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Complementary green analytical procedure index (ComplexGAPI) and software†

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It is not easy to find appropriate tools for the evaluation of the "green" nature of analytical methodologies which involve the use of compounds, materials, or chemicals manufactured prior to the analytical step. Here, we propose a new metric for the evaluation of analytical procedures based on the GAC attributes. The proposed solution expands on the well-known green analytical procedure index by adding additional fields pertaining to the processes performed prior to the analytical procedure itself. Each field of the hexagon that was added to the GAPI pictogram corresponds to a different aspect of the described process and is coloured green if certain requirements are met. To showcase the utility of the proposed metric, it was used to evaluate analytical protocols for the determination of pesticides in urine samples. We believe that, following GAPI's success, ComplexGAPI will also gain attention and eventually trust and acceptance from the chemical community. To facilitate the use of this tool, we have created freeware software for generating the ComplexGAPI pictograms.

Introduction

One of the prominent approaches in chemistry is the philosophy of green chemistry which aims to conduct processes in accordance with the principles of sustainable development. Nowadays, green chemistry principles are widely applied in numerous areas, from government policies, through industrial management, to educational practice and technology development. In the circular economy concept, it is important to balance economic growth, resource sustainability, and environmental protection. Thus it can be claimed that green and sustainable chemistry is a path towards changing the attitudes and paradigms in chemical manufacturing and production.[1] Moreover, the general concept of green chemistry permeates its areas, leading to the revaluation of approaches and giving rise to new ways of thinking. In the particular case of analytical chemistry, the term green analytical chemistry (GAC) is commonly used.

Finding the right way to assess the green character of an analytical procedure is challenging since many different parameters must be taken into consideration.[2] It is generally accepted that hard data on actual environmental impacts are needed to claim that a process or product is sustainable. Here, the developed tools for assessing the greenness of the given analytical procedures come to the rescue (Fig. 1). These tools are juxtaposed and described in detail in several published reviews.[3–5] However, in this area, some questions can be raised as follows: How many parameters are evaluated by these tools? Are these metrics easy to use? How effective are these methods for assessing the green nature of an analytical procedure? The answers to these questions are important, as there are still many examples for analytical protocols reported in the literature that are claimed to be green and eco-friendly by their authors with little tangible evidence, *e.g.*, in the form of a greenness metric score. Furthermore, such new protocols should be compared with the previously developed methodologies (Tobiszewski, *Anal. Chem.*).[6]

Analytical protocols are used to gather data in numerous application areas, which are then used as the basis for making decisions, and so their validity is of high importance.[7] Thus, these data must be characterized by consistent quality. Such quality can be ensured by using a tool called life cycle assessment (LCA) which allows assessing the potential impacts of products, processes, or services through production, usage, and disposal.[8] The life cycle concept is adaptable to analytical methodologies if an analytical protocol as a process and the output of this process in the form of reportable results are considered.[9] However, it is not often applied in the area of analytical chemistry. In fact, it needs standardized guidelines to ensure the high quality of its application. Moreover, the impact assessment methods need to be extended by further human and ecosystem health indicators.[10]

The LCA of an analytical protocol includes quality-by-design (QbD) approaches in every step of the development of a

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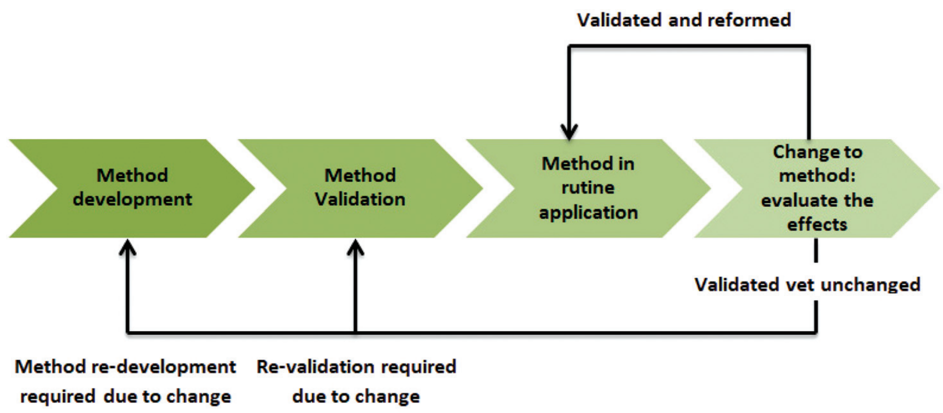

Fig. 1 LCA of an analytical methodology.

new procedure, its validation and operational applications.[4] Moreover, LCA includes additional elements, such as the identification of an analytical target profile (ATP) – a set of criteria that define what will be measured (*e.g.*, analyte content and impurity content) and the performance criteria to be achieved by the measurement (*e.g.*, validation parameters), but without specifying the method.[9] With these features in mind, the LCA of an analytical procedure can be broken down into three stages: method design, method qualification, and continued method verification (Fig. 1).

One of the earliest tools for the assessment of the greenness of analytical procedures is the National Environmental Methods Index (NEMI, Fig. 2).[11] Although NEMI as a greenness assessment tool has its advantages (*e.g.*, it is easy to read by potential users), it also has some drawbacks. The NEMI symbol presents each threat as being below or above a certain value, and therefore it cannot be considered quantitative. Furthermore, this tool does not take into consideration such issues as energy, chemical and reagent consumption, and the amount of waste generated. In addition, searching for each chemical used in the procedure in official lists (EPA TRI list, Resource Conservation and Recovery Act list, *etc.*) is time-consuming. Therefore, it has been modified by de la Guardia *et al.*[12] who proposed the use of a colour scale to improve clarity (Fig. 2).

Another very popular and often used metric is the analytical Eco-scale proposed by Gałuszka *et al.*[13] In this tool, the penalty points are considered and subtracted from a base of 100. The higher the score, the more sustainable the analytical procedure is. The analytical Eco-Scale is characterized by many advantages such as simplicity of use and semi-quantitative calculation of the amounts of chemicals and wastes, information about the environmental impacts of analytical approaches is provided quantitatively, and different aspects of environmental impacts are evaluated. Its drawbacks however include the lack of additional quantifiers capable of discriminating between the micro- and macro-scale of method applications. In addition, the result is not informative in the case of a negative environmental impact, and as such does not facilitate the improvement of the method during the design stage in this aspect.

Recently, two metrics, the Analytical GREEnness calculator (AGREE) and the Red-Green-Blue model, have been introduced.[14,15] AGREE is a comprehensive, flexible, and straightforward evaluation approach that produces an easily interpretable and informative result. In AGREE, the considered criteria are taken from the 12 principles of GAC and are transformed into a unified 0–1 scale. One of the advantages of this metric is the availability of freeware software which makes its applications more straightforward.

The RGB model uses three colours to represent the main attributes of the assessed method.[15] These attributes cover analytical performance (red), compliance with the principles of green chemistry (green), and practical effectiveness (blue). The final colour assigned to the evaluated methodology is a result of the additive synthesis of the primary colours, the intensities of which are expressed by the Colour Score parameter on the scale of 0–100%, distinguishing three separate ranges. These ranges allow the simplification of the application of the RGB model for the assessment of analytical procedures and distinguish the limited number of resultant/final colours of a method. In addition, the quantitative parameter, called "method brilliance", integrating all primary colours, is provided. The evaluation using the RGB model is performed using Excel worksheets.

The RGB model inspired a new perspective on the implementation of sustainable development principles in analytical chemistry, leading to the formulation of the so-called 12 principles of White Analytical Chemistry (WAC).[16] This concept incorporates the main assumptions of GAC, while also addressing the additional expectations. WAC aims to maintain the integrity of the various parameters without directly prioritizing any of the attributes assessed. As the aspiration for sustainable development is striving for a "white" method, the authors of WAC propose the application of the term "white" as a synonym for a well-balanced analytical procedure used in a given application.

In 2018, the green analytical procedure index (GAPI) tool was reported[17] and has since been used by many scientists to

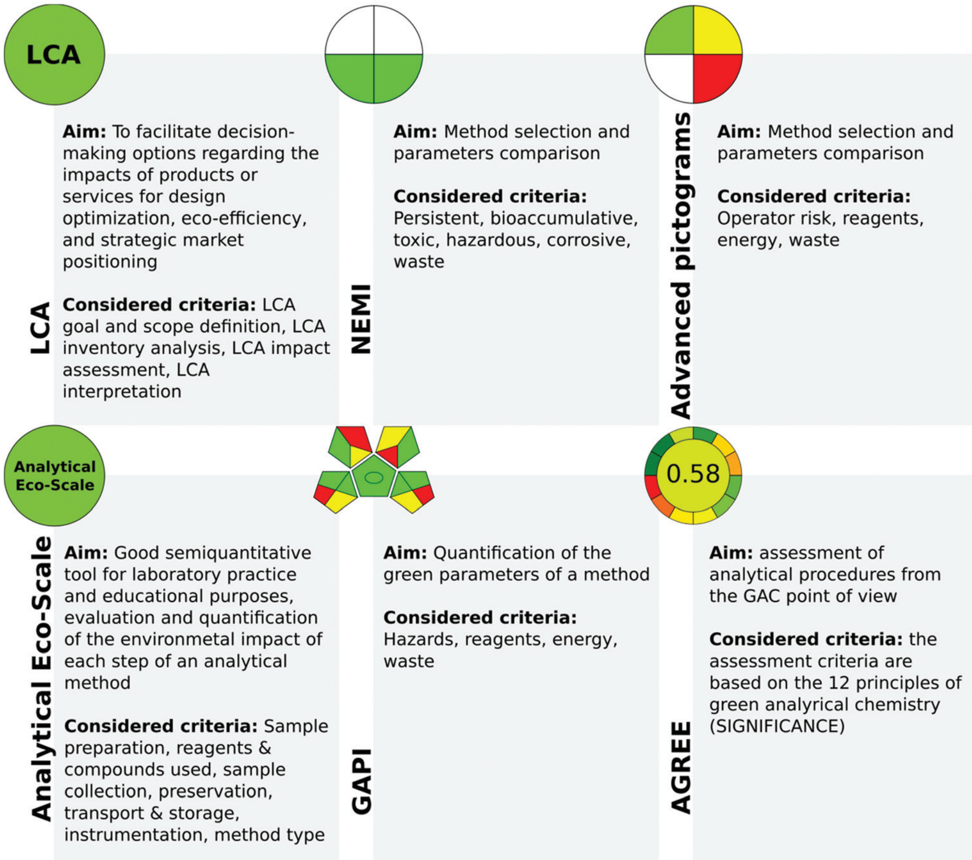

Fig. 2 Characterization of the most popular metrics for the evaluation of the green character of analytical procedures.

evaluate the green nature of the developed procedures, making it relatively successful and already established at the time of writing. The GAPI metric uses a pictogram to classify the greenness of each step of an analytical methodology, applying a colour scale, with two or three levels of evaluation for each stage. In GAPI, reagents, procedures, and instrumentation are evaluated. Thus, many factors are considered, including chemical health and environmental hazard, waste amount and type, and energy requirements. Furthermore, GAPI presents information on the entire analytical protocol. What is very important is that the compact pictogram of GAPI allows for an at-a-glance comparison of several methods and easy selection of the greenest method for a particular study. It could be stated that GAPI evidently indicates the weakest points in analytical procedures.

Considering the above-mentioned tools it could be concluded that they are sufficient and provide reliable and factual results. They do, however, have certain shortcomings when viewed through the lens of the spirit of the original stipulations of green analytical chemistry. GAC is a multi-step approach, and one of its axioms is that the new analytical procedure will meet the desired requirements from the sustainability point of view (Fig. 3).

When re-visiting these original stipulations we can point to an issue with the current assessment tools. Nowadays, many new solvents, sorbents, reagents, columns, *etc*. are produced in order to enhance not only the efficiency but also the green character of a developed procedure and this part, *i.e.*, production/synthesis of new, specific reagents, solvents or other materials prior to sample preparation and final analysis should also be evaluated. While some available metrics for measuring the aspects of a chemical process relating to the principles of green chemistry could be used to assess this stage of method development (*e.g.*, *e*-factor, step economy,

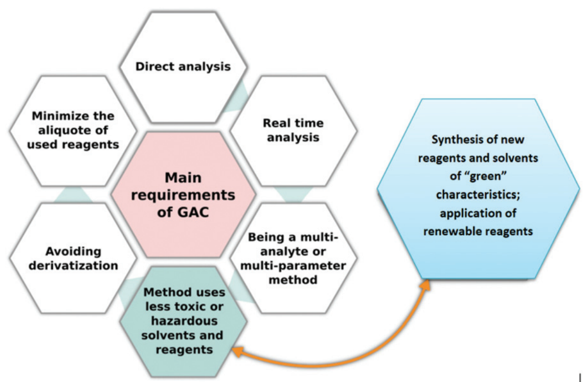

Fig. 3 The development of analytical methodology in accordance with GAC.

atom economy, *etc.*),[18] their application would not be convenient or time-saving. Therefore, we propose a complex green analytical procedure index (ComplexGAPI), an easy tool that complements the existing GAPI metric. One hexagonal field was added to the original GAPI graph and it reflects the processes performed prior to the sample preparation step and final analysis. We believe that by following the path of GAPI success, ComplexGAPI will also gain attention, trust and acceptance from the chemical community. To facilitate the use of the tool, we have created freeware software for generating ComplexGAPI pictograms.

Complementary green analytical procedure index

The premise behind the development of the tool was to allow it to assess as much information as possible about a given analytical methodology, including processes performed prior to analysis, thus providing a more comprehensive evaluation of the procedure's 'greenness'. We believe that the tool proposed here meets these criteria. The complex green analytical procedure index (ComplexGAPI) is a tool that covers all aspects of an analytical procedure, from sample collection, its transport, preservation, and storage to sample preparation and final analysis, but also these aspects and processes which are performed prior to the general analytical methodology. This modification of the original GAPI tool was motivated by questions from many chemists who applied GAPI in their laboratory practice but were finding it difficult to evaluate such processes as the synthesis of new ionic liquids (ILs), deep eutectic substances (DESs), nanoparticles (NPs), *etc.*, and other materials used in the separation step, *e.g.*, phases for columns.

ComplexGAPI was created based on the same principles which guided the development of GAPI: the analytical eco-scale[13] and the eco-scale.[19] In addition, some requirements taken from the CHEM21[20] tool were also taken into consideration in ComplexGAPI development. This makes the new metric easy to use for those who are already familiar with these tools and have used them to assess the green nature of the analytical procedures. They will in fact find the assessment process much more straightforward and less time-consuming thanks to the availability of the software for ComplexGAPI. The ComplexGAPI metric expands the pictogram created for GAPI by adding an additional hexagonal field at its bottom. This field corresponds to the 'green' character of pre-analysis processes. It covers such aspects as yield and conditions, reagents and solvents, instrumentation, work up and purification of the end products (Fig. 4). As in GAPI, the modified tool utilizes a colour scale, with two or three levels of evaluation for each stage. The created pictogram can be used to evaluate and quantify – from green to yellow to red – the low, medium and high environmental impacts associated with each stage of the pre-analysis process and the analytical methodology. Each field reflects a different feature of the described processes and analytical protocol and is filled green if certain requirements are met. The complex green analytical procedure index parameters are described in Table 1.

The design of ComplexGAPI

A basic requirement for the creation of ComplexGAPI, as a modification of GAPI, is legibility, simplicity and user-friendliness. At the same time, it is required to cover the whole range of parameters that characterize the analytical protocol as well as pre-analysis processes (reagents, conditions, and techniques). As the GAPI tool has been described in detail,[17] we will only cover the parameters covered by the additional hexagonal glyph describing the aspects related to the processes taking place prior to the analytical protocol.

Yield/selectivity and conditions. Without a doubt, yield is one of the most important aspects of synthesis. A high yield is recognized as an indicator of success, as the limiting reactants have been almost quantitatively converted into the desired product. In the case of low yield, it is necessary to test the

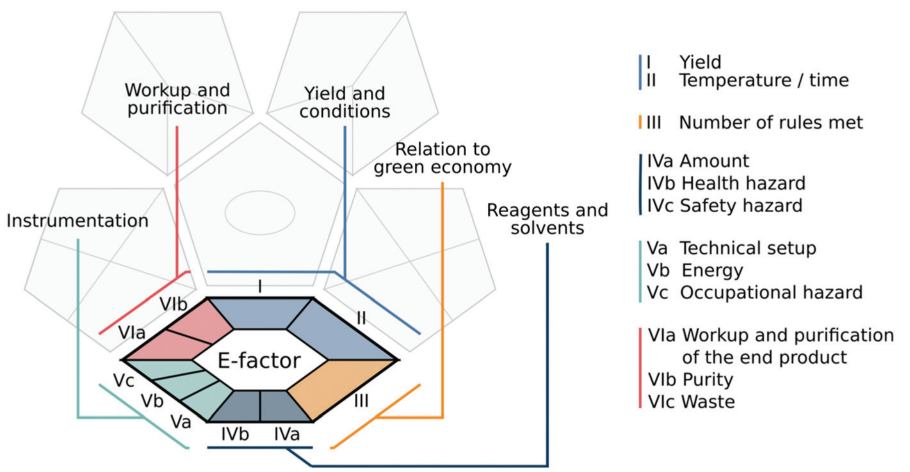

Fig. 4 The ComplexGAPI pictogram, with the original GAPI pictogram greyed out in the background, and particular fields of the added hexagonal glyph grouped and colour-coded for clarity.

Table 1 Comprehensive green analytical procedure index parameter description

Category	Green	Yellow	Red
Pre-analysis processes			
Yield/selectivity and conditions			
Yield (I)	>89%	70–89%	<70%
Temperature/time (II)	Room temperature, <1 h	Room temperature, >1 h Heating, <1 h Cooling to 0 ○C	Heating, >1 h Cooling <0 ○C
Relation to the green economy			
Number of rules met	5–6	3–4	1–2
Reagents and solvents			
Health hazard (IVa)	Slightly toxic, slightly irritant; NFPA health hazard score is 0 or 1	Moderately toxic; could cause temporary incapacitation; NFPA = 2 or 3	Serious injury on short-term exposure; known or suspected small animal carcinogen; NFPA = 4
Safety hazard (IVb)	Highest NFPA flammability, instability score of 0 or 1. No special hazards	Highest NFPA flammability or instability score is 2 or 3, or a special hazard is involved	Highest NFPA flammability or instability score is 4
Instrumentation			
Technical setup (Va)	Common setup	Additional setups/semi-advanced instruments used	Pressure equipment >1 atm; glove box
Energy (Vb)	≤0.1 kW h per sample	≤1.5 kW h per sample	>1.5 kW h per sample
Occupational hazard (Vc)	Hermetization of the analytical process	—	Emission of vapours to the atmosphere
		Workup and purification	
Workup and purification of the end product (VI a)	None or simple processes	Application of standard purification techniques	Application of advanced purification techniques
Purity (VIb)	>98%	97–98%	<97%
ADDITIONAL FIELD:			
E-factor			
$E\text{-factor} = \frac{\text{total mass of waste from process}}{\text{total mass of product}}$			
Sample preparation and analysis			
Sample preparation			
Collection (1)	In-line	On-line or at-line	Off-line
Preservation (2)	None	Chemical or physical	Physicochemical
Transport (3)	None	Required	—
Storage (4)	None	Under normal conditions	Under special conditions
Type of method: direct or indirect (5)	None sample preparation	Simple procedures, *e.g.*, filtration and decantation	Extraction required
Scale of extraction (6)	Nanoextraction	Microextraction	Macroextraction
Solvents/reagents used (7)	Solvent-free methods	Green solvents/reagents used	Non-green solvents/reagents used
Additional treatments (8)	None	Simple treatments (extract clean up, solvent removal, *etc.*)	Advanced treatments (derivatization, mineralization, *etc.*)
Reagents and solvents			
Amount (9)	<10 mL (<10 g)	10–100 mL (10–100 g)	>100 mL (>100 g)
Health hazard (10)	Slightly toxic, slightly irritant; NFPA health hazard score is 0 or 1	Moderately toxic; could cause temporary incapacitation; NFPA = 2 or 3	Serious injury on short-term exposure; known or suspected small animal carcinogen; NFPA = 4
Safety hazard (11)	Highest NFPA flammability, instability score of 0 or 1. No special hazards.	Highest NFPA flammability or instability score is 2 or 3, or a special hazard is used.	Highest NFPA flammability or instability score is 4
Instrumentation			
Energy (12)	≤0.1 kW h per sample	≤1.5 kW h per sample	>1.5 kW h per sample
Occupational hazard (13)	Hermetization of the analytical process	—	Emission of vapours to the atmosphere
Waste (14)	<1 mL (<1 g)	1–10 mL (1–10 g)	>10 mL (<10 g)
Waste treatment (15)	Recycling	Degradation, passivation	No treatment
ADDITIONAL MARK: QUANTIFICATION			
Oval in the middle of GAPI: *Procedure for qualification and quantification*		No oval in the middle of GAPI: *Procedure only for qualification*	

NFPA, *National Fire Protection Association*

underlying chemistry in order to improve selectivity.[20] However, in some scenarios the yield is low, but selectivity in the direction of the desired compound is high and the conversion is also low. In such a case, there is a place for future investigations (*e.g.*, optimization of the synthesis conditions). Based on the CHEM21 parameters, the relevant field will be coloured green for yields >89%, yellow in the case of yields in the range of 70–89%, and red for yields <70%. The ranges for selectivity are the same. For appropriate calculations, please see eqn (1S), (2S) and (3S) in the ESI.†

The conditions of the process performers are also evaluated by ComplexGAPI. Here, temperature and time are taken into consideration jointly, as these factors are closely related. A perfect situation would be if the reaction takes place quickly and at room temperature, however, the use of a higher temperature is often needed to perform synthesis during a satisfactory period of time.[19] Cooling is even more troublesome, as often only fixed temperatures (for instance 0 °C for an ice bath, or −5 °C for an acetone/ice bath) are available. In addition, avoiding moisture is sometimes recommended to obtain reproducible results,[19] and this is not an easy task. In fact, such a step requires the use of inert gases, Schlenk lines, gloveboxes, *etc*., which affects the economy of the whole procedure, but also its overall duration. Thus, temperature and time are considered jointly with colours green, yellow and red corresponding to particular threshold values.

Green economy. Chemistry and economy are two different areas of science, which face environmental challenges and develop divergently.[20–22] The role of green chemistry is not only the protection of the environment by preventing pollution, but also increasing the manufacturing performance and minimizing the production costs.[21] Therefore, green chemistry and green economy are complementary approaches with a synergistic effect when applied jointly to complex problems.[22] Numerous operating costs are decreased through the use of green chemistry, *e.g.*, the cost of waste storage and treatment, or compensation payments for environmental damage.[23–26] Since the integration of green chemistry and green economy facilitates overcoming environmental challenges and leads towards sustainability, aspects related to green economy should be evaluated with respect to reactions and other processes. For this reason, requirements related to both green chemistry and green economy were sectioned out as a separate ComplexGAPI criterion to highlight the importance of the integration of these two approaches. These requirements, together with the corresponding scores, are listed in Table 2. In the event that a given process scores 5–6 points, it is considered to be closer to the ideal green economy and is marked green; if it scores 3–4 points, yellow, and if it scores less than 3 points, red.

Reagents and solvents. The category of reagents and solvents includes aspects related to the health and safety hazard. Every reaction component must be taken into consideration. For its evaluation, the criteria given by the US National Fire Protection Association (NFPA) are used (as is the case in GAPI). These criteria cover health hazards, flammability, reactivity, and specific hazard – the most important issues in this area.

Instrumentation. In the area of instrumentation, three aspects are considered: the technical setup, energy consumption, and occupational hazard. In the case of the first two aspects, if the setup simply consists of a regular flask, reflux condenser, and stirrer, and other elements that do not require a lot of energy (equipment for the controlled admixture of chemicals or special glassware, *etc*.) the field is coloured green. If any additional, but not very complicated, and commonly used sample preparation treatments such as ultrasounds or photo- and microwave-irradiation are employed, the field is coloured yellow. In the case of application of a pressurized vessel, and the need for an inert atmosphere, especially in a glove box, the field is coloured red. These aspects also impact the energy consumed, so these parameters also must be evaluated (Table 1). However, when considering occupational hazard issues, only two cases are distinguished: the field is coloured green when hermetization of the entire process is carried out, and with red in the case of emission of vapours to the atmosphere.

Workup and purification. This set of fields is dedicated to the evaluation of workup and purification of the end product, purity, and waste generated. If none or standard purification techniques are applied such as quenching, filtration, centrifugation, crystallisation or low-temperature distillation/evaporation/sublimation, then the aspects can be considered green. In the case of the application of such processes as solvent exchange or quenching into an aqueous solvent, the field is coloured yellow. The field is coloured red when advanced purification techniques are called for (*e.g.*, HPLC, multiple recrystallizations, ion exchange). The reaction conditions which lead to obtaining a high-purity (>98%) product are marked green. Lower purity is marked yellow (97–98%) and red (<97%).

Table 2 Green chemistry components which bring result in the economy of the process

Requirement	Green chemistry component	Points	Result in the economy of synthesis/reaction/process
Design	Application of experimental design to reduce or eliminate the use or generation of hazardous substances	1	It aids in finding methods and techniques to speed up chemical reactions using small amounts of reagents to produce equivalent results at the same price point
	Assessment of the chemical product's life cycle, including its design, manufacture, use, and ultimately disposal	1	It might also lead to a reduction in the number of synthetic steps and result in increased production and plant capacity while reducing energy and water consumption
Use	Use of raw materials, elimination of wastes and avoiding the use of toxic and/or hazardous reagents and solvents	1	It aids in finding methods and techniques to speed up chemical reactions using small amounts of reagents to produce equivalent results at the same price point
	Prevention of pollution by waste minimization and avoidance of toxic and hazardous substances	1	Using fewer chemicals for product manufacturing results in reduced waste, which in turn reduces the cost of disposing and treatment of chemical wastes
Effort	Effort to minimize the expenditure of energy and chemicals	1	Using fewer chemicals for product manufacturing results in reduced waste, which in turn reduces the cost of disposing and treatment of chemical waste
	Effort to use harmless reactants, alternative solvents, and new pathways of synthesis	1	

Considering the generated waste, it was decided to use the *E*-factor parameter which takes into account not only waste by-products and leftover reactants, but also spent catalysts and catalyst supports, solvent losses, and anything else that can be regarded as a waste.[27] Thus, it can be said that the *E*-factors are derived from the amount of solvents, reagents, and consumables used per unit mass of product made, and the appropriate equation for its calculation can be used (eqn (1)). Sometimes it is easier to calculate the *E*-factor from a different viewpoint, since accounting for the losses and exact waste streams is difficult. In such a case, eqn (2) should be used.

$$E\text{-factor} = \frac{\text{total mass of waste from process}}{\text{total mass of product}} \quad (1)$$

$$E\text{-factor} = \frac{\text{mass of raw materials-mass of product}}{\text{total mass of product}} \quad (2)$$

Waste prevention can be achieved if most of the solvents and the reagents are recyclable (*e.g.*, catalysts, acids or bases that are bound to a solid phase can be filtered off, regenerated, and reused in a subsequent run). In such a way, these compounds are not included as by-products. This is also the case with water which is a significant by-product of many chemical syntheses and other processes and is generally harmless, so its mass can be omitted from the total mass of waste in the calculation. However, in the case when the water is severely contaminated and difficult to reclaim in a form pure enough to apply or discharge to a publicly owned wastewater treatment facility, its mass must be taken into consideration for *E*-factor calculation.[27] The higher the *E*-factor of a chemical process, the greater is the waste generated, the greater its negative environmental impact, and the less sustainable it is. This is why this factor was included in ComplexGAPI to show the green character of the overall process. In this case, only the value of the *E*-factor is included in the graph to facilitate the comparisons of different methodologies used at the same chemical scale.

Software

The proposed tool is accompanied by a simple piece of software that facilitates the use of ComplexGAPI for assessing the greenness of analytical procedures. It was developed in Python using the default[28] Tkinter library. The graphical user interface of the software is shown in Fig. S2.† Its use, outlined in the ESI,† is straightforward. The user chooses parameters corresponding to both the pre-analysis processes and the sample preparation and analysis stages from drop-down menus, and the corresponding ComplexGAPI pictogram is generated live for immediate reference. When ready, the pictogram can be saved either as a raster image (.png) or vector graphic (.svg).

The software is available under the open-source MIT license and can be downloaded from mostwiedzy.pl/complexgapi. The code is made available in an open repository.

Case study

To showcase the utility and convenience of ComplexGAPI, the greenness of three reported analytical methodologies for the determination of pesticides in urine samples was assessed and juxtaposed and evaluated using the developed tool.

The procedures are as follows: Procedure 1 (*in situ*-IL-DLLME-HPLC): magnetic nanoparticle-assisted *in situ* ionic liquid dispersive liquid–liquid microextraction (*in situ*-IL-DLLME) coupled to high performance liquid chromatography (HPLC);[29] Procedure 2 (SFO-DLLME-GC-MS): dispersive liquid–liquid microextraction (DLLME) based on solidification (SFO) of deep eutectic solvent (DES) droplets combined with gas chromatography-mass spectrometry (GC-MS);[30] and Procedure 3 (SB-μ-SPE-GC-MS): membrane-protected stir-bar supported micro-solid-phase extraction (SB-μ-SPE) coupled to GC-MS.[31]

These procedures differ in many aspects, starting from the processes performed prior to the analysis, through the sample preparation step, ending at the final determination. In the first procedure, Fe_3O_4 magnetic nanoparticles and the ionic liquid ($[N_{4,4,4,4}][N(CN)_2]$) were synthesized and characterized before the analytical procedure. The DLLME extraction technique was used to isolate the analytes, while HPLC was applied for the final determination.

In the second procedure, DES (menthol : phenylacetic acid) was synthesized and applied as an extractant. The extraction solvent was forced to pass through a glass filter under an N_2 stream and it was dispersed as fine droplets in the sample solution. Due to the low density of the synthesized extractant, it was collected on top of the sample solution without centrifugation.

In the third procedure, the layered double hydroxide/graphene (LDH-G) hybrid was synthesized by co-precipitation and used as a sorbent in SB-μ-SPE extraction. Furthermore, GC-MS was applied for the final determination of the analytes in urine samples. The result of the evaluation of these procedures for pesticide determination in urine ComplexGAPI is shown in Fig. 5.

By juxtaposing the results of the assessment of the selected procedures for the pesticide determination in urine samples, it is evident where these procedures differ and which aspects should be focused on to avoid certain issues. It should be noted that all methods require the transport of samples and their storage.

The procedure based on DLLME, which in turn is based on the solidification of DES droplets and GC-MS (Procedure 2) seems to be greener than the other two methodologies. This is mainly because the processes related to the synthesis of DES as well as the micro-extraction procedure are based on non-hazardous reagents. In fact, DES synthesis is a very simple process. In this case, 4.68 g of menthol was mixed with 1.36 g of phenylacetic acid in a glass tube and the mixture was heated for 1 h at 60 °C in a water bath. The synthesis occurs in 100% yield and no wastes are generated during this part (*E*-factor = 0). No further steps are required. The procedure

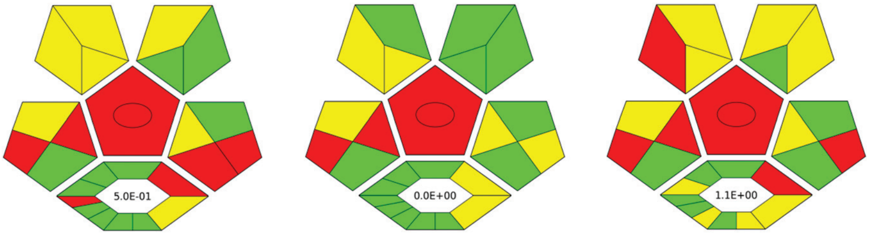

Fig. 5 Evaluation of three selected protocols using the ComplexGAPI tool.

requires small amounts of reagents for the analytical separation, and thus, a few millilitres of wastes are generated. The critical point of Procedure I is the amount of waste generated that is not recycled. In fact, the synthesis of nanoparticles consists of several steps and requires a large aliquot of reagents. The resulting solution requires heating at 180 °C for 20 h. The black magnetite microspheres were thoroughly washed with ethanol and deionized water several times and then dried under vacuum at 50 °C for 24 h. Considering the analytical procedure, the protocol should be refined with respect to waste production and its regeneration. Procedure III fails in many aspects, including reagent consumption, waste generation, and conditions used in the synthesis processes. The synthesis part involves numerous steps, a large volume of reagents as well as their aliquots, and application of high temperature for long periods of time. The procedure does not support green economy and it is characterized by a higher *E*-factor. This is why, in comparison to all the evaluated procedures in terms of the green character, the last one is the lowest-scoring and future modifications are recommended.

Conclusions

As the interest in green analytical chemistry increases, fresh perspectives on metrics that allow the evaluation of the analytical procedures are required. This is why the GAPI tool was proposed in 2018. Although it is widely applied by the researchers, its limitation is that it does not allow the evaluation of the processes which occur before analytical methodology, meaning synthesis and other reactions, preparation of stationary phases, *etc*. In order to meet the needs of the users of the GAPI tool which allows the assessment of the green nature of the analytical procedure, an improved tool, the complementary green analytical procedure index (ComplexGAPI), has been developed, which not only allows the assessment of the analytical procedure in terms of its environmental friendliness but also those processes which precede the analytical procedure itself. An additional hexagonal field was added to the GAPI pictogram to reflect the greenness aspect of the following parameters: yield and conditions, reagents and solvents, instrumentation and workup, and purification. These elements can be used to evaluate the syntheses/manufacturing of organic compounds or solvents, nanomaterials, or stationary phases. The advantage of the ComplexGAPI tool is the availability of software that will facilitate the use of such a solution. The use of the ComplexGAPI to assess the green nature of the entire protocol enables finding at a first glance where the considered procedures differ and to which parts attention should be paid to avoid certain issues. We recommend following the principles of green chemistry in every aspect of laboratory work.

Author contributions

J. P.-W. is the originator of the ComplexGAPI idea and the visual image, while W. W. has developed the software that facilitates the use of ComplexGAPI for assessing the greenness of analytical procedures.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

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