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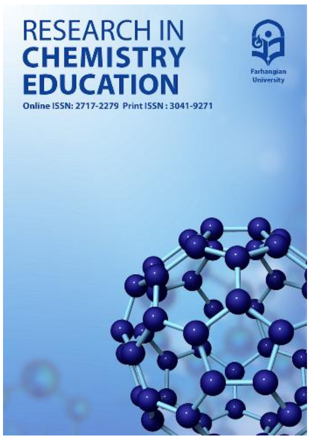
Review of green metrics for chemical reactions: A responsible research approach in chemistry education

1. Faezeh Shahdost-Fard *: Department of Chemistry Education, Farhangian University, P.O. Box 14665-889, Tehran, Iran
2. Amirreza Fallahi Juybari: Department of Chemistry Education, Farhangian University, P.O. Box 14665-889, Tehran, Iran
3. Mohammad Mahdi Merati: Department of Chemistry Education, Farhangian University, P.O. Box 14665-889, Tehran, Iran

*Corresponding Author's Email Address: Shahdost@cfu.ac.ir



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Abstract:

Background and Objective: Green analytical chemistry, an emerging branch on the path toward sustainable development, emphasizes the design of methods and reactions with minimal energy and material consumption, as well as minimizing environmental damage. Considering the rapid growth of analytical techniques, evaluating their compliance with the principles of green chemistry has become essential. This research aims to critically review and analyze existing tools for assessing the greenness of analytical chemistry methods. **Methods:** The present study is a review-analytical investigation that, by reviewing numerous articles in reputable scientific databases, examined various ranking tools for evaluating the greenness of chemical methods and reactions, and discussed and criticized them in terms of strengths, limitations, and combinatorial capabilities. **Findings:** The findings indicate that each ranking tool introduced in this study has advantages and drawbacks according to its conceptual structure and evaluation criteria. Some tools have interpretable visual outputs, while others focus heavily on quantitative assessment or specific aspects such as energy consumption or solvent health. According to the results, selecting an appropriate tool should be based on the type of analytical method, the evaluation purpose, and the desired level of precision. **Conclusion:** : Despite the advances in available tools, a gap remains between current assessment systems and the need for a comprehensive, precise, and multidimensional evaluation framework. Developing hybrid frameworks, applying a responsible research and innovation approach, and educating the new generation of chemists based on green chemistry principles can pave the way for future progress in sustainable analytical chemistry.

Keywords: Green Analytical Chemistry, Metric Tools, Quantitative and Qualitative Assessment, Sustainable Development, Environmental Compatibility

Introduction

Over the past several decades, the need to examine and teach emerging chemical technologies grounded in the principles of green chemistry has been increasingly emphasized worldwide. Nevertheless, the systematic integration of green chemistry into chemistry curricula across all educational levels has not been implemented uniformly, with most efforts concentrated at the graduate level and, to a limited extent, in undergraduate programs (Shahdoust Fard et al., 2024). In this context, the role of general education and particularly, school textbooks as one of the most effective tools for conveying sustainability concepts should not be overlooked.

Furthermore, it should be noted that achieving effective green chemistry education is not limited to curriculum design or the inclusion of sustainability-oriented laboratory experiments; rather, it also depends on how teachers interpret and implement these concepts in the classroom. In other words, teachers' instructional orientations and pedagogical perspectives play a decisive role in the extent to which students understand and accept the principles of green chemistry (Aydın-Günbatar et al., 2025). Magnusson et al. define instructional orientation as a set of teachers' beliefs and goals regarding why and how a subject should be taught, an influential factor that shapes the selection of instructional strategies, the nature of practical activities, and even assessment methods (Magnusson et al., 1999).

One of the most critical challenges facing humanity at the dawn of the twenty-first century is the protection and conservation of the environment and natural resources. In this regard, education plays a fundamental role in shaping and transforming individual lifestyles and habits. The manner in which school textbooks address the principles of green chemistry and present experiments aligned with these principles, in accordance with the educational objectives of different academic levels, can make a substantial contribution to sustainable development and the pursuit of a better world. Along this trajectory, it is also essential to consider the role of chemistry within broader social and industrial contexts.

Chemistry and its related industries play a pivotal role in improving the quality of life, increasing life expectancy, enhancing safety, and fostering a deeper understanding of the world. This discipline contributes significantly to the transition toward sustainable production practices across various industries and to achieving the United Nations Sustainable Development Goals (SDGs) (Anastas & Warner, 2007). Nevertheless, many chemicals currently in use and numerous reaction methods remain hazardous to both human health and the environment (Al-Naqbi et al., 2024). Advancing this transformation requires identifying priorities that can guide development toward positive and sustainable outcomes. In this context, the philosophy of green chemistry serves as a guiding framework for designing environmentally compatible processes, directing researchers toward sustainable approaches in both research and production. In recent decades, as global pollution and environmental challenges affecting humans and other species have intensified, the shift toward green chemistry has accelerated, rendering its industrial applications increasingly inevitable. Consequently, scientists have shown growing concern for both synthetic efficiency and environmental considerations (Tucker, 2010).

Following this trend, from the 1980s and 1990s onward, a range of environmental terms, including clean chemistry, environmental chemistry, green chemistry, benign chemistry, and sustainable chemistry, entered the scientific literature of chemistry. Despite the ambiguous and sometimes controversial definitions associated with these concepts, the term green chemistry gained greater acceptance than the others and gradually became the dominant concept in this field (Linthorst, 2009). Green chemistry reflects a fundamental shift in chemical science toward sustainability, safety, and environmental responsibility, originating from early environmental awareness and now occupying a well-established practical position across various industries (Khawas, 2024).

Green chemistry is defined as the conscious design of chemical products and processes aimed at reducing or eliminating the use and generation of hazardous substances. This approach seeks to minimize adverse environmental impacts throughout the entire lifecycle of a product, from raw material acquisition to end-of-life disposal. The term design plays a central role in the definition of green chemistry, as it emphasizes that environmental sustainability must be intentionally incorporated from the outset of development, guided by specific criteria and principles. Green chemical products and processes can facilitate the transition to a circular economy and contribute to the realization of Sustainable Development Goals. Since green chemistry is based on deliberate decision-making and cannot be achieved by chance (Anastas & Kirchhoff, 2002), it offers a proactive response to environmental challenges and, by helping to reshape negative perceptions of chemistry, provides a foundation for expanding scientific collaboration and fostering innovative approaches in both academia and industry (Marques & Machado, 2021).

Such broad and forward-looking considerations lie at the core of the Responsible Research and Innovation (RRI) approach. RRI extends beyond adherence to general principles of research integrity and professional conduct, encompassing the capacity to reflect societal interests and environmental needs within everyday laboratory practices. This approach emphasizes that the sustainability assessment of methods should not be limited solely to technical efficiency or chemical performance; rather, it should be designed to take multiple perspectives and values into account, so as to simultaneously generate scientific, social, environmental, ethical, and economic value (Mehlich, 2023). Nevertheless, the principles of RRI have remained largely disconnected from the design of chemical reactions and systems. In this context, green chemistry assessment systems play a crucial role as key tools for evaluating the sustainability and environmental impacts of chemical methods. These systems have been developed not only to preserve the analytical performance of methods but also to reduce the consumption of hazardous chemicals, minimize waste generation, and improve energy efficiency (Gamal et al., 2021). Accordingly, by providing structured frameworks, they enable comprehensive evaluations of the degree to which analytical methods comply with green chemistry principles across various dimensions, such as reagent toxicity, waste volume, energy consumption, and other sustainability indicators. Moreover, by revealing methodological weaknesses, these metrics facilitate the optimization of analytical procedures toward enhanced environmental compatibility (Tobiszewski, 2016).

The present study aims is to provide a comprehensive and systematic review of the conceptual and practical evolution of green chemistry, its fundamental principles, and its role in the development of sustainable analytical methods. With a particular focus on green chemistry ranking systems, this review examines and compares their structural features in assessing the environmental sustainability of analytical chemistry methods. In addition, adopting a critical perspective, the strengths and limitations of traditional assessment tools are analyzed, and by introducing recent innovative and hybrid approaches, a clear overview of the current status and future directions of greenness indicators in analytical chemistry is presented. Despite the expansion of green analytical chemistry, previously published reviews in this field have addressed only selected subsets of ranking tools and have generally focused on a limited number of specific indicators. Consequently, none of these reviews has analyzed the full spectrum of green assessment tools in an integrated and systematic framework. Therefore, the present study seeks to deliver a comprehensive evaluation accompanied by a conceptual classification, considering the strengths, limitations, and application domains of these tools. The novelty of this research lies in offering an integrative perspective on the entire ecosystem of green assessment methodologies and elucidating their interrelationships, distinctions, and complementary capabilities, an approach that has not been systematically and cohesively explored in prior studies.

Research Background

Green chemistry is recognized as one of the principal instruments for achieving sustainable development and is closely linked to the concept of the circular economy. In fact, both frameworks focus on reducing environmental impacts while enhancing resource efficiency, and they are frequently applied in a complementary manner within international policies and research initiatives. For instance, Chen et al. (2020) emphasized that integrating green chemistry principles into the circular economy framework can serve as an effective strategy for reducing waste generation and energy consumption. Recent studies have also shown that the ability to identify the “greenest” synthetic pathway among multiple alternatives is considered a valuable competency for the new generation of chemists operating within the rapidly growing green economy. While single-parameter indicators provide limited information and are insufficient for making informed decisions regarding greener processes, multivariate indicators have been demonstrated to be far more effective in this regard (Mercer et al., 2012).

Accordingly, a range of modern Green Analytical Chemistry (GAC) metrics and assessment tools has been developed to evaluate and compare the greenness of analytical methods, attracting increasing attention in both academic education and industrial research. Among these tools, the National Environmental Methods Index (NEMI) is recognized as one of the earliest references, compiling a variety of green methods and techniques (Keith et al., 2007). However, such collections are often insufficiently organized to simultaneously emphasize the environmental compatibility of methods and offer practical applicability for individual analysts. Subsequently, numerous studies have introduced and evaluated additional tools, and several works have attempted to provide more comprehensive reviews in this field. Nevertheless, focusing solely on technical aspects has proven inadequate, and existing evaluations have yet to fully capture all dimensions of sustainability (Nimushakavi et al., 2025; Mohr et al., 2025).

Recent research further suggests that linking green chemistry with the RRI framework can open new horizons for sustainable development. This approach highlights the necessity of involving researchers, policymakers, industry stakeholders, and society at large in the design and evaluation of analytical methods, ensuring that social, ethical, and environmental consequences are considered alongside scientific performance and efficiency.

Despite extensive efforts to introduce green chemistry principles, metrics, and assessment tools, existing review studies have not yet encompassed all dimensions of sustainability and have largely focused on technical or environmental aspects. Moreover, the integration of innovative approaches such as RRI into the design and validation of analytical methods has not been fully realized. Consequently, a significant gap remains between available assessment tools and the actual need for comprehensive, multidimensional, and education-oriented evaluation frameworks. This gap underscores the necessity of developing hybrid assessment frameworks and enhancing chemistry learners’ familiarity with modern sustainability assessment tools as a fundamental step toward more effective education and research in the field of green chemistry.

Methodology

This study adopts a review analytical research design aimed at examining the conceptual and practical evolution of green chemistry and its role in the development of sustainable analytical methods. The required data and information were collected through systematic searches of reputable scientific databases, and studies were selected that directly addressed green chemistry, its principles and ranking tools, the role of education across different academic levels, and its relationship with sustainable development.

Following data classification, educational approaches and policy-related perspectives were first examined. Subsequently, assessment tools for analytical chemistry methods were comparatively analyzed in terms of their strengths, limitations, and potential for integration. Finally, adopting a critical perspective, the effectiveness of these tools in addressing the real needs of society and industry was evaluated.

Results

1. Fundamental Principles of Green Chemistry

Given the necessity of designing chemical processes and products in line with sustainability and environmental impact reduction, the concept of green chemistry has moved beyond a purely theoretical framework and has been translated into practical and applicable principles. These principles, first proposed by Paul Anastas and John Warner in 1998, are recognized as a comprehensive guideline for directing researchers, industry practitioners, and policymakers toward sustainable development. The twelve principles of green chemistry, briefly presented in Table 1, provide a structured framework in which each stage of the design and implementation of chemical processes is aligned with the goals of sustainable development (Anastas & Eghbali, 2010; Ivanković et al., 2017).

Table 1- Twelve Principles of Green Chemistry

No	Principles of green chemistry	brief description
1	Prevention of pollution	Preventing waste generation with the aim of better management and reducing post-production cleanup steps
2	Atomic economy	Designing reactions with the aim of incorporating the initial percentage into the final product and producing the least amount of waste
3	Low-risk syntheses	Using raw materials and applying reaction conditions with the aim of creating less toxicity to human health and the environment
4	Designing safer materials	Designing materials with effective performance and minimal toxicity
5	Using safer solvents and materials	Elimination or replacement of toxic and hazardous solvents and auxiliaries with safe and environmentally friendly alternatives
6	Energy-efficient design	Reducing energy consumption by performing reactions at ambient temperature and pressure and using high-efficiency technologies
7	Renewable raw materials	Preference for using renewable raw materials such as biomass instead of finite resources
8	Reduction of derivatization steps	Avoiding unnecessary steps such as protection with the aim of reducing material consumption and waste generation
9	Catalyst	Use of catalysts (chemical or biological) to increase efficiency, reduce energy and waste
10	Design for degradability	Designing materials to reduce the risk of degradation after the end of their useful life
11	Real-time monitoring	Developing methods for real-time process control to prevent the production of hazardous materials
12	Inherent safety in design	Selecting materials and designing processes to reduce potential hazards such as explosions or fires

Based on the twelve articulated principles, the primary goal and focus are directed toward production processes that should be more efficient and safer while involving fewer hazardous substances. However, only some of these principles (such as the design of safer chemicals, the use of renewable feedstocks, and design for degradability) go beyond the optimization of production processes and directly address the environmental characteristics of materials from the perspective of input and output flows (Falcone and Hiete, 2019). Many of the green ranking assessment tools introduced in the following sections adopt these principles as their theoretical foundation. Therefore, a thorough understanding of these principles is considered an essential step in analyzing the performance and design rationale of green assessment systems.

2. Criteria of Green Analytical Chemistry

One of the most dynamic and rapidly expanding research areas within green chemistry is the development of methods aligned with sustainability principles, known as green analytical chemistry (Di Marco et al., 2019). Although the principles of green chemistry were originally formulated with a focus on synthetic chemistry, some of these principles are directly applicable to other branches of chemistry as well. Among the twelve principles, those related to pollution prevention (Principle 1), the use of safer solvents and auxiliaries (Principle 5), energy-efficient design (Principle 6), and the reduction of derivatization steps (Principle 8) show the greatest compatibility with analytical activities (Gałuszka et al., 2013).

In this context, two main approaches define the relationship between analytical chemistry and green chemistry (Rao et al., 2025). The first approach considers analytical chemistry as a tool for evaluating and verifying the environmental performance of chemical products and technologies. The second approach emphasizes that analytical processes themselves can be designed according to green principles to reduce energy consumption, chemical usage, and waste generation.

The twelve principles of green analytical chemistry provide a conceptual framework for the development and assessment of sustainable analytical methods. These principles were formulated as a complement to the traditional principles of synthetic green chemistry and are summarized as follows (Gałuszka et al., 2013):

1. Use of direct analytical techniques to minimize or eliminate sample preparation steps.
2. Reduction of sample size and number to decrease resource consumption and waste generation.
3. In situ measurements to avoid costly sample transportation and storage.
4. Integration and combination of analytical steps to save energy and time.
5. Application of automated and miniaturized methods to reduce chemical consumption.
6. Avoidance of unnecessary derivatization steps to prevent additional waste generation and increased reagent use.
7. Reduction or appropriate management of chemical waste generated from analytical processes.
8. Preference for multi-parameter or multi-analyte methods to enable simultaneous determination of multiple substances.
9. Reduction of energy consumption throughout all stages of analysis.
10. Use of reagents and materials derived from renewable resources instead of fossil-based or non-recyclable sources.
11. Elimination or substitution of toxic or hazardous reagents with safer alternatives for both users and the environment.
12. Enhancement of operator safety by designing methods that minimize the risk of direct contact with hazardous substances.

By establishing a link between environmental objectives and analytical performance, these principles are increasingly being employed in the development of green assessment ranking tools and methodologies.

3. Introduction and Review of Assessment Tools

Although analytical chemistry plays a pivotal role in monitoring environmental pollutants, it can itself exert adverse environmental impacts due to high solvent consumption and waste generation (Armenta et al., 2008). In response to this challenge, green analytical chemistry has emerged with the aim of institutionalizing sustainability principles within this field. However, assessing the extent to which analytical methods align with these principles requires tools capable of objectively and comparably quantifying the "greenness" of a method. Consequently, researchers have endeavored to develop assessment tools that enable quantitative, comparable, and structured evaluation of analytical methods from an environmental perspective (Płotka-Wasylka, 2018). In the following sections, the conceptual framework, evaluation metrics, and practical capabilities of these tools are briefly examined.

3.1. NEMI Index

The development of the NEMI represents one of the earliest attempts to evaluate the compatibility of analytical methods with the principles of green chemistry (Mohr et al., 2025). This tool, as a visual and semi-quantitative approach, consists of a circular chart divided into four quadrants. As illustrated in Figure 1, each quadrant assesses a key environmental aspect. These four quadrants correspond to: (a) the presence or absence of persistent, bioaccumulative, and toxic (PBT) chemicals; (b) the use of hazardous chemicals; (c) the corrosiveness of the sample based on pH range; and (d) the amount of waste generated (Sinzervinch et al., 2023).

Figure 1- Symbolic representation of NEMI.

For each of the four quadrants in the NEMI diagram to be displayed in green, specific conditions must be satisfied, including: (a) none of the chemicals used should be classified as persistent, bioaccumulative, and toxic (PBT) substances in the Environmental Protection Agency’s Toxic Release Inventory (EPA-TRI); (b) the materials used should not be listed as hazardous wastes in the TRI; (c) the average pH of the sample should fall within the range of 2 to 12; and (d) the total amount of waste generated should not exceed 50 g. If any of these conditions is not met, the corresponding quadrant in the diagram remains white (Keith et al., 2007).

The main advantage of NEMI as a tool for assessing greenness is the simplicity of its visual interpretation. By a single glance at the circular NEMI symbol, the user can obtain general information about the environmental compatibility of the method under consideration. This feature makes it a practical tool for rapid and preliminary comparison among different analytical methods (Tobiszewski et al., 2015).

However, NEMI also has two main limitations. First, the information provided by this tool is highly general and non-quantitative; in fact, the NEMI symbol merely indicates whether a given feature exceeds a predefined threshold, without specifying its magnitude or intensity. Therefore, it cannot be regarded as a truly semi-quantitative tool (Shaaban and Mostafa, 2018). Moreover, this index lacks dedicated software or a computational platform for automated evaluation, meaning that analyses are performed manually based on user-provided information. Because the index is reported solely in a binary (0/1) format, it lacks sufficient sensitivity to changes in the level of method sustainability, and modifications to this index could improve its performance.

3.2. Modified NEMI Index

To improve the performance of the NEMI index and increase the accuracy of assessment, a modified version based on the principles of green chemistry was introduced in 2009. In this approach, five main components: environment, energy consumption, health, safety, and waste generation are evaluated. The results of this assessment are presented in the form of a pentagonal symbol, with each side colored green, yellow, or red, indicating full, partial, or poor compliance with environmental criteria, respectively. The assignment of these colors is based on numerical values defined in Table 2 (Raynie and Driver, 2009). Although this tool lacks dedicated computational software and is designed primarily based on visual and semi-quantitative evaluation, its structure facilitates direct and relative comparison among various analytical methods. Figure 2 illustrates a schematic representation of this tool, depicted as a colored pentagon that visually indicates the degree of compliance of each component with environmental criteria (Shishov and Mokhodoeva, 2024).

Table 2- Evaluation criteria for color in the modified NEMI

component	green color	yellow color	red color
Environment	Less than 50 grams of environmentally hazardous materials	Between 50 and 250 grams of environmentally hazardous materials	More than 250 environmentally hazardous substances
energy	Energy consumption ≤ 0.1 kWh per sample	Energy consumption ≤ 1.5 kWh per sample	Energy consumption ≥ 1.5 kWh per sample
health	Low Toxicity Materials (NFPA* = 0, 1)	Moderately Hazardous Chemicals (NFPA = 2, 3)	Extremely toxic or carcinogenic chemicals (NFPA = 4)
safety	Low Flammability Components (NFPA = 0, 1)	Components with a moderate flammability index (NFPA = 2, 3)	Components with the highest flammability risk (NFPA = 4)
Residue	Less than 50 grams of waste	Less than 250 grams of waste	More than 250 grams of waste

NFPA*: National Fire Protection Association of the United States

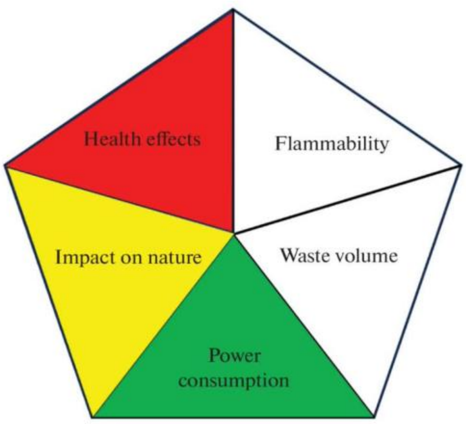

Figure 2- Symbolic representation of the modified NEMI index.

The modified NEMI index was designed to address the limitations of the original version and to enable a more precise assessment of the greenness of analytical methods. In this approach, the use of a colored pentagon with three levels green, yellow, and red allows the evaluation to move beyond a simple qualitative state, thereby facilitating relative comparisons among methods. Nevertheless, the absence of dedicated computational software remains a limitation, as evaluations are performed manually, which can introduce sources of human error. Overall, it can be concluded that the modified NEMI index provides an effective tool for comparing the environmental compatibility of various analytical methods through a systematic and multidimensional approach. It is recommended that future research prioritize the development of intelligent software for the automatic and more accurate calculation of this index, thereby enabling the assessment of the sustainability of analytical methods with greater ease and precision.

3.3. Eco-Scale Index

The Eco-Scale index is a semi-quantitative tool for for the greenness assessment of chemical methods. In this model, an ideal method is assigned a score of 100, from which penalty points are subtracted based on four parameters: chemicals used, associated hazards, energy consumption, and waste generated, to yield the final score. Scores above 75 indicate highly green methods, scores above 50 denote acceptable green methods, and scores below 50 signify inadequate green methods (Van Aken et al., 2006). Key advantages of this index include its ease of calculation, comprehensive parameters, and suitability for rapid assessments. However, the lack of dedicated software for automated calculation remains one of its limitations (Gałuszka et al., 2012). The practical effectiveness of this index in evaluating analytical methods has been validated in numerous studies. For instance, in a comparative evaluation, eight chromatographic methods for determinating of Cannabinoids were assessed using the Eco-Scale index, with one method classified as highly green, achieving a score of 80 (Ribeiro et al., 2024).

To enhance the accuracy of this tool, a modified version of the Eco-Scale has also been proposed, which incorporates an evaluation of waste detoxification, thereby enabling a more thorough examination of the environmental impacts of analytical methods (Płotka-Wasylka et al., 2015).

3.4. GAPI Index

The GAPI[1] index was designed to provide a comprehensive tool for evaluating the greenness of analytical chemistry methods. Unlike some earlier indices that consider only part of the analytical process, GAPI encompasses all stages of the analytical cycle, from initial sampling through sample preparation, measurement, and reporting. This broad scope enables a more accurate assessment of the environmental impacts of the entire process (Shi et al., 2023).

The visual representation of this index takes the form of a diagram with five main zones, collectively comprising 15 specific criteria related to various aspects of the analytical method. Each criterion is indicated by one of three colors: green, yellow, or red, representing low, medium, or high environmental impact, respectively. This color-coded display provides a clear and rapid visualization of the strengths and weaknesses of the analytical method. Figure 3 and Table 3, respectively, present a schematic representation of this index and its evaluation criteria (Potka-Wasilka, 2018).

[1] Green Analytical Procedure Index

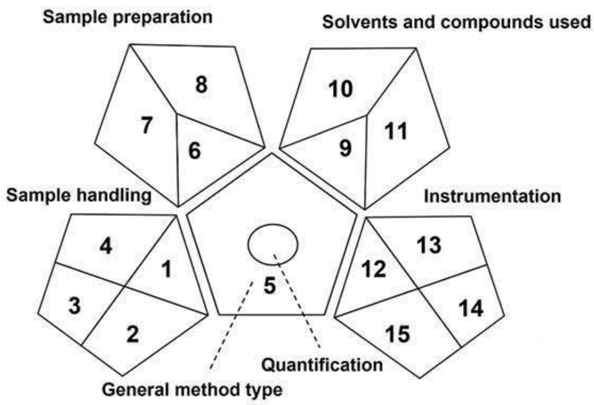

Figure 3- Schematic representation of the GAPI ranking assessment.

Table 3- Evaluation criteria in the GAPI index.

Category	green	yellow	red
Sampling (1)	In-line	On-line or on-site	Off-line
Preservation (2)	Not required	Physical or chemical method	Physicochemical method
Transportation (3)	Not required	Required	Special conditions
Storage (4)	Not required	Normal conditions	Special conditions
Type of method (5)	No sample preparation	Simple method (e.g., filtration, sedimentation)	Requires extraction
Extraction scale (6)	Nano-extraction	Micro-extraction	Macro-extraction
Solvents / reagents (7)	Solvent-free	Green solvents	Environmentally incompatible solvents
Additional steps (8)	None	Simple procedures	Advanced procedures
Amount consumed (9)	< 10 g or mL	10–100 g or mL	> 100 g or mL
Toxicity (10)	NFPA = 0, 1	NFPA = 2, 3	NFPA = 4
Safety (11)	NFPA = 0, 1	NFPA = 2, 3	NFPA = 4
Energy (12)	< 0.1 kWh per sample	< 1.5 kWh per sample	> 1.5 kWh per sample
Occupational hazards (13)	Fully enclosed process	-	Release of vapors into the environment
Amount of waste (14)	< 1 g or mL	1–10 g or mL	> 10 g or mL
Waste management (15)	Recycling	Deactivation / stabilization	Non-recyclable and non-stabilizable

One of the notable features of the GAPI index is its ability to provide a visual and semi-quantitative assessment. In other words, the user can grasp the overall picture at a glance, while still being able to compare different methods with greater precision.

3.5. ComplexGAPI Index

The ComplexGAPI index is essentially an extended version of the GAPI tool, which preserves the original pictogram structure while adding a new section to evaluate pre-sampling stages and specialized characteristics of the analytical process.

In other words, ComplexGAPI can be regarded as GAPI with enhanced functionality and improved assessment accuracy in areas not covered by the original tool (Mansour et al., 2024). The symbolic representation of this index and its additional information are presented in Figure 4 and Table 4, respectively (Potka-Wasilka and Wojnowski, 2021).

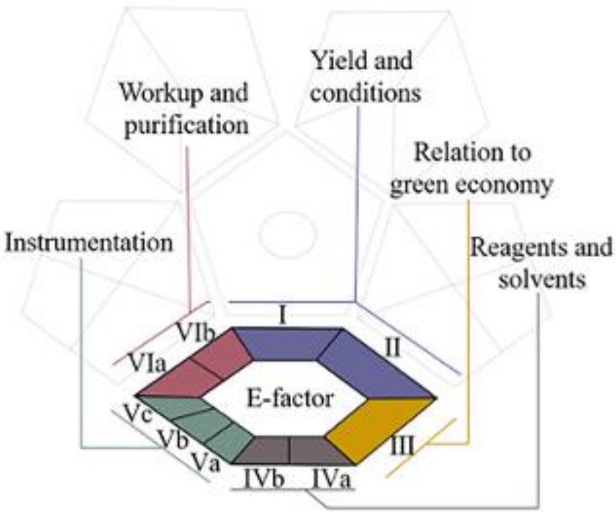

Figure 4- Schematic representation of the ComplexGAPI ranking assessment.

Table 4- Additional information in the ComplexGAPI index compared to GAPI.

No	Description
I	Yield
II	Reaction temperature / time
III	Number of green chemistry principles fulfilled
IVa	Amount of chemicals consumed
IVb	Health hazards
IVc	Safety hazards
Va	Required technical settings
Vb	Energy consumption
Vc	Occupational hazards
VIa	Finalization and purification process
VIb	Purity of the final product
VIc	Amount of waste generated

In addition, considering the amount of waste generated, the E-factor component was incorporated into ComplexGAPI to enable a more accurate evaluation. This component not only accounts for waste arising from by-products and unreacted reagents, but also considers catalysts, consumed solvents, and other residual materials. In brief, the E-factor measures the amount of materials used (such as solvents and reagents) relative to the mass of the final product. The closer this ratio is to zero, the more sustainable the process is, as it indicates lower waste generation (Potka-Wasilka and Wojnowski, 2021).

Furthermore, to facilitate evaluation, a free software tool has been developed for implementing both the GAPI and ComplexGAPI versions, allowing users to analyze the greenness of their selected methods in a visual and structured manner. This software provides only the pictogram diagram and, unlike some numerical tools such as AGREE (discussed later), does not generate a specific numerical output. Nevertheless, it enables step-by-step selection of sample preparation and analytical stages based on predefined guidelines. The software for this index is freely available at https://mostwiedzy.pl/complexgapi.

Although ComplexGAPI is a much more comprehensive index than the original GAPI, it remains a semi-quantitative tool, and its evaluation process requires more detailed data than the basic GAPI version. This requirement may pose challenges for some operational users or under specific practical conditions.

3.6. AGREE Index

Figure 5- Schematic representation of the AGREE ranking assessment and the corresponding color grading scale.

One of the modern tools for evaluating the compatibility of analytical methods with the principles of green chemistry is the AGREE index. This tool is based on the 12 principles of green analytical chemistry and assigns a score between 0 and 1 to each principle, thereby enabling a quantitative and comprehensive assessment of analytical methods. As shown in Figure 5, the output diagram of this index is designed as a circular chart resembling a clock face, in which each segment (1 to 12), corresponding to one of the green chemistry principles, displays the degree of greenness using a color gradient. This tool is freely available at https://mostwiedzy.pl/AGREE (Kaneh et al., 2021; Sajid and Potka-Wasilka, 2022).

Notable features of the AGREE index include quantitative analysis of the degree of compliance of each principle with the evaluated method, automatic averaging to calculate the final greenness score, an attractive visual presentation that allows rapid interpretation by users, and the ability to compare multiple methods in terms of environmental sustainability. However, one limitation of this tool is the equal weighting assigned to all principles, which may reduce assessment accuracy in certain applications (Pena-Pereira et al., 2020).

Today, the AGREE index is widely used as one of the modern and comprehensive tools for evaluating the compliance of analytical methods with the principles of green chemistry. Moreover, in several studies, such as the development of analytical methods based on optical and electrochemical sensors, AGREE has been used in combination with ComplexGAPI to assess the biocompatibility of methods in biological samples. This combined use of tools provides a more accurate insight into the environmental impacts of analytical methods (Davoodi-Rad et al., 2025; Arhami et al., 2025; Ghiasi et al., 2025).

3.7. AGREEprep Index

The AGREEprep index, developed as a targeted extension of the AGREE tool, is specifically designed with a particular focus on the sample preparation stage in analytical chemistry methods. This innovative tool was introduced to enable a more precise evaluation of this stage, which is considered one of the most contaminating and complex parts of the analytical workflow (Wojnowski et al., 2022). The software for this index is available at https://mostwiedzy.pl/pl/wojciech-wojnowski,174235-1/agreeprep.

The visual structure generated by this tool (Figure 6), similar to that of AGREE, is presented as a circular diagram consisting of ten segments with values ranging from 0 to 1, in which the colors shift from green to red based on the input data (Pena-Pereira et al., 2022). One limitation of this index is its exclusive focus on the sample preparation stage; therefore, for a comprehensive evaluation of the entire analytical process, it must be used in combination with indices such as AGREE or GAPI.

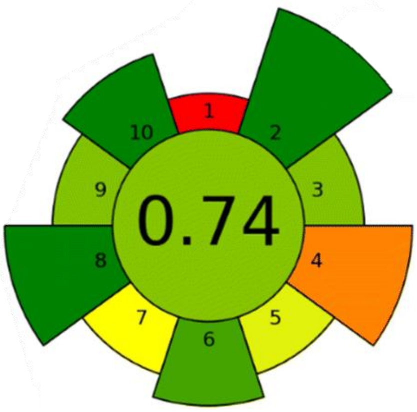

Figure 6- Schematic representation of the AGREEprep ranking assessment.

3.8. HPLC- EAT[1] Index

The HPLC-EAT index is a specialized tool for evaluating the environmental compatibility of high-performance liquid chromatography (HPLC) methods and was first introduced in 2011 by Yaser Jaber and co-workers. This quantitative tool focuses on the type and amount of solvents used, assessing their environmental, safety, and health impacts, and assigns a numerical score to each method that reflects its level of greenness (Yasser Gaber et al., 2011). In this approach, the final score is calculated using an equation in which three indicators, health, safety, and environmental impact, are defined for each solvent and multiplied by the mass of that solvent. The sum of these values for all solvents used constitutes the final HPLC-EAT score. A lower score indicates a greener method, as it reflects the use of safer solvents with lower environmental pollution (Nimoushakavi et al., 2025).

Although this index operates in a quantitative and precise manner, it lacks a visual representation, unlike tools such as AGREE or GAPI, and focuses solely on solvents; therefore, it does not account for other aspects of analytical method sustainability.

3.9. AMVI Index

In HPLC methods, the excessive consumption of organic solvents is one of the major sources of environmental pollution. In this context, the AMVI index was introduced as a simple tool for evaluating solvent consumption. AMVI is calculated by dividing the total volume of solvent consumed during a chromatographic run by the number of identified analyte peaks. A lower AMVI value indicates a greener method, as it reflects lower solvent consumption per analyzed compound (Hartman et al., 2011). Unlike tools such as NEMI or Eco-Scale, which provide multidimensional evaluations, AMVI focuses solely on the intensity of solvent volume consumption and does not consider other aspects such as toxicity or energy usage.

The practical applicability of this index has been confirmed in various studies. For example, in one study, five liquid chromatographic methods for determining of clindamycin were evaluated, and AMVI values ranging from 3.8 to 25.5 mL were

[1] HPLC-Environmental Assessment Tool

reported. This index helped researchers identify the simplest and least solvent-intensive method in terms of greenness (Saad et al., 2019).

3.10. AMGS Index

The AMGS index is a quantitative Excel-based tool introduced in 2019 and made freely available through the ACS website. This tool considers three key dimensions for calculating the final greenness score of an analytical method: the instrument energy consumption score, the solvent energy score, and the solvent EHS[1] score. In this framework, a lower final score corresponds to a higher level of environmental compatibility of the analytical method (Imam and Abdelrahman, 2023). Conceptually, this ranking tool shares similarities with the AMVI and HPLC-EAT indices, but it offers greater scope and accuracy. While AMVI focuses solely on solvent volume consumption per analytical peak and HPLC-EAT weighs the health, safety, and environmental aspects of solvents, AMGS incorporates instrument energy consumption in addition to solvent-related factors, providing a more comprehensive perspective. Moreover, unlike HPLC-EAT, which lacks a visual user interface, AMGS features a simple and user-friendly environment that enables rapid and quantitative comparison of analytical methods (Nimoushakavi et al., 2025).

3.11. RGB[2] Index

The RGB index is a multidimensional tool for evaluating analytical chemistry methods from three key perspectives. In this tool, analytical performance (e.g., accuracy and precision) is represented in red, adherence to green chemistry principles in green, and operational quality (e.g., innovation and comprehensiveness) in blue. Each dimension is scored on a scale from 0 to 100, and the average of these scores is considered the final score. The output diagram is a colored circle that visually displays the balance of these three aspects. The closer the final score is to 100, the more balanced and sustainable the method is considered. This index has been applied in various studies, including spectroscopic and chromatographic methods (Potka-Wasilka et al., 2020).

RGBfast is a simplified version of the RGB model developed for faster and automated evaluation of analytical methods. Instead of comprehensively assessing all three dimensions (analytical performance, environmental compatibility, and operational quality), it focuses on six key criteria, enabling a more rapid analysis. The Excel file designed for this tool allows users to obtain the final score and related greenness indices quantitatively without complex calculations. Due to its sufficient accuracy, ease of use, and speed, this tool is particularly practical for preliminary method evaluations and rapid comparison between methods (Nowak and Arduini, 2024).

3.12. VIGI[3] Index

The VIGI is one of the novel tools designed for evaluating the level of innovation in analytical methods. It is accessible through the link https://bit.ly/VIGItool. This index provides a comprehensive assessment of the innovative aspects of a method by considering ten key criteria, as shown in Table 5. It also serves as a complement to common green, blue, and red indices. The evaluation in VIGI is based on a survey approach, and the result is presented in the form of a star diagram with ten vertices, representing the innovation score of the evaluated method (Figure 7) (Fuente-Ballesteros et al., 2025). Additionally, a threshold value of 50 is defined, meaning that a method achieving this score is considered innovative (Manousi et al., 2024).

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[1] Environmental Health and Safety
[2] Red, Green, Blue
[3] Violet Innovation Grade Index

Table 5. Detailed description of features and criteria of the VIGI ranking tool.

No	Criterion	Question: Does the analytical method…?	Purple (10 points) High Innovation	Regular Purple (5 points) Moderate Innovation	Light Purple (0 points) Moderate Innovation
1	Sample preparation and instrumentation	In-line	Strongly Agree	Somewhat Agree	Disagree
2	Data processing and software	Not required	Strongly Agree	Somewhat Agree	Disagree
3	White analytical chemistry and its derivatives	Not required	Strongly Agree	Somewhat Agree	Disagree
4	Regulatory compliance	Not required	Strongly Agree	Somewhat Agree	Disagree
5	Materials and reagents	No sample preparation	Strongly Agree	Somewhat Agree	Disagree
6	Miniaturization	Nano-extraction	Strongly Agree	Somewhat Agree	Disagree
7	Automation	Solvent-free	Strongly Agree	Somewhat Agree	Disagree
8	Interdisciplinary approach	None	Strongly Agree	Somewhat Agree	Disagree
9	Sensitivity	< 10 g or mL	Strongly Agree	Somewhat Agree	Disagree
10	Novel approach	NFPA = 0, 1	Strongly Agree	Somewhat Agree	Disagree

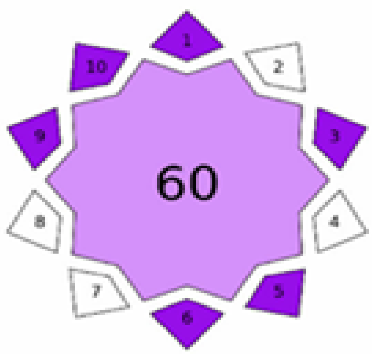

Figure 7- Schematic representation of the VIGI ranking assessment.

3.13. BAGI Index

The BAGI (Blue Applicability Grade Index) has been proposed as a new ranking tool for evaluating the practical applicability of an analytical method. BAGI can be considered as a complement to established green criteria. This tool assesses ten key features, including the type of analysis, the number of analytes determined simultaneously, the number of samples that can be analyzed per hour, the types of chemicals and equipment used, required instruments, the number of samples that can be processed simultaneously, the need for pre-concentration, the degree of automation, the type of sample preparation, and the sample volume. By evaluating these features, an assessment symbol, as shown in Figure 8, is generated (Manousi et al., 2023; Locatelli et al., 2022). The software for this index is available at https://bagi-index.anvil.app/.

Figure 8- Schematic representation of the BAGI ranking assessment.

3.14. GSST[1] Index

The GSST is one of the first systems specifically designed by process development specialists in the pharmaceutical industry to aid in selecting appropriate solvents. This interactive tool aims to facilitate decision-making regarding solvents by providing a set of key characteristics, such as physical properties, safety, environmental impact, and health considerations for many solvents. It allows users to choose the most suitable option based on their process needs. The arrangement of solvents in this tool is based on PCA[2], with solvents that share similar characteristics being placed close to each other. Although this tool does not align with all principles of green chemistry and does not provide a comprehensive evaluation of an analytical method, it is a useful tool for initial screening and selecting more sustainable solvents (Kowtharapu et al., 2023).

3.15. iGAL[3] Index

One of the innovative tools for assessing the environmental performance of chemical processes is the Green Chemistry iGAL, which focuses on Process Mass Intensity (PMI). This tool was designed and developed through a collaborative effort between the IQ[4] Consortium, the Green Chemistry Roundtable of the ACS[5], and a group of academic experts. While iGAL does not directly address all twelve principles of green chemistry, it provides a quantitative framework that effectively demonstrates the impact of green chemistry innovations in reducing chemical waste in the pharmaceutical industry (Diorazio et al., 2021).

3.16. PMI-LCA[6] Index

The PMI-LCA index is an Excel-based tool designed for estimating the overall PMI and performing LCA in the production of small pharmaceutical molecules. The tool is adaptable to support both linear and convergent process types. While it does not cover all aspects comprehensively, it is a practical tool for monitoring the progress of sustainability improvements and reducing environmental footprints in production processes. The ranking system within this tool evaluates four key indicators: net mass consumed, energy use, GWP[7], and water resource depletion. Additionally, two optional indicators, acidification and eutrophication, can also be assessed (Benison & Payne, 2022).

[1] Green Solvent Selection Tool
[2] Principal Component Analysis
[3] Innovation Green Aspiration Level
[4] Innovation and Quality
[5] American Chemical Society
[6] Process Mass Intensity - Environmental Life Cycle Assessment Tool
[7] Global Warming Potential

3.17. ChlorTox Index

The ChlorTox Scale index is an innovative tool in the field of green analytical chemistry, designed to quantitatively assess the health and environmental hazards posed by chemicals. This tool is based on comparing the hazardous properties of chemicals to a reference substance, chloroform. In this method, the hazard level of chloroform is initially calculated using a WHN[1] model, which results in a value of 5.75 for chloroform. Other chemicals are then evaluated relative to this reference number, and the final output is reported as the ChlorTox Unit, which is essentially the mass equivalent of chloroform (Yin et al., 2024). Although this index relies on numerical calculations and lacks visual diagrams, it can serve as a valuable complement to other green metrics, particularly for analyses focused on the safety and health considerations of chemicals.

3.18. HEXAGON Index

HEXAGON is one of the quantitative assessment tools proposed in line with the principles of green chemistry, developed to support the optimal selection or evaluation of analytical methods. In this ranking tool, objective criteria related to analytical performance, sustainability, environmental impacts, and economic cost are assessed by defining penalty points across six independent blocks. These six blocks include analytical quality, toxicity and safety, waste generation, carbon footprint, economic costs, and sample processing and method characteristics (Yin et al., 2024). Each block is scored on a scale from 0 to 4, and the results are presented in the form of a regular hexagonal diagram (Figure 9), enabling a rapid and visual comparison of different methods. The effectiveness of this tool has been tested in various case studies, with results indicating its high accuracy and practical applicability (Busterkoudt et al., 2019).

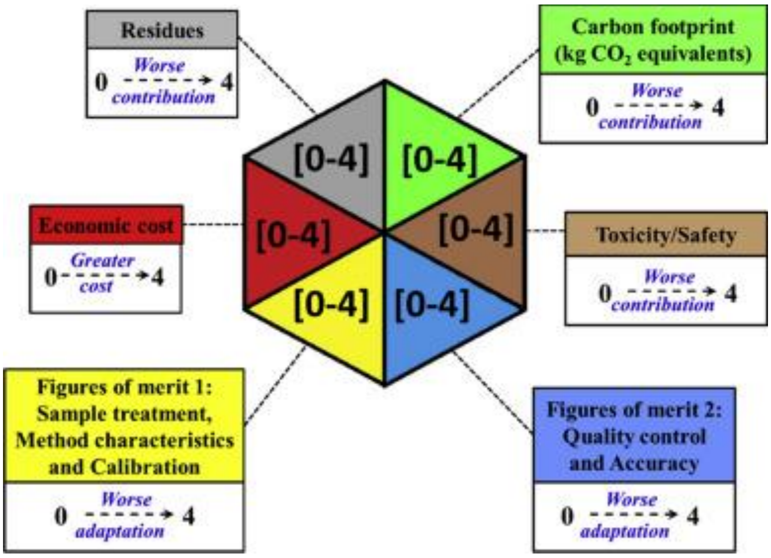

Figure 9- Schematic representation of the HEXAGON ranking assessment and the scale required for determining the analytical method.

Discussion and Conclusion

Despite cultural differences, diverse educational approaches, and varying levels of access to laboratory equipment across countries, global collaboration and the exchange of experiences can facilitate the implementation of green chemistry. International communication also provides an opportunity to harmonize education and curricular standards with contemporary developments (Souri, 2024).

[1] Weighted Hazards Number

However, expanding education and strengthening scientific collaboration represent only part of the pathway toward achieving green chemistry. Another essential aspect is careful and objective evaluation of the degree of greenness of analytical methods. In recent decades, global environmental challenges have made, the compatibility, sustainability, and environmental impact of laboratory methods a fundamental requirement for sustainable development.

Accordingly, a set of 18 major indicators introduced in recent studies was analyzed to provide a comprehensive overview of existing approaches to evaluating the greenness of analytical methods.

Basic and Modified Tools:

NEMI, with its four-quadrant diagram, offers a rapid and visual tool for identifying hazardous aspects; however, one of its main limitations is the lack of a numerical output reflecting impact intensity. The modified NEMI, by incorporating components such as energy consumption, health, and waste level, provides greater differentiation compared to the original version, yet it still relies on manual calculations. Eco-Scale, as a semi-quantitative tool with a scoring system out of 100, is practical for preliminary assessments, although fixed weighting and penalty-based scoring may overlook certain considerations.

Lifecycle Oriented and Pictogram Based Indicators:

GAPI and ComplexGAPI offer a significant advantage by covering the entire analytical cycle, from sampling to waste disposal, enabling the identification of weaknesses through pictogram-based visualization. ComplexGAPI, by adding specialized parameters such as yield, temperature/time, E-factor, and energy consumption, provides higher accuracy than GAPI, but requires detailed data and time consuming calculations. In contrast, AGREE and AGREEprep, based on the 12 principles of green analytical chemistry, generate standardized numerical outputs. AGREEprep is specifically designed for the sample preparation stage, and its combination with GAPI or ComplexGAPI can result in a comprehensive assessment. Nevertheless, equal weighting of principles in AGREE may be restrictive in certain applications.

Chromatography-Specific and Energy/Solvent Indicators:

For HPLC methods, tools such as HPLC-EAT, AMVI, and AMGS are widely used. HPLC-EAT provides a quantitative score by modeling the health, safety, and environmental impacts of solvents. AMVI measures solvent volume consumption per peak and, despite its simplicity, delivers valuable information on material intensity. AMGS evaluates instrument energy consumption, solvent energy, and EHS indicators, offering a more comprehensive picture of the sustainability of liquid chromatography methods. Despite their advantages, these tools are primarily applicable to HPLC and are not fully generalizable to other analytical techniques.

Multidimensional, Operational, and Innovation Oriented Indicators:

RGB simultaneously evaluates efficiency, greenness, and operational quality, presenting a balanced view of analytical methods. VIGI measures the degree of innovation and can serve as a complementary tool for assessing emerging technologies such as automation. BAGI emphasizes practicality and applicability, making it useful for evaluating methods suitable for educational and industrial environments. GSST is a specialized tool for selecting environmentally friendly solvents in pharmaceutical applications, whereas iGAL and PMI based indicators focus on process mass intensity and waste reduction, which are particularly important in chemical industries. Together, these indicators demonstrate that integrating operational, environmental, and innovation dimensions can make assessments more applicable to real laboratory settings.

Lifecycle and Hazard Oriented Indicators:

Lifecycle-based tools such as PMI-LCA and ChlorTox provide deeper analyses of environmental impacts throughout the entire life cycle of materials and methods. ChlorTox, by introducing the concept of chloroform equivalent mass, enables highly precise assessment of hazard and toxicity. HEXAGON, by considering six main axes, offers a comprehensive multidimensional approach. Despite their high accuracy, tools in this category alone do not provide a fully holistic picture.

Overall, the review of available tools indicates that no single indicator can comprehensively cover all dimensions of the greenness of analytical methods. Each tool reflects only part of reality by emphasizing a specific aspect. Therefore, selecting an appropriate tool should be based on the type of analytical method, the evaluation objective, and the availability of data and resources. Under such conditions, the combined use of multiple tools can provide a more comprehensive and reliable assessment of method greenness. At the same time, future progress in this field requires the development of composite indicators and dynamic weighting models, the design of user-friendly software with automated calculation capabilities to reduce human error, and the application of artificial intelligence for faster and more accurate multicriteria analysis.

In this context, adopting the RRI approach can provide an effective framework for guiding the development and application of green assessment tools. The key to success in this approach lies in establishing effective dialogue among multiple stakeholders, including researchers, policymakers, industries, and the public, in order to identify and manage potential positive and negative impacts at early stages of analytical method design and development (Burget et al., 2017). Implementing RRI in green analytical chemistry can lead to the selection and application of assessment tools that better address real societal and environmental needs. This approach also facilitates the design of composite indicators and the development of intelligent evaluation software that considers not only technical performance but also ethical, social, and environmental aspects. Training the next generation of chemists in interdisciplinary collaboration skills and challenge based learning will ensure that the principles of green chemistry and responsible research are integrally embedded in the design, evaluation, and validation of future analytical methods.

Conflict of Interest

The authors have declared no conflicts of interest.

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