# Green Analytical Chemistry

**Sergio Armenta, Salvador Garrigues, Miguel de la Guardia, and Francesc A Esteve-Turrillas**, University of Valencia, Valencia, Spain





## Glossary

**Automation** The use of various elements of an analytical process with minimal or reduced human intervention.
**Direct analysis** The analysis of a sample without any sample treatment.
**Eco-scale** Quantitative criterion to evaluate method greenness.
**Greenness** Environmental impact of an analytical methodology.
**Life cycle assessment** A technique to evaluate the environmental impacts associated with all the steps of a procedure.
**Miniaturization** The scaling down of mechanical, optical and electronic devices and analytical operations.
**Passivation** The change of chemical form or hazard reagent or waste to reduce its reactivity or toxicity.
**Sensor** A device employed to detect changes in its environment and send the information to an electronic processor.

## Green Analytical Chemistry and Green Chemistry

Since the 1970s decade, novel analytical methodologies have been introduced to improve the analytical figures of merit of previous methods, and also to reduce the undesirable side effects, like operator risk, environment contamination, consumption of reagents and solvents, waste generation, and so on. In this sense, different strategies were considered to improve analytical methods based on automation, miniaturization, direct and multianalyte analysis, and reduction of solvents, reagents and wastes together with the replacement of toxic reagents by innocuous ones, as it can be seen in Fig. 1 that shows the progress on the concepts related with green analytical chemistry and the main milestones since the 1970s.

The increasing environmental conscience of analytical chemistry was firstly introduced as "Ecological Paradigm" by Malissa, in 1987, indicating that today Analytical Chemistry must be closely implicated in the preservation of our ecosystem and actively contribute to the protection of the environment and the operator safety.

De la Guardia and Ruzicka in 1995 edited the first international scientific journal issue devoted to sustainable methods and introduced the "Environmentally Friendly Analytical Chemistry" concept, based on the replacement or reduction of toxic chemicals to harmless ones by the incorporation of (i) robotics, (ii) miniaturized chromatograph systems, (iii) flow techniques as flow injection analysis or sequential injection analysis, and (iv) sensor technologies.

Green Chemistry concept was introduced by Anastas and Warner in 1998[1] indicating the environmental implication in the development of chemical products and processes. Thus, Green Chemistry must contribute to avoid, or reduce, the negative impacts of chemical activities on human health and the environment. This concept is based on (i) the reduction of reagent and solvent consumption, (ii) the reduction of wastes, (iii) the proposal of recycling, passivation or degradation of toxic wastes, and (iv) the use, if possible, of remote sensing and direct analysis of samples without treatment. The 12 Principles of Green Chemistry were proposed as a list of guidelines to conduct in order to make more environmentally sustainable (greener) a chemical, process or product. They were summarized under the acronym PRODUCTIVELY and emphasized aspects like atom economy, toxicity of reagents, energetic efficiency, or method safety.

The "integrated environmentally friendly approach" was proposed by de la Guardia in 1999 based on the evaluation of the whole analytical process in the frame of the ecological paradigm in order to preserve accuracy, sensitivity and selectivity of the analytical method, but also reducing cost and sample handling, and improving operator safety and comfort, repeatability, and laboratory productivity. To achieve this, the use of strategies based on in-field sampling, on-line analysis, and on line decontamination/passivation of wastes was proposed.

Green Analytical Chemistry was introduced by Anastas in 1999 and deeply discussed in the books of Koel and Kaljurand, and de la Guardia and Armenta. Green Analytical Chemistry combines in a unique frame all the aforementioned strategies. The reduction of reagent and solvent consumptions must be mainly directed to the steps of the analytical process, such as sample extraction and preparation, and analyte separations. Automation and minimization of analytical methods allows the reduction of both, reagents and generated wastes. Additionally, special efforts must be focused in the development of direct methodologies for the in-field, non-invasive and remote analysis. Green Analytical Chemistry does not limit the progress of novel analysis methods, but compromises

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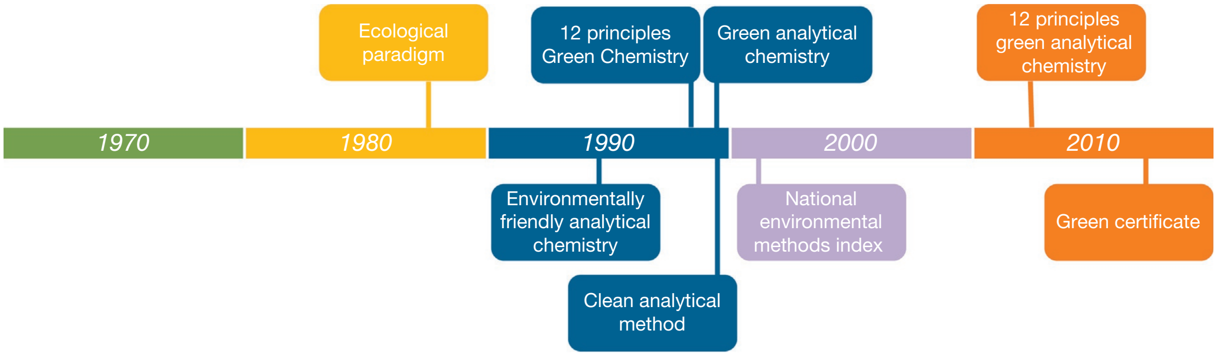


*Milestones*

| 1970 | 1980 | 1990 | 2000 | 2010 |
|---|---|---|---|---|
| Flow injection analysis<br>Microwave-assisted digestion<br>Solid-phases pectrophotometry<br>Cloud point extraction<br>Chemometrics | Supercritical fluid extraction<br>Microwave-assisted extraction<br>Head-space injection<br>Passive sampling | Solid-phase microextraction<br>Sequential injection analysis<br>Micrototal analytical system<br>Nano LC<br>Molecular imprinting SPE<br>Multicommutation flow systems<br>Single drop microextraction<br>Stir bar sorptive extraction | Lab-on-valve<br>Ultra high performance LC<br>Electrochemical sensors | Rise of Smart materials<br>Smartphone-based methods<br>Lab-on-skin |

**Fig. 1** Progress and milestones of Green Analytical Chemistry.

them with the preservation of the environment. The history of Green Chemistry and Green Analytical Chemistry concepts has run in parallel since their formulation. However, from the 12 Principles of Green Chemistry, only few are applicable to analytical chemistry approaches, such as: (i) prevention of wastes, (ii) use of safe and not toxic reagents and solvents, (iii) increase energy efficiency, and (iv) avoid derivatization steps. The objectives and needs of an analytical method slightly differ from those of general chemistry and, consequently, additional principles related to Green Analytical Chemistry were required. Thus, Galuzska et al.[2] enunciated the 12 Principles of Green Analytical Chemistry, under the acronym SIGNIFICANCE, introducing aspects as the use of chemometric data treatment to reduce number of samples, the use of integrated systems to improve efficiency, use of natural solvents, or the incorporation of miniaturized systems.

## Strategies for Greening the Analytical Methods

One of the reasons for the success of Green Analytical Chemistry is that its development does not involve any increase of the cost of analysis. On the contrary, green methods are, in general, faster than classical ones, require less reagents and solvents, reduce the sample handling, and avoid or, at least, reduce the waste generation and their toxicity. So, there is a high interest on greening the available analytical methods and to do it several alternatives and strategies have been proposed.

Fig. 2 depicts the way followed in the literature to replace traditional sample processing and off-line measurements, usually made in the past in batch mode, for efficient methods to do at-line, on-line and also non-invasive determinations, thus avoiding chemical and physical treatment of samples.

The dream of a Green Analytical Chemistry is to obtain, as much as possible, information about the sample without touching it and avoiding damage. For this reason, remote sensing, especially when it is made through tele-detection is the greenest alternative and, nowadays, it is frequently employed to evaluate environmental figures, as the quality of air, soil moisture and other parameters, biota analysis or specific application such as determining the presence of oil spills and other contaminations in the sea surface. However, it is clear that remote sensing cannot be a general strategy and, thus, alternative processes, based on the use of sensors and photo images for analytical purposes, are the point-of-care alternative to tele-detection. Because of that, there is an increasing interest on the use of simple sensors, smartphones and photo cameras to determine general and specific parameters of different types of samples. Once again this strategy permits safe, reagent free and fast analytical methodologies which permit a democratic approach maintaining available the benefits of analysis to all the people in the world.

The limited sensitivity and selectivity of image processing methodologies made necessary the use of analytical instruments to obtain signals from samples and, from a sustainable point of view, direct procedures involving electroanalytical or spectrometric measurements are required for some minor and trace component determinations. In many cases, this can be done by using portable instrumentation and, in some cases, without sample damage. Nowadays, portable instruments as Raman, near and middle infrared spectrometers, ion mobility spectrometers, and X-ray energy dispersion instruments are available for direct determination of

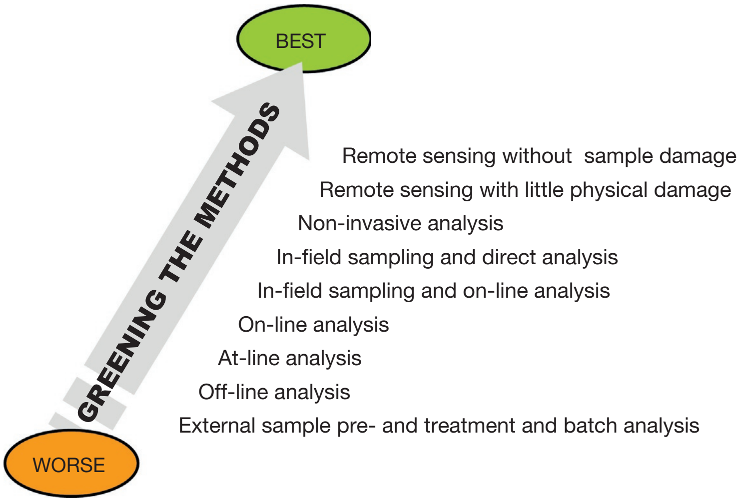


**Fig. 2** Hierarchical organization of sample analysis approach in order to move from multistep and high pollutant risk methods to reagent-free methodologies. Adapted and reproduced from de la Guardia, M.; Garrigues, S. (eds.). Challenges in Green Analytical Chemistry. RSC Publishing: Cambridge. (2011). ISBN: 9781849731324, with kind permission from the Royal Society of Chemistry.

analytes in gas, liquid or solid samples, together with the use of classical selective electrodes with a great value for in-field analysis of many water parameter and chemical components.

Wearable sensors, defined as systems enabling personalized mobile information processing, offer great promise for a wide range of medical diagnosis, environmental monitoring, and defense applications. In this sense, Liu et al.[3] introduced the term "lab-on-skin" to describe a set of soft, flexible, and stretchable electronic devices, which conformally contact with the epidermis to deliver a range of functionalities, resembling a clinical laboratory.

In many cases, the complexity of samples, the nature and concentration of the target analytes, together with the unavailability of portable systems, obliges us to follow the classical steps of the analytical procedures based on sampling, sample transport and storage, sample pretreatment, analyte extraction and/or pre-concentration, analyte separation and, finally, determination. In these cases there continue to have opportunities for method greening and, in this sense, miniaturization, automatization and the search for alternative innocuous or, at least, low toxic reagents can be employed. As it can be seen in Fig. 3 all the aforementioned steps are suitable to be greener and have contributed to the development of Green Analytical Chemistry.

Miniaturization of methods scales down the amount of sample, reagents, solvents and wastes employed and it is a good environmentally friendly alternative on both, teaching and application laboratories, for reducing the side effects of analytical methods. On the other hand, miniaturization strategies involve an implicit reduction of consumed energy contributing to the sustainability of the analytical method.

In the sample treatment step, miniaturization allows a drastic reduction of the consumption of solvents and sample handling to preconcentrate target analytes also avoiding matrix troubles. Classical liquid–liquid extraction can be reduced to a single drop extraction and the general use of solid phase extraction (SPE) has highly increased the selectivity of extraction procedures based on the use of new phases and materials and permits to on-line couple micro-SPE with chromatography determinations.[4] Classical solid phase microextraction (SPME) procedures, which can be used for the analysis of trace analysis in environmental, clinical, forensic, food and pharmaceutical sectors using the direct immersion or the headspace configuration has evolved to biocompatible SPME devices to be used directly in vivo for intravenous drug and metabolite monitoring.

The automatization of analytical procedures, from classical flow injection analysis (FIA) to lab-on-a-valve and multicommutation, reduces the contact of operators with samples and reagents, increasing method safety and, additionally, avoiding excessive consumption of reagents because only small portions of these were mixed, just before the measurement step, with standards and samples. It allows preserving the reagents and standard solutions to be employed on different analytical sessions.[5]

The introduction of robotized stations to perform sample treatments in a completely automated way, such as the automated SPE or SPME stations, pressurized solvent extraction systems, microwave ovens and so on, avoid the exposure of operators to reagents and solvents.

Energy consumption of analytical methods is not always a big environmental trouble due to the relatively low power of the main instruments. However, sample preparation could involve high energy consumption due to the common use of high temperature digestion procedures, as classical ones based on sample dry ashing and wet ashing. Thus, one of the ways for greener the methods is to move from hard techniques to do the total decomposition of samples to soft ones, which try to make a quantitative extraction of the target analytes without destroying the matrix nor to extract matrix components. So, in the last years the advancements on microwave-assisted and ultrasound-assisted methodologies to do both, sample digestion and analyte extraction, have contributed to drastically reduce the energy consumption of the whole analytical procedures. In this particular aspect, it must be highlighted that soft sample treatment procedures also contribute to minimize analyte losses or contaminations and reduce matrix effects on making

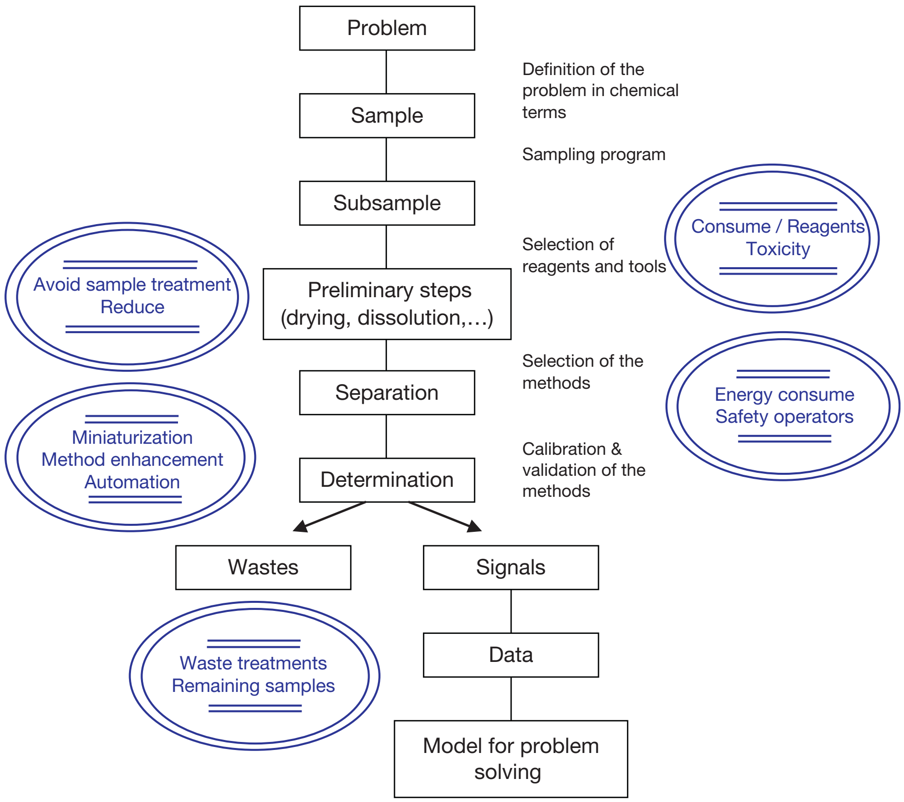


**Fig. 3** Steps of the analytical process to be considered in the frame of the Ecological Paradigm. Reproduced from de la Guardia, M.; Armenta, S. Comprehensive Analytical Chemistry, Vol. 57. Green Analytical Chemistry: Theory and Practice. Elsevier, Amsterdam. (2011). ISBN: 9780444537096, with kind permission of Elsevier.

final determinations. On the other hand, soft sample treatments pave the way to move from total analyte determinations to speciation analysis.

The search for alternative non-toxic reagents and solvents is one of the objectives of the Green Chemistry and Green Analytical Chemistry and to this end, extensive efforts have been made to look for agro-solvents or pressurized gases for analyte extraction[6] and the development of new reagents able to improve the selectivity of measurements. In this case, smart materials, both nanomaterials and bioinspired materials as molecular imprinted polymers or aptamers have been proposed to made direct extraction and preconcentration of analytes from complex samples with the assistance of restricted access materials (RAMs) or metal organic frameworks (MOFs), thus offering exciting possibilities to simplify methods involving sample treatment and also offering significant advantages for analyte separations and method sensitivity enhancement.

An additional way to greener the analytical methods is to incorporate a step concerning solvent or reagents recovery, waste passivation or waste decontamination to the whole procedure.[7] A correct management of wastes is a part of the social responsibility of analysis and that external waste treatment is an extra cost of methods which in many cases involves the accumulation of residues with an increase of environmental and safety risks. The aforementioned strategies could be integrated in the method protocol, thus, improving procedure greenness.

## Evaluation of Method Greenness

There are different procedures to evaluate the environmental impact or "greenness" of analytical methodologies. A procedure widely used in other areas is the well-known life cycle assessment (LCA). The general idea of LCA is that all environmental burdens, related to a product or service, have to be assessed, from the raw materials to waste removal. The main problem regarding the applicability of this tool is the necessity to know all the stages of the life-cycle of the product or service involved. LCA has been used to evaluate the green character of an organic solvent.

Another procedure developed to evaluate the green character of analytical methodologies is the National Environmental Methods Index (NEMI) database, developed by US government agencies in collaboration with private companies. This procedure evaluate the PBT (persistent, bioaccumulative and toxic) character of reagents and solvents, hazardous (listed on the TRI list), extreme pH conditions of the analysis, below 2 or upper than 12, and the amount of waste generated (more than 50 g), in a simple and visual circle diagram describing the aforementioned four fields (see Fig. 4). The sector of the diagram turns to green if the

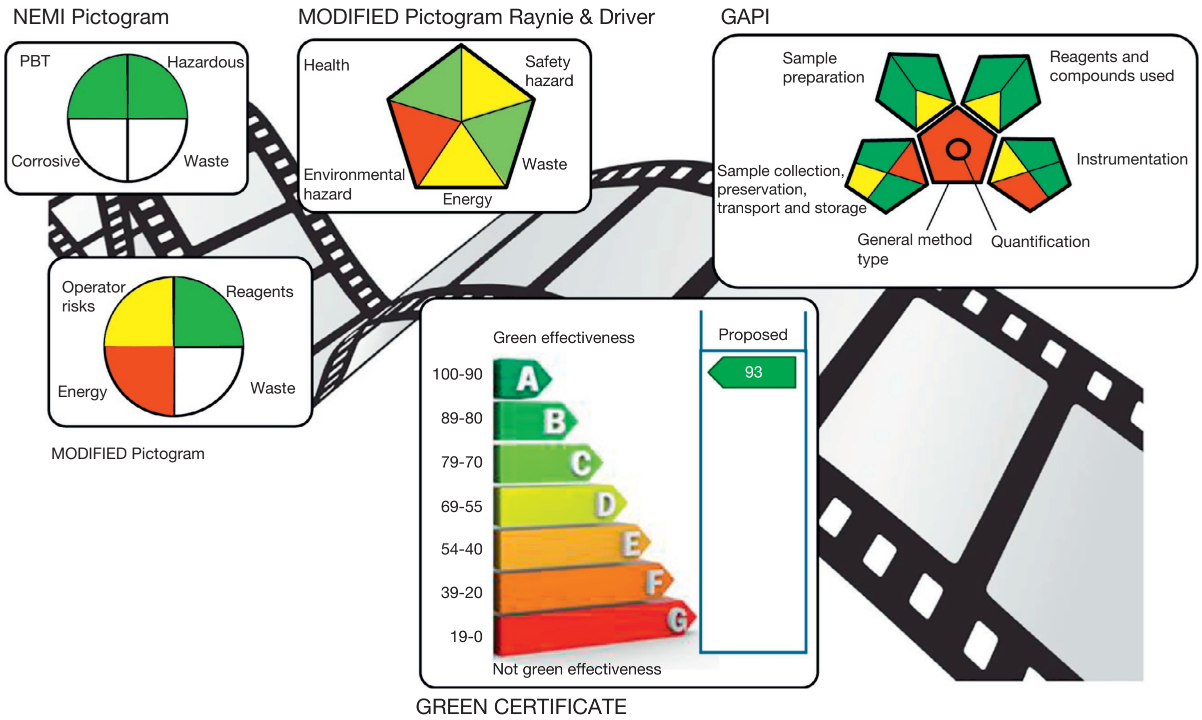


**Fig. 4** Evolution of greenness indicators through the time.

method is considered "green" or environmentally friendly, being the main drawback of the methodology the absence of energy consumption evaluation. This pictogram was modified to include five different categories and three levels of "greenness" (red, yellow and green): (i) health, (ii) environmental hazard, (iii) energy, (iv) waste, and (v) safety hazard. Another NEMI modified pictogram with three levels of "greenness" and four sections was proposed in 2011 including (i) operator risks, (ii) consumption of reagents, (iii) energy consumption, and (iv) amount of wastes.

Galuzska et al. developed a quantitative criterion named Eco-scale to evaluate the method greenness, based on the approach proposed by Van Aken et al. for evaluating the greenness of organic synthesis.[8] This criterion is based on the application of penalty points, starting from the ideal 100 mark green analysis, concerning amount of reagents, hazards related to reagents and solvents, energy consumption and wastes. A modification of the Eco-scale was proposed, named Green Certificate[9] to obtain the penalty points using mathematical equations and classify the methods using a color code associated to a letter; from A to G, being A the greenest one (see Fig. 4).

Recently, a new criterion named Green Analytical Procedure Index (GAPI) was proposed.[10] GAPI is based on the NEMI and the Analytical Eco-Scale and evaluates the green character of an entire analytical methodology, from sample collection to final determination. GAPI used a three-level category from green through yellow to red depicting low, medium to high, respectively to quantify the environmental impact involved in each step of analytical methodologies.

Other developed methodologies consider the environmental impact and nature of threat using multivariate statistical techniques. Using self-organizing maps, the comparison of the green character of different analytical methodologies has been also performed. To implement multivariate techniques, a multicriteria decision analysis (MCDA) tool was developed to rank the analytical procedures. In Analytical Chemistry only the Technique for Order of Preference by Similarity to Ideal Solution (TOPSIS) and Preference Ranking Organization Method for Enrichment Evaluations (PROMETHEE) methods have been applied for the classification of analytical methods. TOPSIS was applied to assess the set of analytical methodologies for pharmaceutical determination in wastewater samples using eight input criteria. PROMETHEE has been applied to assess 25 methodologies for pesticide determination in water using nine input criteria.

Strategies to evaluate the greenness character of a specific methodology such as liquid chromatography (LC) have been proposed. Hazard evaluation of mobile phases in LC has been done using the high-performance liquid chromatography-environmental assessment tool (HPLC-EAT) based on the safety, health and environmental factors and the weight of every used chemical. An alternative of this procedure is the analytical method volume intensity (AMVI) that evaluates the total solvent consumption per chromatographic peak of interest. This procedure takes into consideration the multianalyte capability of the method, but disregards solvent toxicity aspects.

Based on the Chemical Hazard Evaluation for Management Strategies (CHEMS-1) procedure to score and ranking chemicals used in the industry, solvents commonly used in an analytical laboratory were also ranked according to their green nature. CHEMS-1 criterion is based on the toxicity of chemicals to humans and environment and chemical exposure potential.

The main drawbacks of proposed procedures refer to: (i) simple pioneering pictograms provide only qualitative information and (ii) more complex eco-scale, green certificate and most of the multivariate procedures provide just a number without any information about the nature of threats.

In summary, nowadays, the level of knowledge of the Green Analytical Chemistry concept among the analysts is not comparable to the reported methodologies to "quantify" or "evaluate" the environmental impact or "greenness" of analytical procedures. In order to avoid that Green Analytical Chemistry remains as a philosophical concept, it should be applied to the analytical laboratories. Additional efforts should then be carried out to obtain an easily applicable and universally recognized "greenness" evaluation approach suitable for method selection.

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