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REVIEWS

Green Chemistry Metrics in Analytical Chemistry

A. Yu. Shishov[a], * **and O. B. Mokhodoeva**[b]

[a] Institute of Chemistry, St. Petersburg State University, St. Petersburg, 198504 Russia
[b] Vernadsky Institute of Geochemistry and Analytical Chemistry, Russian Academy of Sciences, Moscow, 119991 Russia
*e-mail: andrey.shishov.rus@gmail.com

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Abstract—The development of environmentally friendly methods of analytical chemistry has been one of the dominant areas of scientific research in recent decades. Environmental performance indices have become a valuable tool for assessing and quantifying the environmental impact of performing chemical analysis. This review article considers the main environmental indices presented in the literature, including aspects such as the safety of used chemical reagents, analytical performance, energy consumption, and waste generation. The review reflects recent advances in green indices and their potential role in a transition to greener and more sustainable analytical practices.

Keywords: green chemistry, chemistry of sustainable development, white chemistry, environmental indices

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Green analytical chemistry is a direction in analytical chemistry that involves the development and implementation of environmentally friendly methods to reduce the impact of analytical processes on the environment and minimize waste generation [1]. It includes a wide range of strategies such as the use of safer solvents and energy-efficient methods. The development and practical use of so-called green chemistry metrics, qualitative and quantitative indicators of the impact of analytical processes on human health and the environment, is one of the important aspects of green analytical chemistry [2, 3]. These indices are intended to provide a standardized basis for assessing the environmental characteristics of analytical methods, both for the purpose of comparing them and selecting the most optimal ones for solving specific problems and for improving the developed approaches in the interests of sustainable development.

This review surveys the main environmental friendliness indices chronologically in the order of their appearance, namely:

- A screening method for ranking and scoring chemicals by potential human health and environmental impacts Chemical Hazard Evaluation for Management Strategies (CHEMS-1);
- National Environmental Methods Index (NEMI);
- Green assessment profile;
- Analytical Method Volume Intensity (AMVI);
- HPLC Environmental Assessment Tool (HPLC-EAT);
- Analytical Eco-Scale for assessing the greenness of analytical procedures);
- Green Analytical Procedure Index (GAPI);
- Hexagon;
- RGB Additive Color Model;
- Analytical GREEnness Metric Approach and Software (AGREE);
- Complementary green analytical procedure index (ComplexGAPI);
- Concept of white analytical chemistry;
- Chloroform-oriented toxicity estimation scale (ChlorTox Scale).

Screening method for ranking and scoring chemicals by potential human health and environmental impacts Chemical Hazard Evaluation for Management Strategies (CHEMS-1), 1997. It is likely that, as soon as chemists received the first data on the possible negative effects of certain substances on human health or the environment, attempts have been made to rank the levels of hazard of these compounds. Currently, concepts such as LD50 (semilethal dose, the average dose of a substance that causes the death of half of the members of a test group), toxicity levels (extremely toxic, average lethal dose lower than 15 mg/kg; highly toxic, average lethal dose of 15–150 mg/kg; moderately toxic, average lethal dose of 151–1500 mg/kg; and low toxic, average lethal dose higher than 1500 mg/kg) [4], hazard classes of harmful substances (1st class, extremely dangerous substances; 2nd class, highly dangerous substances; 3rd class, moderately dangerous substances; and 4th class, low-hazardous substances) [5], and other scales are actively used. However, the same substance can be safe for humans but dangerous for other living organisms; for example,

Table 1. Hazard criteria used in the CHEMS-1 method

Criterion	Type of impact	Comments
Impact on humans		
LD50	Acute	The average dose of a substance, expressed in units of substance mass per unit mass, causing the death of half the members of the test group within 14 days when administered orally as a single dose
LC50	Acute	Concentration of a substance in the air (gas or dust) that would cause the death of half the members of the test group when inhaled continuously for 8 h or less
Carcinogenicity	Chronic	The properties of substances to cause the formation of malignant tumors according to the classification of the US Environmental Protection Agency (EPA) and the International Agency for Research on Cancer (IARC)
Other harmful effects	Chronic	Mutagenicity, effects on development, effects on the reproductive system, and neurotoxicity
Environmental impact		
LD50	Terrestrial acute	The average dose of a substance, expressed in units of substance mass per unit mass, causing the death of half the members of the test group within 14 days when administered orally as a single dose
LC 50	Aquatic acute	Concentration of a chemical in water that causes the death of 50% of fish within 96 h
LC 0	Aquatic chronic	Highest dose administered without causing observable toxic effects
Accumulation potential		
Biological oxygen demand (BOD) half-life	Stability	Time required for a chemical to biodegrade until its BOD in water is reduced by half
Half-life by hydrolysis	Stability	Time required for the amount of a chemical to be reduced by half as a result of a hydrolysis reaction in water at pH 7
Aquatic bioaccumulation factor	Bioaccumulation	The ratio of the concentration of a chemical substance in an aquatic organism to its concentration in the surrounding aquatic environment in a steady state
Emission factor	Emission volume	Coefficient used to determine the chemical toxicity hazard determined by the volume of annual emissions

The average dose of a substance, expressed in units of substance mass per unit mass, causing the death of half the members of the test group within 14 days when administered orally as a single dose Concentration of a substance in the air (gas or dust) that would cause the death of half the members of the test group when inhaled continuously for 8 h or less. The properties of substances to cause the formation of malignant tumors according to the classification of the US Environmental Protection Agency (EPA) and the International Agency for Research on Cancer (IARC).

theobromine, which is found in high concentrations in chocolate, is relatively safe for humans but toxic to dogs. In this regard, the use of one scale is not always sufficient for a comprehensive understanding of the true danger of a substance or process. From an environmental point of view, it is necessary to take into account not only a single exposure to a specific substance but also to scale and predict the consequences of emissions of harmful substances into the environment and their accumulation. To solve this problem, a screening method for ranking and scoring chemicals by potential human health and environmental impacts (CHEMS-1) based on the use of several hazard parameters was proposed in 1997 [6].

In this approach, all substances are divided into three groups according to impact criteria. The first group is responsible for the impact on human beings; the second group is responsible for the impact on the environment, and the third group refers to the accumulation of substances in the environment. Table 1 summarizes the applied criteria of the method and their interpretation.

The test substance is characterized in terms of each of the presented criteria; as a result of this, it is assigned a certain number of points. In this method, there is no single scale for all criteria, and individual formulas are used in each particular case. For example, the assessment of carcinogenicity is based on the classification of the International Agency for Research on Cancer (IARC) and the United States Environmental Protection Agency (EPA), according to which substances and physical factors are divided into four groups: group 1, substances carcinogenic to humans; group 2A, substances with a high probability of being carcinogenic to humans; group 2B, substances carcinogenic to humans with a moderate probability; group 3, substances that cannot be classified as carcinogenic to humans due to lack of data; and group 4, substances probably not carcinogenic to humans. If a substance falls into group 1, it is assigned a maximum value of 5 points. Substances from groups 2A and 2B are assessed at 4 and 3.5 points, respectively, while substances from groups 3 and 4 are not assessed (0 points).

For the factor of hydrolysis of a substance in a water reservoir, the maximum (2.5 points) and minimum (1.0 point) hazard values are assigned to substances with half-hydrolysis times of 500 and 4 days, respectively.

Once all points have been awarded, the human impact and environmental impact points are added together and the total is multiplied by the accumulation points. Factors of release and accumulation in the environment take into account not only the danger of substances to humans on one-time contact, for example, in a laboratory, but complex harm to both humans and nature. For example, cadmium is more dangerous in case of one-time contact, and chromium compounds are more dangerous in large-scale use, taking into account greater emissions into the environment.

In general, despite the cumbersome mathematical apparatus, the method allows a sufficiently detailed assessment of the danger of chemicals to human health and the environment, but it is not without drawbacks. According to the authors of this method, it is possible to find reliable results in terms of many factors not for all substances, and it is necessary to use either data for related compounds or computer modeling methods. Factors such as ozone depletion; toxicity to birds; phytotoxicity; exposure to microorganisms, algae, and invertebrates; photolysis or other decomposition reactions; and the distribution of metals in the environment due to acid–base interactions and complexation are also not taken into account. This method is considered as a screening for the primary classification of the hazards of substances, and it is not used to assess the environmental friendliness of analytical procedures specifically.

National Environmental Methods Index (NEMI), 2002. Attempts to standardize analytical procedures have been made not only in individual publications but also at the legislative level. For this purpose, the ACS Green Chemistry Institute has developed the National Environmental Methods Index [7], which is a searchable database of environmental analysis methods including analytical characteristics, equipment requirements, analysis protocols, statistics, relative costs, etc. The database was created as a tool for researchers and analytical laboratory specialists to search and compare analysis methods and data obtained at all stages of environmental monitoring. The vast majority of NEMI techniques are designed for the analysis of aqueous media. Representative techniques for atmospheric air, animal tissues, and soil/bottom sediments are also included.

Initially, the methods for compiling this database were presented by the United States Environmental Protection Agency (EPA) and the United States Geological Survey (USGS). Currently, permission to include a procedure in this database can be obtained by any scientific organizations and public and private companies. There is no charge for introducing procedures, but they should be in a strictly documented format and published (i.e., be publicly available). With the NEMI, the user can access brief descriptions of procedures and full-text contents. Current search options include the analyte (name or CAS number), the type of test media (water, air, soil/sediment, or tissue), the instrument and detector used (over 80 options), the method subcategory (biochemical, organic, inorganic, microbiological, physical, or radiochemical), etc. From the point of view of assessing environmental friendliness, the NEMI method uses a simple pictogram in the form of a circle divided into four parts (Fig. 1). The first quarter circle indicates that the analysis does not use toxic, bioaccumulative, and hazardous reagents or solvents in accordance with the Toxic Release Inventory (TRI) [8]. The second quarter confirms the absence of the reagents used in the lists of hazardous wastes in accordance with the regulations of the Resource Conservation and Recovery Act (RCRA) [9]. The third quarter is responsible for the absence of corrosive effects; that is, the pH of the medium ranges from 2 to 12. The fourth part indicates that the total amount of waste generated throughout the analysis does not exceed 50 g. If these criteria are met, the corresponding sector is green; if not, it is white. This is the first attempt to obtain a visual assessment of the environmental friendliness of a methodology. However, the main disadvantage of NEMI visualization is that the results are qualitative, and the source of non-environmental friendliness is not clearly shown in the pictogram [10].

Green assessment profile, 2009. The following green assessment index was proposed by Raynie and Driver [11] at the 13th Annual Green Chemistry and Engineering Conference held in 2009. The index is a pictogram containing five segments and three-color differentiation. Table 2 and Fig. 2 show evaluation criteria and an example of a color pictogram for this method. However, this index, like that proposed earlier, does not allow one to fully assess what exactly is the main source of nongreen analytical procedures.

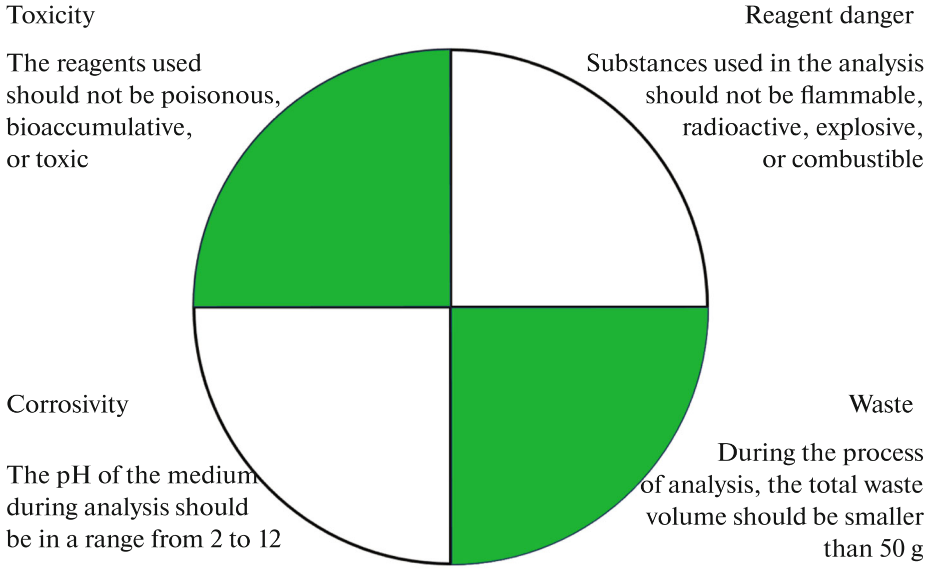


Fig. 1. Graphical representation of the National Index of Environmental Monitoring Methods.

Among other things, this is due to the fact that it is difficult to simultaneously evaluate all stages of chemical analysis. Thus, the Analytical Method Volume Intensity (AMVI) was proposed for a more detailed assessment of individual stages of implementation of specific analysis techniques.

Analytical Method Volume Intensity (AMVI), 2011. In 2011, Hartman et al. [12] proposed the Analytical Method Volume Intensity (AMVI) index, which consists of measuring the total volumes of solvent consumed and waste generated during the implementation of an analytical method. While they noted that this metric can be applied to any analytical technique, they focused on using AMVI for HPLC analysis techniques in the first paper.

The essence of the method is to sum up the entire solvent used both at the stage of HPLC analysis and at the stage of sample preparation and normalize it to the amount of analytes. As an example, a comparison of procedures when the entire analysis required 100 mL of solvent and only one substance was used as an analyte and when the total solvent volume was 200 mL but more than ten analytes were determined. In the latter case, the procedure was more environmentally feasible in terms of solvent consumption. Hartman et al. [12] mentioned various ways to decrease solvent consumption by reducing the size of a chromatographic column and analysis time and using other approaches.

Despite the apparent obviousness, this method focuses on the need to take into account an important parameter such as the consumption of reagents; unlike other indices, it allows one to compare a separate parameter rater than the overall environmental friendliness. It should be noted that this method can be used, for example, to estimate not only the consumption of solvents but also the energy costs required for obtaining analytical information. For example, electric energy consumption to determine the concentra-

Table 2. Criteria for assessing environmental friendliness according to the Green assessment profile

Criterion	Green	Yellow	Red
Health effects	Low toxicity, mild irritant	Moderately toxic, can cause temporary disability	Serious health hazard within a short period of exposure
Flammability according to the National Fire Protection Association	From 0 to 1	From 2 to 3	4
Impact on nature	Application of less than 50 g of hazardous substances	Application of 50 to 250 g of hazardous substances	Application of more than 250 g of hazardous substances
Energy consumption	Low consumption (titration)	Medium consumption (GC, HPLC)	High consumption (GC–MS)
Waste volume	Less than 50 g	Less than 250 g	More than 250 g

tion of one analyte (AAS spectrometry) or several analytes (XRD and ICP analysis) can be evaluated.

HPLC Environmental Assessment Tool (HPLC–EAT), 2011. Another index of the environmental performance of chromatographic techniques, HPLC–Environmental Assessment Tool (HPLC–EAT), which is also based on measuring the consumption of solvents when performing chromatographic analysis, was published simultaneously with the AMVI method [13]. However, the HPLC–EAT method has a slightly more complex mathematical apparatus that takes into account both the volume of solvents and their toxicity. The HPLC–EAT software, which is publicly available and allows one to obtain a numerical value characterizing the overall environmental friendliness of the solvents used for HPLC analysis, was developed to simplify calculations.

Analytical Eco-Scale, 2012. All of the above methods for assessing environmental friendliness are either too extensive or, conversely, too local. The first comprehensive procedure for assessing the greenness of analytical procedures referred to as the Analytical Eco-Scale was proposed in 2012 by Gałuszka et al. [14]. The score is calculated based on subtracting penalty points from a score of 100, which corresponds to an ideal green analysis method. Penalty points are assigned to a method depending on the nature and quantity of solvents and reagents used, energy consumed, the number and labor intensity of analysis stages, automation, the volume of generated waste, and methods of waste disposal.

According to this scale, a procedure can be considered ideal from an environmental point of view if it meets the following conditions:

(1) Solvents or reagents do not pose any physical and environmental hazards or health hazard to the operator.

(2) Energy consumption is lower than 0.1 kWh per sample.

(3) No waste is generated.

In fact, only a few procedures that involve direct measurements and do not require transportation, preservation, or sample preparation can meet these criteria. Figure 3 presents a schematic diagram for evaluating analytical procedures, according to which parameters such as sampling, sample delivery, the need and method of preservation, sample preparation, analysis itself, and the need for preliminary calibration are assessed. As an example, Table 3 shows the calculation of penalty points for energy consumption and generated waste.

IR spectroscopy and enzyme immunoassay are energy-nonconsuming analysis methods, and they do not have penalty points. With the use of atomic absorption or gas chromatography, 1 penalty point is awarded, and 2 points are awarded for nuclear magnetic resonance or X-ray methods. Gałuszka et al. [14] also described the evaluation of the consumption and danger of reagents. If less than 10 mL or 10 g of a reagent is used, 1 penalty point is awarded, but if it is a toxic reagent, then the number of points is multiplied by its hazard class. Thus, according to this scale, it is more environmentally friendly to use a large volume of a less hazardous reagent. If any gases or vapors are released into the air in the course of analysis, 3 penalty points are assigned. However, if the analytical process is isolated, no penalty points are awarded. A detailed algorithm has been developed for calculating penalty points for all parameters with specific examples [14]. A score above 75 characterizes a procedure as excellent. A score in the range of 50–75 corresponds to an acceptable procedure. A score of less than 50 is considered unsatisfactory.

It should be noted that the Analytical Eco-Scale is the first index that provides a quantitative assessment of the greenness of a procedure, which can be compared with the ideal assessment and with assessments of other procedures. In this approach, there is no

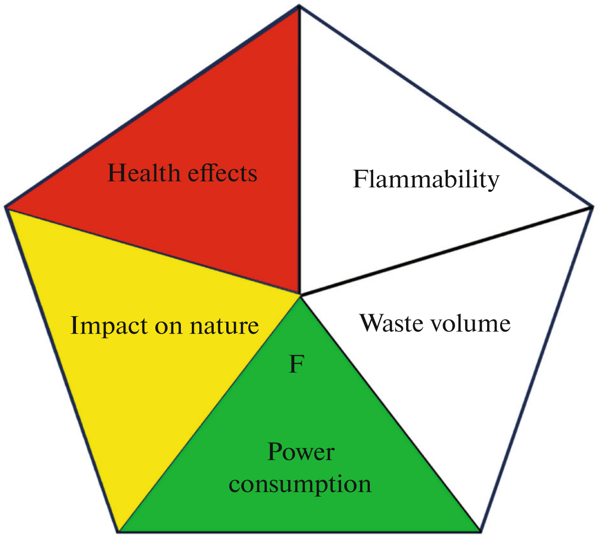


Fig. 2. Graphical representation of the Environmental Assessment Profile.

Table 3. Example of calculating penalty points according to the Analytical Eco-scale

Parameter	Value	Number of penalty points
Energy consumption	<0.1 kW per sample	0
	<1.5 kW per sample	1
	>1.5 kW per sample	2
Waste	None	0
	< 1 mL (g)	1
	1–10 mL (g)	3
	> 10 mL (g)	5

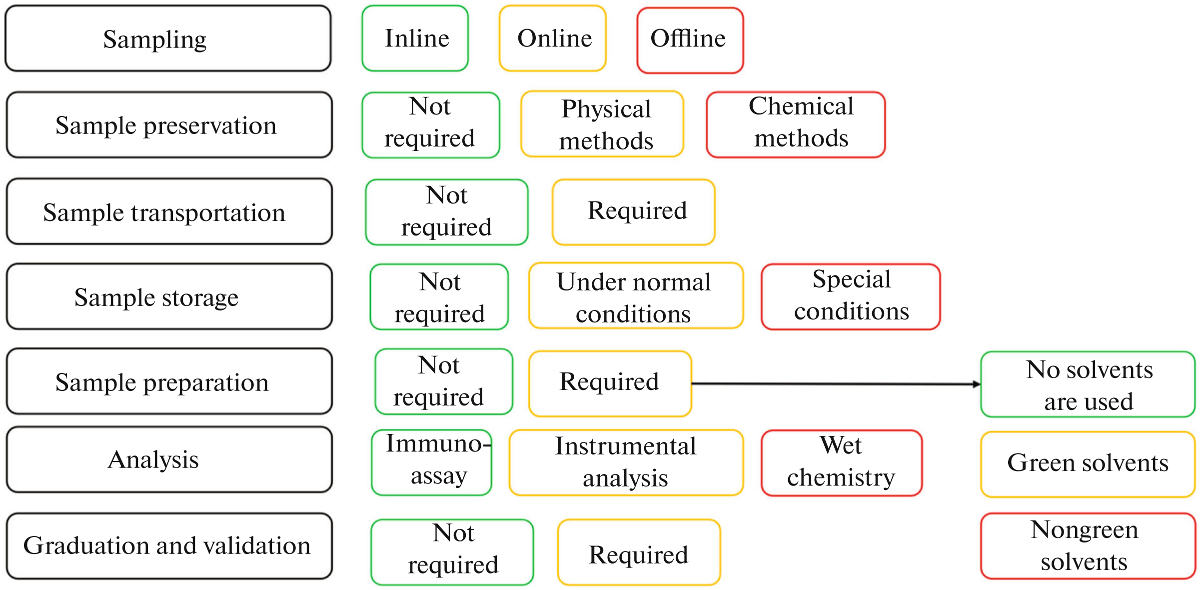


Fig. 3. Block diagram for assessing an analytical procedure according to the Analytical Eco-scale.

graphical representation of the result. The main disadvantage of the eco-scale is that it is impossible to determine which part of the procedure has the greatest negative effect without a detailed analysis. These limitations have necessitated further development of environmental performance indices taking into account accumulated experience.

Green Analytical Procedure Index (GAPI), 2018. As an alternative assessment method, a new approach, which can be considered a development of the NEMI and Green assessment profile methods but is much more informative, was proposed in 2018 by Płotka-Wasylka [15]. The essence of this method also consists in the color differentiation of various parameters of an analytical procedure but using a larger number of parameters. In this case, the result of the environmental assessment is a pictogram (Fig. 4) consisting of five segments, each of which is a pentagon. The first figure is responsible for sampling and sample transportation and storage. The second figure refers to sample preparation; the third figure corresponds to reagents and materials, and the fourth figure corresponds to equipment and waste. The central pentagon is responsible for the complexity of the sample preparation procedure. If the method is direct and it does not require sample preparation, it is colored green; if minimal labor consumption, such as filtration, is required, it is colored yellow. If more complex procedures such as extraction are needed, the central figure is red. If the method is generally quantitative, a black circle is added to the center of the pictogram.

To select the color of a particular segment, Płotka-Wasylka [15] introduced some boundary conditions. For example, the first cell of a sector responsible for sampling is colored green, yellow, or red in the case of direct (inline), online, or offline analysis, respectively. The second cell is colored green if there is no need for preservation, yellow if either chemical or physical preservation is required, or red if both physical and chemical preservations are required [15]. The result is a pictogram colored in different colors, which reflects most of the stages of the procedure. The proposed GAPI index is a good semiquantitative tool for laboratory practice and educational purposes. The index not only provides the user with an overall assessment of the environmental friendliness of the procedure but also allows a visual and rapid assessment of the most nongreen stages in the analytical procedure. The disadvantage of this approach is the lack of a numerical expression for assessing environmental friendliness.

Hexagon, 2019. The Hexagon algorithm was proposed by Ballester-Caudet et al. [16] in 2019; it consists of five blocks, which characterize different stages of analysis by calculating penalty points similarly to the Analytical Eco-Scale. The first block, which evaluates the figures of merit of a procedure, is divided into two groups: the first lists the conditions and characteristics of sample preparation (Table 4), determination method (Table 5), and calibration and the second group takes into account the frequency and time-consuming standardization of the procedure and accuracy check. In the second block, the actual safety of the procedure, the toxicity of reagents, and chemical risks are assessed using data from the Globally Harmonized System of Classification and Labeling of Chemicals (GHS). The third block takes into account the amount of waste generated as a result of the analysis, its processing, and the availability of reusable materials. The environmental impact is quantified in the fourth block

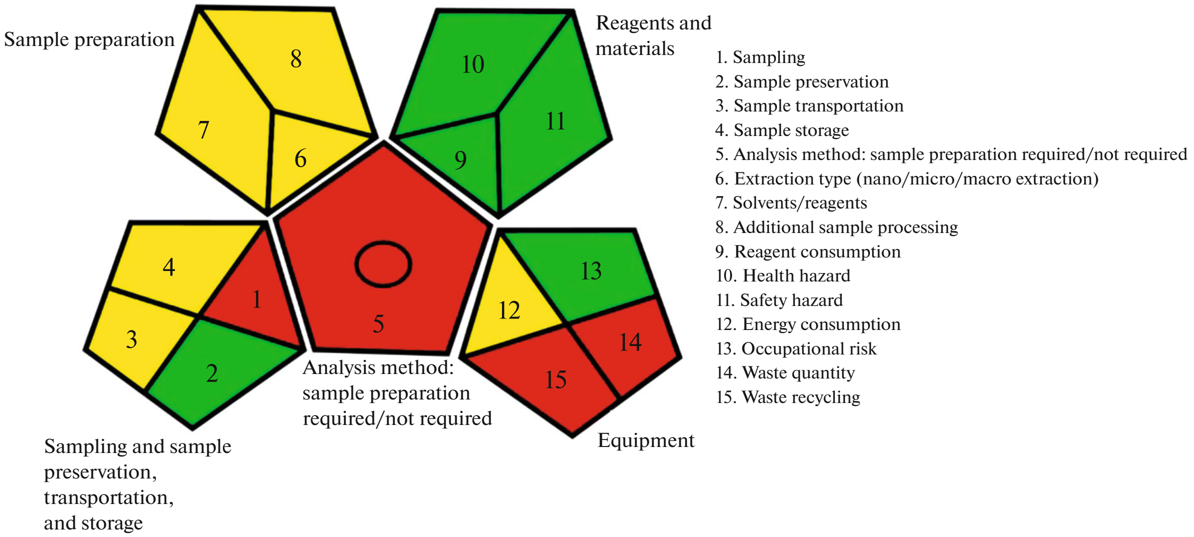


Fig. 4. Graphical representation of the Environmental Compliance Index of analytical procedures.

by carbon footprint (kg CO_2), which takes into account the energy consumption of the equipment used and the time required to carry out the analysis. Finally, the fifth block represents economic calculations related to the costs of materials used, equipment, electricity consumption, and staff wages. Carbon footprint and annual costs are measured in absolute terms. The sum of the penalty points from the first three blocks and the estimated values of carbon footprint and cost are ranked in the overall quantitative score on a certain scale, and the final result is presented as a regular hexagon with six equilateral triangles (Fig. 5). As can be seen, both a visual assessment of the procedure and a quantitative assessment with consideration for penalty points are proposed. In addition, this method for the first time addresses the issue of the economic component of the chemical analysis procedure.

RGB Additive Color Model, 2019. The RGB (an abbreviation for the words red, green, and blue) additive color model, which is widely used in color synthesis technology, was adapted by Nowak and Kościelniak [17] in 2019 to characterize analytical methods. In this interpretation of the model, the red color represents the analytical characteristics of the method (precision, accuracy, and sensitivity), the green color represents compliance with the principles of green chemistry, and the blue color evaluates the practicality of the method in terms of economic costs and time consumption.

The RGB model is additive because colors are obtained by adding to black. In the color synthesis technique, the screen is black in the absence of radiation; the mixing of three primary colors in a certain proportion gives white color. When mixing blue and red, green and red, and green and blue, the results are magenta, yellow, and cyan, respectively (Fig. 6).

A data table (Table 6) with the resulting additive color characterizing the method is obtained by expressing the intensity of each primary color (Color Score, CS) as a percentage of the ideal value, where 33.3% is the Lowest Acceptable Value (LAV) and 66.6% is the Lowest Satisfactory Value (LSV).

In addition to the qualitative assessment expressed by color, Nowak and Kościelniak [17] also proposed to characterize procedures with a quantitative assessment in the form of a geometric weighted average of individual intensity values of the primary colors. Nowak and Kościelniak [17] referred to this parameter, expressed as a percentage, as the method brilliance (MB).

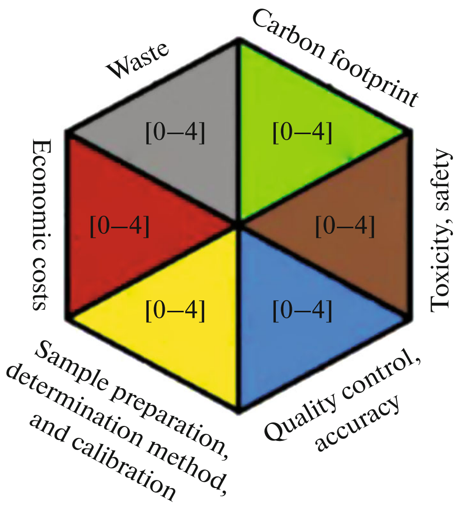


Fig. 5. Presentation of the result according to the Hexagon algorithm.

Table 4. Characteristics of sample preparation according to the Hexagon algorithm

Description of sample preparation stages and materials used		Penalty points
Conservation	None	0
	Physical	1
	Chemical	2
Storage	None	0
	Normal conditions	1
	Special conditions	2
Quantity	Micro	0
	Macro	1
Reagents and solvents	None	0
	≤ 3	1
	> 3	2
Weight of reagents and solvents used	< 1 g	1
	1–10 g	2
	10–50 g	3
	> 50 g	4
Instrumental determination	No need for dilution or preconcentration	0
	Dilution/concentration by a factor of 5	1
	Dilution/concentration by a factor of more than 5	2
Number of analyzed samples per week	≥ 50	0
	50–1	1
	< 1	2
Preliminary processing	None	0
	Filtration	1
	Stirring/heat drying	2
	Acid decomposition	3

To evaluate procedures using the RGB model, a special algorithm was developed based on a standard Excel spreadsheet, which is in the public domain. The proposed model is flexible due to the ability to adjust the general characteristics of a procedure in accordance with the subjective assessment of primary color intensities and other parameters used. This flexibility is good because it allows one to choose the most optimal procedure from several alternatives and allows for the opposite option, that is, the prediction of potential applications of developed procedures by comparing estimates obtained in accordance with different sets of variables in this model.

Analytical GREEnness Metric Approach and Software (AGREE), 2020. In 2020, a certain symbiosis of approaches was proposed based on both obtaining a single assessment of the environmental friendliness of a procedure and creating an easy-to-read pictogram, from which it is clear which stage makes the greatest or lowest contribution to the greenness of the procedure (Fig. 7). The result of this work was the AGREE method, which is an online calculator [18]. According to this method, each of the known 12 principles of green analytical chemistry has a numerical value from 0 to 1, where 0 refers to complete noncompliance with a specific principle and 1 refers to complete compliance. The average value obtained for each of the criteria is the result of evaluating the entire procedure. The resulting figure is indicated inside a pictogram, which is a circle with sectors, each of which is responsible for one of the principles. The color of the central sector is an averaged color from red to green obtained by averaging all 12 colors. The method is one of the most comprehensive and convenient methods both for reading such pictograms and for creating them using publicly available software (https://mostwiedzy.pl/AGREE). Pena-Pereira et al. [18] compiled a detailed instruction for a more detailed understanding of how each parameter is evaluated. For example, 0 points are assigned if the procedure involves offline analysis; 0.25, 0.75, and 1 point are assigned for the principle of automation (at-line), online analysis, and direct (inline) analysis, respectively. The sample consumption is estimated using the equation

$$\text{Score} = -0.142\ \ln(\text{amount of sample in g or mL}) + 0.65.$$

The assessment of each criterion is described in more detail in a publication of Pena-Pereira et al. [18].

Complementary green analytical procedure index (ComplexGAPI), 2021. The GAPI method has become quite widespread, and it is already often used by analytical chemists. In 2021, Płotka-Wasylka and Wojnowski [19] proposed an expanded version of the index called ComplexGAPI, which has an additional color sector under the main pictogram. The complexity of the method implies taking into account the processes implemented before the implementation of the analytical procedure itself. For example, these are processes used for the synthesis of sorbents, extractants, auxiliary materials, nanoparticles, and other materials used at the stage of separation and preconcentration. All these processes are rarely assessed because most indices are focused on evaluating only the parameters and consumption of reagents at the stage of directly performing chemical analysis. The pictogram (Fig. 8) displays ten additional sectors, which are respectively responsible for the yield of the reaction product, the synthesis temperature, the economic component, the danger and toxicity of solvents and reagents, the use of devices to create elevated pressure at the stage of synthesis, the energy consumption of the devices, the tightness of the process, conditions for the purification of the final product, and its purity. Boundary conditions were proposed for each parameter to designate the corresponding sector in green, yellow, or red. The E factor equal to the ratio of the total volume of waste to the total weight of the target product is indicated in the center of this pictogram. This factor takes into account not only by-products and residual reagents but also spent catalysts, catalyst supports, solvent losses, and anything else that can be considered waste.

Thus, this method complements the already proposed GAPI approach and draws attention to the need to evaluate not only the chemical analysis procedure itself but also the processes preceding it because the use of 10 mg of a sorbent looks environmentally friendly, if you do not take into account that 100 mL of a toxic or volatile organic solvent was spent for its synthesis.

Concept of White Analytical Chemistry (WAC), 2021. The considered tools for assessing the greenness of analytical procedures take into account their compliance with the 12 principles of green chemistry formulated more than 20 years ago [20]. However, this is insufficient for correlating the developed procedures with the concept of sustainable development, which includes three main economic, social, and environmental components [21]. In this regard, a more comprehensive approach was proposed to take into account, along with the criterion of safety and environmental protection, the analytical efficiency of procedures (accuracy, sensitivity, reproducibility, and determination and detection limits) and economic efficiency (cost, availability, duration, and simplicity) [22]. This approach is based on the above mentioned RGB color model, where the red sector is responsible for analytical efficiency, the green sector assesses the environmental impact, and the blue sector summarizes the economic component [17]. As a result, the concept of white analytical chemistry appeared to combine all the listed requirements for safety, functionality, and practical significance of analytical methods, in accordance with which 12 principles of white analytical chemistry were formulated [23, 24].

Table 5. Characteristics of the determination method according to the Hexagon algorithm

Description of the determination method		Penalty points
Method category	Direct determination	0
	Online	1
	Offline	2
Operating mode	Automatic	0
	Semiautomatic	1
	Manual	2
Portability	Yes	0
	No	1
Method/Sample	No sample destruction	0
	With sample destruction	1
Analytes/Sample	Multielement	0
	Single element	1
Analysis time	<10 min	0
	10–100 min	1
	>100 min	2
Sustainability	Yes	0
	No	1

The concept of white analytical chemistry expands the principles of green chemistry and provides a balance between the environmental friendliness of the developed procedures and equally important analytical and economic characteristics, giving them equal and complementary significance. To assess the compliance of procedures in the aspect of white analytical chemistry, several approaches have been proposed to date. One of the latter is based on the RGB 12 color coding algorithm (advanced additive RGB color model). It is reduced to filling three sectors of a table in an Excel spreadsheet by entering numerical values from 0 to 100, where 0 does not correspond and 100 fully corresponds to the 12 principles of white analytical chemistry, respectively (four principles for analytical efficiency, a red sector; four principles for the

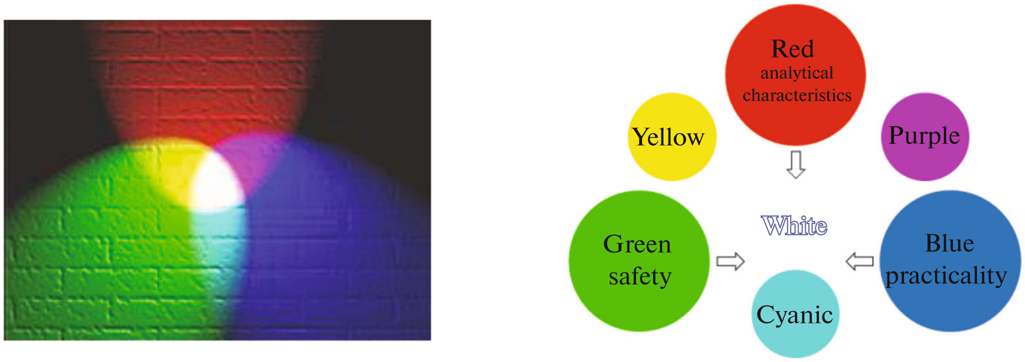


Fig. 6. Additive RGB color model.

Table 6. Representation of the result according to the additive RGB color model

Resulting color	Color intensity			General recommendations
	red	green	blue	
White	≥66.6%	≥66.6%	≥66.6%	The procedure is well balanced in relation to three main components. Recommended for use
Magenta	≥66.6%	≥66.6%	≥33.3%	The procedure can be recommended in the absence of a greener alternative
Yellow	≥66.6%	≥33.3%	≥66.6%	The procedure can be recommended for a small number of analyzed samples
Cyan	≥33.3%	≥66.6%	≥66.6%	The procedure can be recommended if the requirements for analytical characteristics are not strict
Red	≥66.6%	≥33.3%	≥33.3%	The procedure can be recommended when the number of analyzed samples is small and there is no greener alternative
Blue	≥33.3%	≥66.6%	≥33.3%	The procedure can be recommended if the requirements for analytical characteristics are not strict and in the absence of a greener alternative
Green	≥33.3%	≥33.3%	≥66.6%	The procedure can be recommended when the number of analyzed samples is small and if the requirements for analytical characteristics are not strict
Colorless (Grey)	≥33.3%	≥33.3%	≥33.3%	The procedure is generally acceptable, although there are no obvious advantages. You can conditionally consider its use if there are no alternatives
Black	<33.3% (for one or more parameters)			The use of the procedure is questionable due to noncompliance of one or more basic components with the requirements

volume and toxicity of the reagents used and generated waste, a green sector; and four principles for economic efficiency, a blue sector) and obtaining the result in the form of a generalized whiteness parameter (Fig. 9).

Chloroform-Oriented Toxicity Estimation Scale (ChlorTox Scale), 2023. It becomes important to reliably assess the hazard of a single reagent because most of the described environmental indices involve the ranking of reagents and chemicals used by hazard levels. The chloroform-oriented toxicity estimation scale (ChlorTox Scale) proposed in 2023 by Nowak et al. [25] is a more objective tool not related to color perception. In this case, it was proposed to use chloroform as a standard reference substance well studied in terms of chemical risks for the environment and for users. The index is calculated according to the formula

$$\mathrm{ChlorTox} = \frac{\mathrm{CH_{sub}}}{\mathrm{CH_{CHCl_3}}} m_{\mathrm{sub}},$$

where $\mathrm{CH_{sub}}$ and m_{sub} are the toxicity (Chemical Hazard) and the weight of the substance used, respectively, and $\mathrm{CH_{CHCl_3}}$ is the toxicity of chloroform.

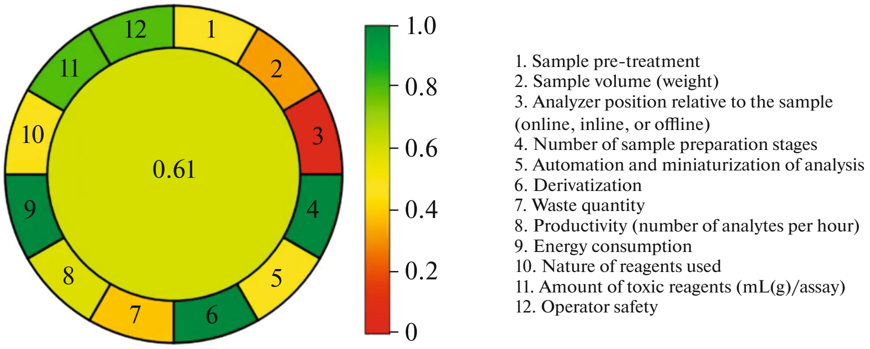
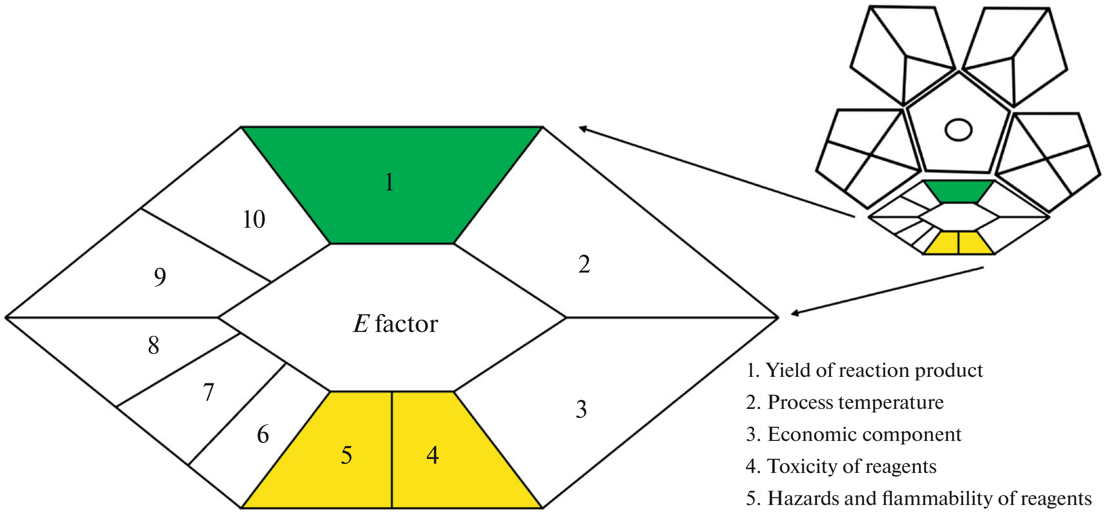
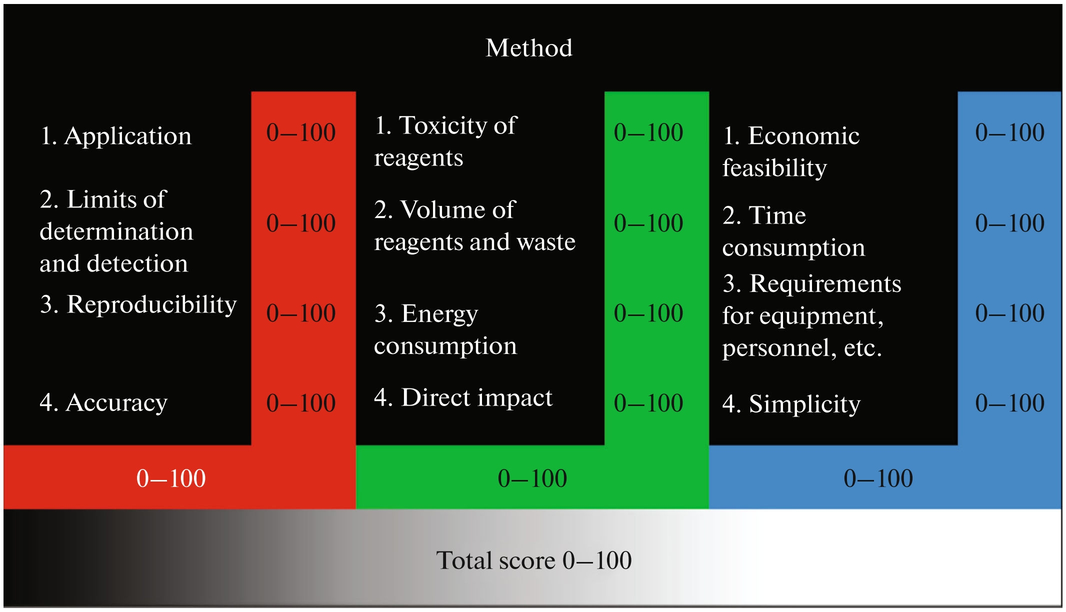


Fig. 7. Graphical representation of the Green Index of analytical procedures.



1. Yield of reaction product
2. Process temperature
3. Economic component
4. Toxicity of reagents
5. Hazards and flammability of reagents
6. Using devices to create increased pressure
7. Energy costs
8. Process integrity
9. Conditions for purification of the final product
10. Product purity

Fig. 8. Graphical representation of the Complementary Green Analytical Procedure Index.



Method

1. Application	0–100	1. Toxicity of reagents	0–100	1. Economic feasibility	0–100
2. Limits of determination and detection	0–100	2. Volume of reagents and waste	0–100	2. Time consumption	0–100
3. Reproducibility	0–100	3. Energy consumption	0–100	3. Requirements for equipment, personnel, etc.	0–100
4. Accuracy	0–100	4. Direct impact	0–100	4. Simplicity	0–100
0–100		0–100		0–100	

Total score 0–100

Fig. 9. Presentation of the result according to the RGB 12 color coding algorithm.

Nowak et al. [25] proposed to calculate the toxicity values of substances using one of the two approaches: Weighted hazards number (WHN) and CHEMS-1. The former consists in searching for relevant information on the hazards posed by certain chemicals in publicly available safety data sheets presented in the generally accepted Globally Harmonized System of Classification and Labeling of Chemicals (GHS) format. The CHEMS-1 screening method for ranking and assessing chemicals for potential effects on human health and the environment, which was described above, is based on the use of the Hazardous Substances Data Bank (HSDB) integrated into the PubChem database [26]. For new or little-known chemical reagents, it is recommended to assess their toxicity in a simplified manner, for example, by reference to other substances with similar chemical structures and well-characterized properties.

The ChlorTox values characterizing different substances can be summed to estimate the overall chemical risk predicted for the entire method (Total ChlorTox). In this case, it is necessary to take into account the substances used for auxiliary stages, such as graduation, washing, etc. The results are interpreted as follows: a method with a Total ChlorTox value of 1 g poses the same potential risks as a method using 1 g of pure chloroform per test as the only hazardous chemical reagent. Similar approaches to the theoretical expression of risks for a selected group of pollutants based on toxic equivalence coefficients are already known and used in environmental toxicology [27, 28]. In practice, potential risks on the ChlorTox scale should be considered semiquantitative with a reasonable degree of uncertainty. Obtaining ChlorTox results should preferably be accompanied by the use of similar tools designed to assess the risks that the method poses to the environment and the user.

CONCLUSIONS

This review presents various environmental friendliness indices of both analytical procedures as a whole and their individual stages. Until recently, concepts such as green chemistry, renewable energy, nature-like technologies, E factor, and nuclear efficiency were rather theoretical studies and aroused the interest of enthusiasts. Nevertheless, the negative consequences of scientific and technological progress are becoming obvious not only to environmental specialists but also to the entire public. The world system has long gone beyond the limits to growth described in the famous report of the Club of Rome on the project "Problems of Humanity" in 1972. In this regard, the development of tools for objective assessment of the greenness of analytical procedures is an integral part of the sustainable development paradigm. The above data indicate that all currently available tools were developed in the United States and the European Union, where entire institutes, bills, and government regulations on green chemistry have been developed and operate. According to the authors, if not the use of such tools, then at least an idea of the development of research in this area is necessary.

As a conclusion, we can say that today there is no universal method for assessing analytical procedures in terms of their compliance with the principles of green or white chemistry. Currently used metric tools, such as CHEMS-1, NEMI, Eco-Scale, GAPI, ComplexGAPI, AGREE, HEXAGON, RGB12, etc., are in most cases based on rather subjective models. However, rational use of several considered methods can be very informative when it is necessary to compare several analytical procedures and select the most effective one from a safety point of view. In scientific publications, these indices can be used to validate newly developed procedures and compare them with both the ideal and other procedures.

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CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

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