analytical performance

Table 2
Comparison between GAPI and ComplexGAPI parameter description.

Pre-analysis processes			
Yield/selectivity and conditions	**I**	Yield	**ComplexGAPI**
	II	Temperature/time	
Relation to the green economy	**III**	Number of rules met	
Reagents and solvents	**IVa**	Health hazard	
	IVb	Safety hazard	
Instrumentation	**Va**	Technical setup	
	Vb	Energy	
	Vc	Occupational hazard	
	VIa	Workup and purification end product	
	VIb	Purity	
Sample preparation and analysis			
Sample preparation	**1**	Collection	**GAPI**
	2	Preservation	
	3	Transport	
	4	Storage	
	5	Type of method: direct or indirect	
	6	Scale of extraction	
	7	Solvents/reagents used	
	8	Additional treatments	
Reagents and Solvents	**9**	Amount	
	10	Health hazard	
	11	Safety hazard	
Instrumentation	**12**	Energy	
	13	Occupational hazard	
	14	Waste	
	15	Waste treatment	
Type of procedure		Circle (quantitative)/no circle (qualitative)	

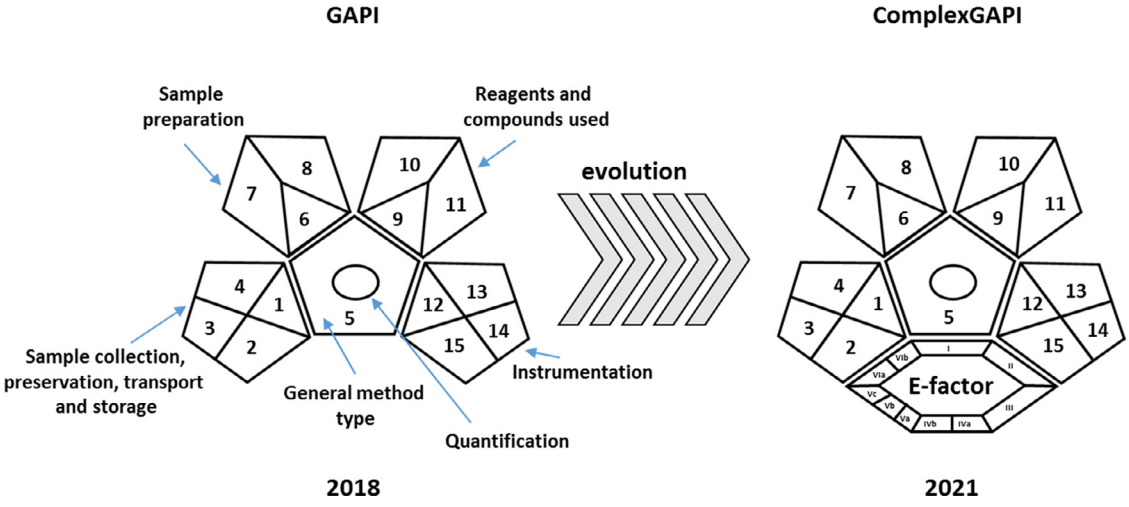

Fig. 5. Pictogram of the GAPI (left) and its evolution after 3 years, the ComplexGAPI (right).

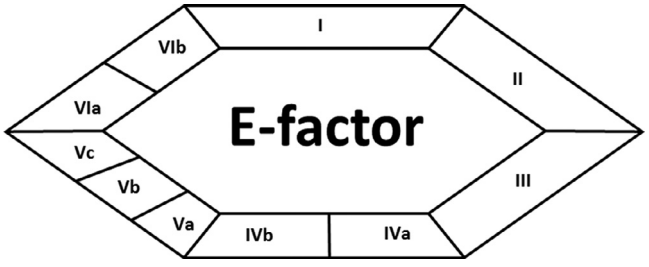

Fig. 6. Magnification of the "E-factor" hexagon.

and greenness. This is further complicated by the fact that standardized and unbiased tools are often lacking.

In all the tools seen so far, some give greater credit to some parameters, while others are totally not considered (costs and times, reuse of materials, type of personnel required, frequency of maintenance/quality control on the tool, etc.).

Even the RGB (red, green, blue) model based, as occurs in electronic devices, on the mixing of three primary colors of light to produce an impression of white is not excluded. The RGB additive color tool therefore exploits the three primary colors in order to indicate the main elements relating to the method under examination. Specifically, red indicates analytical performance, green indicates how much the method respects the principles of green chemistry, while blue refers to practical productivity/effectiveness.

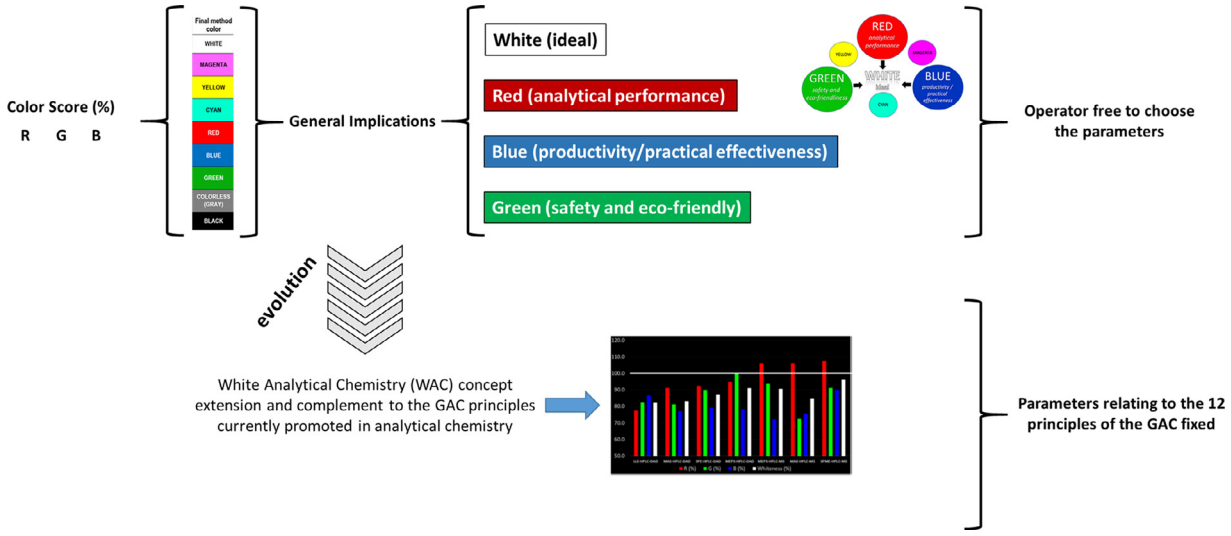

Fig. 7. RGB and WAC model.

In this tool, an analytical method goes blank if it satisfactorily possesses all the primary attributes in the different parameters that this model considers. White is attributed to the most complete and coherent method, while combinations of the three primary colors give rise to secondary colors such as yellow, magenta or cyan, which represent satisfactory methods in terms of two parameters but lack the remaining primary color, so they are neither complete nor coherent.

Similarly, a red, green, or blue method has only one acceptable parameter (missing the other two). Red is assigned to analytical efficiency expressed through validation criteria (precision and trueness, LOD and others), green implies compliance with GAC principles, while blue represents productivity and practical/economic efficiency.

After having considered all the parameters, to the method as a whole is attributed a color resulting from the various shares of the primary colors and an evaluation of the procedure can be obtained based on the result. In fact, the farther the resulting color is from white (in the RGB space), the lower the overall average green potential of the method, as shown in Fig. 7.

To evaluate whether a method conforms to the idea of red, green, and blue, this is quantitatively measured using a Color Score (CS) ranging from 0% to 100%. The method acquires one of these elementary colors only if the corresponding CS is ≥66.6% (to which a "lower satisfactory value" or LSV is attributed). Otherwise, the method is assumed to lose this primary color. If its CS is ≥33.3% (which is given a "lower acceptable value" or LAV), the method is colorless with respect to this primary attribute and transparent/neutral for two other attributes.

To attribute the value, it is the operator that define the limits of the LSV and LAV (for example for a parameter such as trueness, an LSV can be set to 3% and the LAV to 5%) and based on the results of the method calculates the percentage value to be attributed to that parameter and from this the corresponding color.

Thus, if one CS is tolerable and two other CS values are satisfactory, the method is magenta, yellow, or cyan (depending on the resulting overall percentage and the weight given to the individual CS). If two CS values are in the acceptable range and one is in the satisfaction range, the method is red, green, or blue. If all three CS values are acceptable but unsatisfactory, the method is colorless (represented by the gray color). However, if at least one CS is <33.3%, the method goes black and non-transparent to other attributes. In other words, it is always ultimately black because all other primary colors are blocked out. This approach is justified by the logical reasoning that if at least one primary attribute is unacceptable, any other positive feature of the method is obscured in the final evaluation.

The RGB model can allow a user to:

i) Uniquely evaluate the method and produce a graphical coding of its characteristics.
ii) Choose the best method to apply.
iii) Have the possibility to compare the methods based on the evaluations obtained by the RGB algorithm.
iv) Observe also theoretical elements that can be useful in the development of future methods.

As seen for the GAPI and ComplexGAPI tools, the RGB model is also quite flexible and can be implemented freely. If on the one hand this element guarantees its flexibility, on the other hand it limits its standardization since according to the "sensitivity" of the operator the tool can be more or less complex and complete. RGB allows for different color intensities, allowing greater precision to be considered in the method evaluation. The original set seemed to be sufficient, but could be implemented by a much more extensive set of colors (for example if you want to apply it in other fields other than Analytical Chemistry such as Biochemistry, the study of equilibria in solution, reaction kinetics, chemical synthesis, etc.).

The concept of WAC was then developed from the RGB tool as an evaluation element of a method. The WAC represents an extension and a complement to the principles of the GAC. The WAC in particular allows bypassing the RGB problem (as well as GAPI and ComplexGAPI) regarding the direct attribution of different weights to the given rules [12], the methodological specificity should be found in the level of criticality in the evaluation of the fundamental rules for its application.

Similarly, the WAC not only takes into account these elements of the RGB model (based on the same procedure and scheme), but also inserts other key criteria that influence the quality of the method, analytical (red) and practical (blue). Referring to the RGB color model, according to which the mixing of red, green and blue light beams gives the impression of white, a white analytical method shows the coherence and synergy of analytical, ecological and practical attributes. The degree of whiteness can also be quantified, based on the evaluation of the single principles, as a convenient parameter useful in comparisons and in the choice of the optimal method. WAC is closer to the idea of sustainable development thanks to a more holistic view, as it seeks a compromise that avoids an unconditional increase in greenery at the expense of functionality.

In particular, the transition to the WAC meant that for the color red (analytical performance) we moved from considering precision, trueness and sensitivity to considering the purpose of the application, LOD

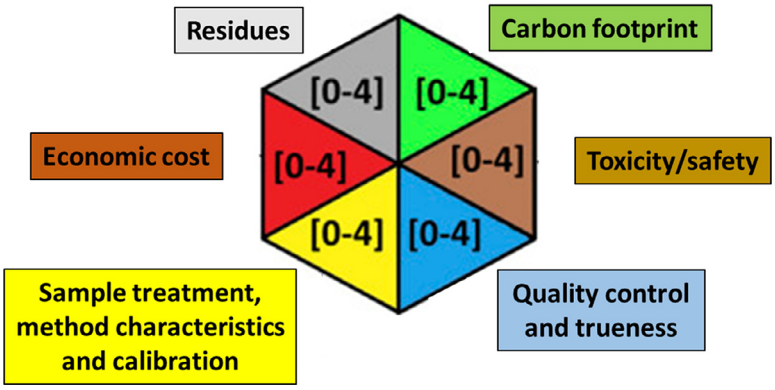

Fig. 8. Pictogram of the hexagon-CALIFICAMET (from 0 to 4 the parameter gets worse).

and LOQ, precision and trueness. For the green color (safety and eco-friendliness) from the mere quantity of chemicals and their toxicity, and "other hazards" without specifying anything else, to considering the toxicity of the reagents, quantity of reagents, energy consumption, direct impact (safety, use of animals, etc.). For the blue color (productivity/practical effectiveness) from cost per analysis, sample throughput and sample material consumption, to considering parameters such as cost-efficiency, time-efficiency, requirements (sample consumption, advanced instruments skills, facilities, etc.) and operational simplicity (miniaturization, integration and automation, portability). As can also be seen from Fig. 7, these "evolutionary" elements have led to an "implemented" RGB tool that considers all 12 GAC principles.

A very important element in these tools is the sufficient self-criticism of the authors in the evaluation of their methods, which leads to an overestimation of the scores (perhaps by excluding some criteria that could worsen the green profile). The RGB and the WAC tools, although based on subjective evaluations, "*force*" to evaluate all the criteria considered and therefore to an exhaustive elaboration.

Based on what has been seen for both the RGB and WAC models, in order to obtain a standardized tool it would perhaps be appropriate to evaluate whether to develop a further evolution of the WAC where, while keeping the parameters relating to the 12 principles of the GAC fixed, additional specifications are also inserted highlighted in the GSP. Another "critical" element of both the RGB and WAC tools is linked to the non-immediacy in understanding the several elements and for this reason, a future development could envisage a graphical interface that allows for a more immediate evaluation of where to intervene in order to reduce the impact and improve its green profile. Hussain and coworkers [52], also reporting the recent progresses in the white analytical chemistry-based biological, food and environmental applications, recently reviewed examples of RGB and WAC tools applications.

3.6. hexagon-CALIFICAMET

In this panorama, especially as regards the environmental impact, a step forward was made when in 2019 Jornet-Martínez and coworkers proposed the CALIFICAMET [53]. In fact, this tool makes it possible to evaluate the performance of a method with respect to its sustainability, the associated risks, the analytical characteristics, and the relative costs by means of a score from 0 (satisfactory) to 4 (unsatisfactory).

In the development phase, in which other research groups are also involved [54,55], the CALIFICAMET tool includes the evaluation of five variables (as reported in Fig. 8):

i) Sustainability of the method and estimation of the carbon footprint as a metric parameter to evaluate the negative impact of a methodology and the study of the residues generated in terms of quantity.
ii) Type and potential recycling.
iii) Associated chemical and health risks (assessed based on toxicity, hazard and safety considerations of the reagents/materials involved).
iv) Analytical performance (qualified through the adequacy of the figures of merit to the solution of the problem faced) related to sample treatment, method and calibration, quality control and trueness.
v) Cost of the methodology (estimated from the consumption of reagents and energy, hours of personnel and instrumentation required for a given number of samples that is then normalized to one).

The CALIFICAMET tool also includes penalty points, which serve to increase the level of impact quantification. The absence of penalty points indicates a method that contemplates the use of nontoxic reagents or solvents, low waste generation (or subject to appropriate treatment), low energy consumption and an excellent cost to benefit ratio. If in one of the criteria considered by the CALIFICAMET tool (for example, safety for both the analyst and the environment), PPs are evaluated, and the higher the PPs number, the worse the final evaluation of the method will be.

In CALIFICAMET, the analytical procedures are evaluated both considering the figures of merit concerning the sample treatment, the characteristics of the method and the calibration procedure, but also the quality control and the trueness.

In assessing toxicity and safety, the degree of toxicity and danger of the chemical products used and the possible exposure of personnel to risks are considered. On the other hand, the amount of waste generated and its treatment are wholesale considered under the item relating to waste.

Regarding the calculation of the carbon footprint [55] this parameter is specifically aimed at the environmental impact. The CALIFICAMET tool also calculates the annual economic cost associated with the procedure.

Even if this tool contemplates most of the elements necessary for the methods comparison, it shows limitations in its use as it does not consider all the fundamental parts related to the sampling and does not allow, for example, the distinction between micro- and macro-procedures.

Currently in the literature, there is only one article in which the Hexagon-CALIFICAMET is applied as a tool for evaluating the green profile [56], an indication of how this tool has not found great success in the scientific community. Perhaps this is related to the fact that other more performing, complete, and clearer tools such as AGREE (2020) and AGREEprep (2022) were developed at the same time.

3.7. AGREE and AGREEprep

The various tools described above are characterized by many advantages but also have several disadvantages, such as:

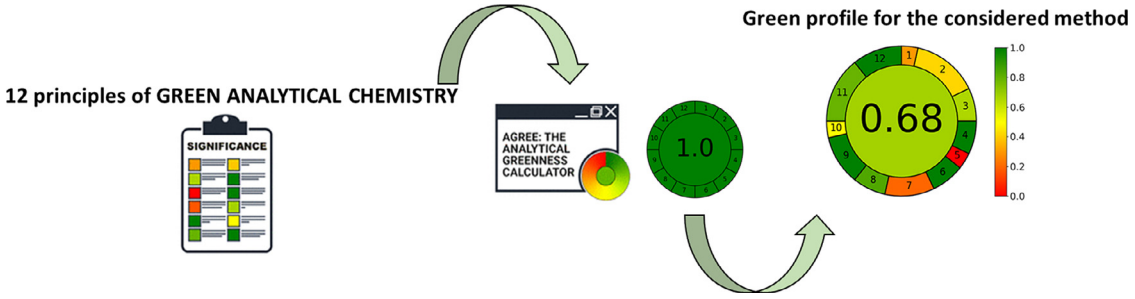

Fig. 9. Pictogram of the AGREE.

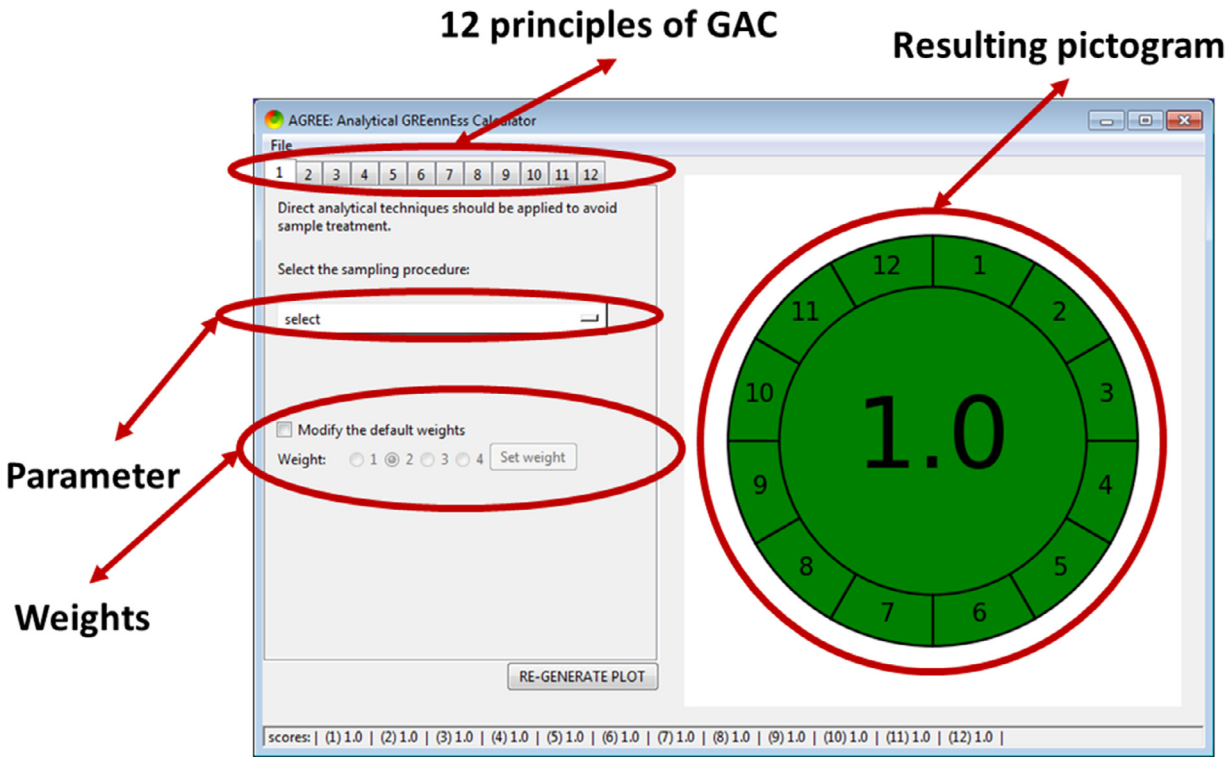

Fig. 10. AGREE software and its interface.

i) Consider a few evaluation parameters.
ii) Evaluation of criteria as non-continuous functions.
iii) The results do not always contain information on hazards.
iv) Provide general information on the method.
v) Do not always distinguish between micro- and macro-procedures.
vi) Sometimes, you leave "too much freedom" in entering the parameters, creating potentially biased evaluations.

Another essential element is that the previous tools often provide output without considering each of the 12 principles of the GAC. Therefore, the development of a complete, simple, and immediate metric tool to evaluate the procedures is of primary importance. In 2020, Pena-Pereira and colleagues reported a handy tool, AGREE [12], which allows to answer many of the disadvantages highlighted in the previous models.

In particular, the AGREE model, which responds to the 12 principles of the GAC [18] (as highlighted in Fig. 9), has the advantage of a completeness in the input including many parameters previously not considered.

The software interface (Fig. 10) is divided into 12 "windows" in which the 12 principles of the GAC are explained and considered. Through an algorithm that evaluates all the inputs (binary, discrete or continuous functions), it is possible to obtain the construction (on the right of Fig. 10) of the pictogram relating to the procedure.

Since it is structured in specific "sections" for each principle of the GAC, it has been possible to assign a differential weight to each one according to the specific analytical method being evaluated (for some researchers it is necessary to ensure simplicity, for others to reduce the use of reagents or the generation of waste). Is necessary to highlight that these weights are defined by default (as general software setting), but they can be changed/modified when the operators justified this change.

The AGREE tool also makes it easy to understand the output through pictograms despite the high number of parameters that generated the result. As in previous ones (from 0 to 4 for hexagon-CALIFICAMET, percentage values for RGB and WAC, 3 colors for GAPI and ComplexGAPI, score scale for the Analytical Eco-scale), a reference scale is used in the interval 0–1 (where 0 is unsatisfactory and 1 is satisfactory). Then the result derives from the product of the evaluation results on the single principle. The result of the evaluation of the method is a round and colored pictogram which presents the number in the center, which is the overall index of the green profile (together with the coloring obtained for this area). Around the circle, there are 12 sections, each of which corresponding to one of the performance criteria considered in the model. The length of each section reflects the specific weight (pre-set or mod-

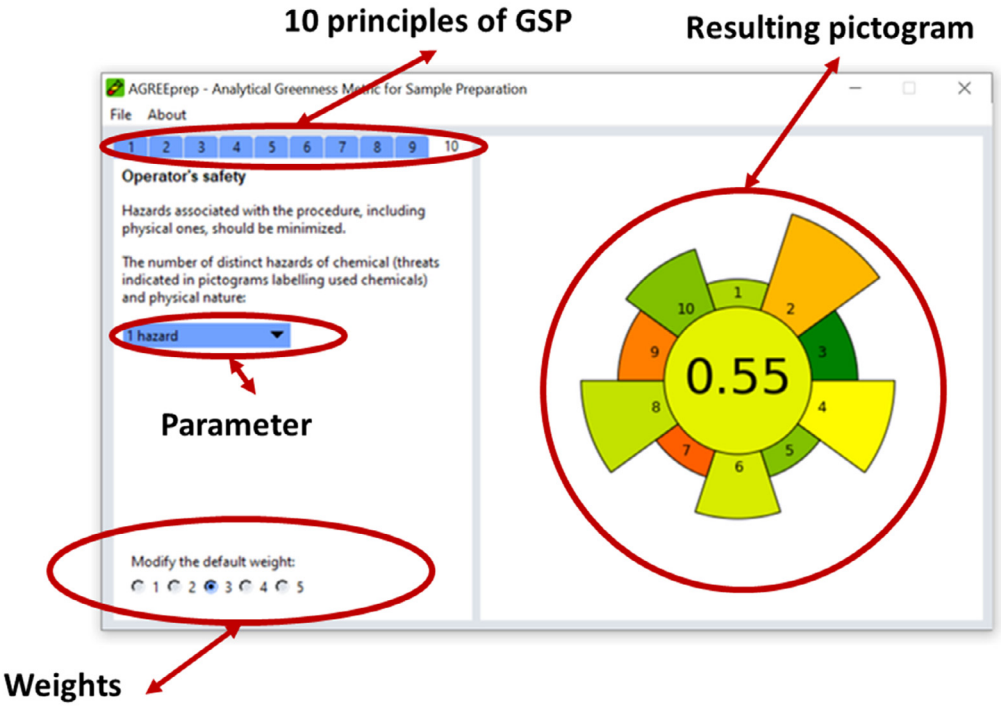

Fig. 11. AGREEprep software and its interface.

ified by the operator with due justification) assigned to the respective evaluation criterion, while as with the inner circle, the color of each section represents the performance in this criterion.

A significant factor is that the software that allows you to generate an AGREE pictogram is free and available online [57]. The AGREE tool, therefore, has many advantages compared to what has been seen:

i) More comprehensive (considers all 12 principles of the GAC).
ii) More flexible (different weights can be assigned to the various parameters considered).
iii) Easy interpretation of the results (colored pictogram that highlights, in the wake of GAPI and ComplexGAPI, the strengths and weaknesses of the method).
iv) Easy to use and run (free software).
v) Fast to deliver the output.

The previous AGREE protocol (and software) works very well with regard to the 12 principles of the GAC according to the acronym "*SIGNIFICANCE*" but finds limitations in the specific field of sample preparation. For this reason, Wojnowski and collaborators [13] have updated and implemented this free "platform" based on the specific sample preparation needs. This is how the AGREEprep system was born. As observed for AGREE, AGREEprep is based on the 10 principles of GSP and the software, in this case, is divided into 10 windows, as well as the different sized of the sectors in the pictogram depending on the weight.

Also in this case the free software can be downloaded from the Internet site [58] and, once installed, can be used in a very simple and intuitive way (exactly such as AGREE), resulting in an assessment of the green profile of the sample preparation procedure. Also in this version for the specific field of sample preparation, the graphical interface is completely similar (and easy to understand/apply) to that used for the AGREE software. The operating principle related to the inputs, the weights of the various parameters, and the output is exactly identical to the AGREE tool and reported as an impact score on a scale from 0 (unsatisfactory, red) to 1 (satisfactory, green). Many characteristic elements of different sample preparation techniques were considered in the development of the AGREEprep:

i) Conventional and unconventional procedures.
ii) Some criteria (2, 4, 5, 6 and 8) apply logarithmic functions to assign the correct score to the parameter.
iii) It is possible to discriminate the different sample preparation techniques based on the most recent applications found in the literature.
iv) It is possible to discriminate, by applying the logarithmic functions, between typical impacts of microextraction techniques.

In this section have seen how AGREE and AGREEprep can meet the needs of a standardized tool to evaluate the green profile of a method. As in the other tools seen previously, a limitation could be represented by the "*freedom*" in assigning the weight of the single parameter (see Figs. 10 and 11). In fact, this element, having repercussions on the length of the corresponding segment of the pictogram, could be too subject to the "*sensitivity*" of the operator and not standardized and definite.

In the case of the AGREE and AGREEprep tools, there are many articles in the literature (as reported by a recent review by Imams and coworkers [59]), a sign that these tools actually meet most of the requirements and needs of the scientific world (particularly in the field of Analytical Chemistry). In these works was further highlighted the main advantages in terms of standardization, flexibility, possibility of applying different weights according to the specific parameter considered (as well as the specific pre-analytical technique and/or instrumental configuration). An example of the flexibility of these tools is well represented by the study by Aboras and coworkers [60], where AGREE procedures are applied in a green adherent degradation kinetics study of Nirmatrelvir and related to the characterization of degradation products using LC–MS with in silico toxicity profile. Individually, only a couple of recent articles consider both tools in the evaluation of the method [61,62] reporting both pictograms.

4. Future perspectives: zero impact laboratory

This future perspective certainly represents the goal that we have been trying to achieve in recent years through the application of the principles of GC, GAC, and GSP. Surely the component relating to the

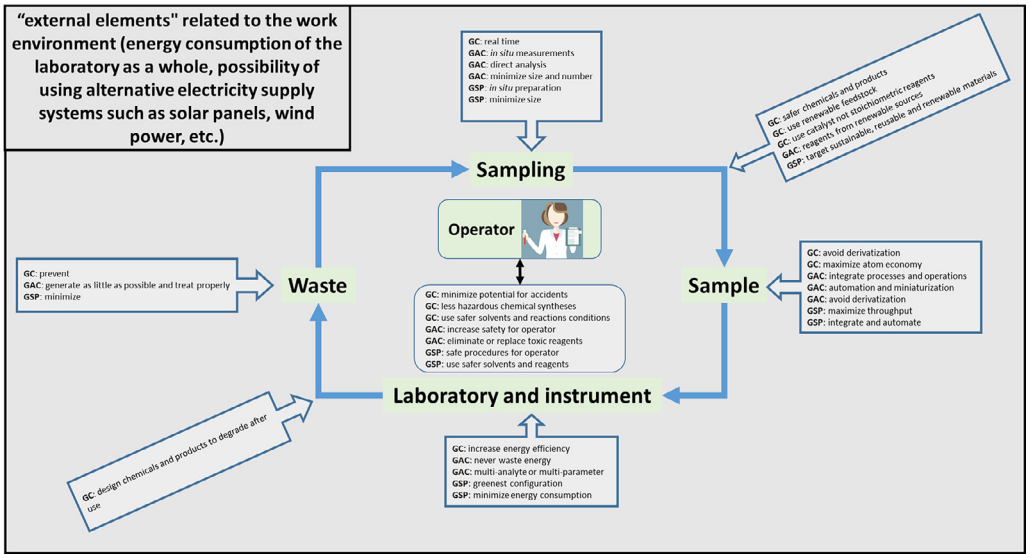

Fig. 12. Virtuous circle for a zero impact laboratory.

supply of energy represents one of the major stumbling blocks as the instrumentation required nowadays is "hungry" in this sense, as well as having to take into consideration all the "outline" necessary for the analysis (air conditioning, accessories such as vortex, agitators, ultrasonic baths, etc.).

Another element can be given by the fact that multiple pictograms must be used to be able to evaluate the method (for example AGREE and AGREEprep). Additionally, it is not possible to use a single platform with a single pictogram as output that represents (in detail) the whole method (from sampling to the result), including "*external elements*" related to the work environment. In this group can be considered the energy consumption of the laboratory as a whole, the possibility of using alternative electricity supply systems such as solar panels, wind power, geothermal, hydropower, ocean and bioenergy. Among the various alternative sources, bioenergy would perhaps be the last choice, while very promising are solar panels, wind power, geothermal, hydropower, and ocean. Even within these other sources of energy, advantages and disadvantages are observed, especially related to the amount of energy produced and the disposal of the devices once they run out (especially for solar panels).

In these external elements, all the recent tools/materials/systems developed specifically for energy saving could also be inserted (also for example thermal break windows to maintain the internal temperature and avoid heat/cool dissipation), for the reduction of environmental impact, engineered materials for the dissipation of the heat produced by the instrumentation, etc.

The idea is to achieve a total reduction of the impact of this activity through the application of a virtuous circle that can be schematized as in Fig. 12.

This schematic representation takes into account what has been indicated in the previous paragraphs, but integrates everything with other general considerations which, through a multidisciplinary approach that also includes the engineering and electronic and systems component, can represent a valid approach for future management challenges " total green". In order to develop a "zero impact laboratory" in the future, it will therefore be necessary to evaluate all these elements related to the general consumption of energy (electrical and thermal) by producing instrumentation that is less "thirsty" for energy, leading to a miniaturization of the devices as well as an increased portability to allow measurements in the field (also considering rechargeable power systems using renewable sources) and which do not require sample preparation processes (and/or derivation).

In this way, the variables to be considered in the energy balance and in the consumption of materials would be reduced to a minimum, as well as minimizing the health risk associated with the waste produced by the process. Overall, these elements would certainly lead to a reduction in the environmental impact by rigorously following the principles of the GC, the GAC, and the GSP.

5. Conclusions

In this work we have reported the state of the art regarding the evaluating green profile of modern sample preparation techniques trying to highlight the limits and advantages of the various proposed procedures (LCA, NEMI, Analytical Eco-scale, GAPI and ComplexGAPI, RGB models and WAC, AGREE and AGREEprep and hexagon-CALIFICAMET). Furthermore, in the text an attempt has been made to indicate other elements which perhaps had not been taken into consideration until now, but which could be very valuable in the evaluation of this element.

The objective of chemists engaged in research in this field, also in the light of recent national and international tenders, which increasingly insist on the concept of reducing the environmental impact, promises to be very noble and not easy to achieve. The challenges that await us are still many and the path, not easy, will increasingly require a multidisciplinary approach (often even with unexpected fields) to reach the so-called "gold standard", i.e. the possibility of creating and developing a zero impact laboratory. An important element of this review is that, thanks to the deepening of the various tools developed in the evaluation of the green profile, it was possible to introduce the concept of zero impact laboratory in an "explicit" way for the first time.

This could be a starting point for multidisciplinary projects aimed at disproving a preconception of Society regarding the "faults" of Chemistry, highlighting how this discipline actually serves to optimize the benefits for humanity without influencing Gaia. An example of this general concept is related to the absence of changes in the interactions of living organisms on Earth with the surrounding inorganic components to form a complex synergistic and self-regulating system that helps maintain and perpetuate the conditions for life on the planet.

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Declaration of Competing Interest

Authors declare no competing or conflict of interests.

Data availability

No data was used for the research described in the article.

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