Review Article

Green Analytical Chemistry and its Metrices – An Initiative for a Greener and Safer Tomorrow

Kumbhar Riddhi*, Desai Shuchi
Department of Quality Assurance, Rofel Shri G.M. Bilakhia College of Pharmacy, Vapi, Gujarat, India.
*Corresponding author's E-mail: riddhikumbhar95@gmail.com

ABSTRACT

For analytical methodologies, development and validation include optimization of some critical   parameters like accuracy, sensitivity, reproducibility, simplicity, cost effectiveness, flexibility and speed but other aspects like operator's safety and environmental impact of analytical methods are not commonly considered. Because of this Green Analytical Chemistry started as a search for practical alternative to prevent excess waste generation, use of safer solvent and auxiliaries, energy saving and reduction of derivatization.

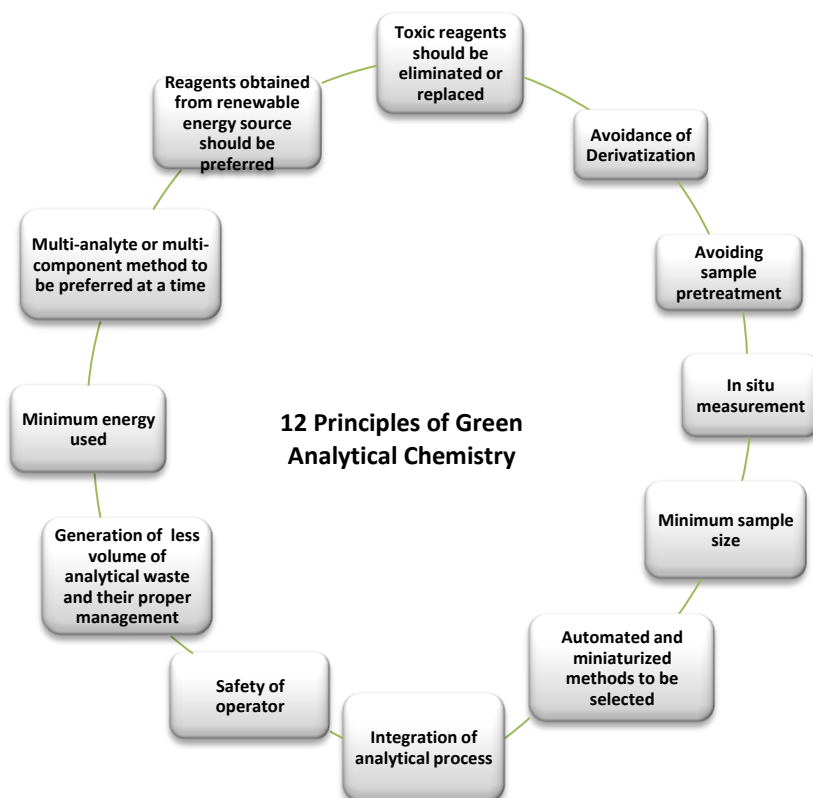**Keywords:** Analytical Eco-scale, Chemometrics, Atom economy, Environmental factor

INTRODUCTION

Green Chemistry is the use of chemistry methodologies that reduce or eliminate the use and generation of feedstocks, products, by-products, solvents etc., that are hazardous to human health and environment. [1,2] In 1999 the term "Green Analytical Chemistry" was proposed and in the same year, the father of green chemistry, Anastas, drew the attention to the need to develop green analytical methodologies. A simple question can be asked, "Why bother about the environmental impact of analytical laboratories?". In the common sense there is an opinion that the impact of analytical chemistry is small compared to pharmaceutical or petrochemical industries. The main reason why this problem is important and urgent are listed below:

One typical liquid chromatograph generates more than 1L of organic waste daily; it is estimated that 130000 are in operation, which gives considerable amount of 34 million liters annually.

The 12 principles of Green Chemistry proposed by Anastas and Warner are [3]:

12 Principles of Green Analytical Chemistry

- Toxic reagents should be eliminated or replaced
- Avoidance of Derivatization
- Avoiding sample pretreatment
- In situ measurement
- Minimum sample size
- Automated and miniaturized methods to be selected
- Integration of analytical process
- Safety of operator
- Generation of less volume of analytical waste and their proper management
- Minimum energy used
- Multi-analyte or multi-component method to be preferred at a time
- Reagents obtained from renewable energy source should be preferred

Strategies of Green Analytical Chemistry

Table 1: Some green analytical methods proposed in the literature [3]

Green Strategy	Flow method	Analyte	Reagent	Green Aspects
Replacement of toxic reagents	FIA-UV Multi-Syringe FIA-UV	Fe Nitro- substituted phenols	Guava leaf extract	[4] Use of Guava extract as colorimetric reagent [5] Flow-through disk-based system–organic solvent extraction
	FIA-UV	Nitrate	HCLO$_4$	[6,7] Use of SPE to avoid interferences
	SIA_UV	Phosphate		
	HPLC	Colorants	Triton X-100	[8] Use Triton X-100 as mobile phase and to modify the C-18 column
	HPLC	uv filters	EtOH-water-acetic acid-hydroxypropyl-β-cyclodextrin	[9] Use cyclodextrin as mobile phase
	HPLC	Steroids, amino acids and protein	Aqueous mobile phase	Use of thermos-responsive copolymers as mobile phase
	Fluorimetry	Hg(II)	Clorophylla	Use of chlorophyll as reagent
	Anodic and cathodic	Cd, Pb, Co, Ni	Bismuth film electrode	Replacement of mercury-based electrode
	Stripping Voltammetry	3-nitrofluoranthene	Silver solid amalgam electrode	Replacement of mercury-based electrode
	Adsorptive Stripping voltammetry			
	VP-FTIR	Ethanol	-	VP-FTIR avoids the use of chlorinated solvents
Minimization of reagents and wastes	Multicolumn-uv	Cyclamate	NaNO$_2$/KI	Solenoid Micropumps
	Multicolumn-uv	Carbaryl	PAP	Solenoid valves
	Multicolumn-HG-AFS	Hg		Solenoid valves
	Multicolumn- FTIR	Benzene	CHCl$_3$	Solenoid valves
	FIA-FTIR	Malathion	CHCl$_3$	Closed FIA-manifold
	FIA-uv	Chloride	Hg(SCN)$_2$/Fe(II)	Hg(SCN)$_2$ immobilized in epoxy resin
	FIA-chemiluminescence	Chlorpyrifos	Luminol or periodate	Controlled reagents released from a solid phase
	Double-line SIA-uv	Cu, Fe, Mn, Zn	1,10-phenanthroline/ formaldoxime/ Zincon	
	FIA-SPS	Fe(II)	Acid and reducing agent	SPS-Reduce reagent consumption
	µFA-vis	Cu(II)	2-carboxy-2-hydroxy-5-	Micro-fluidic manifold

			sulfoformazyl benzene	
	µ uv assay	Malondialdehyde	Thiobarbiyuric acid and ethyl acetate	Micro extraction uv
	Capillary HPLC	Flavonoids	Acetonitrile	Reduction of the organic solvent volume to less than 1ml per run
	UPLC	Lovastatin	Acetonitrile	Reduction of the organic solvent volume to less than 1.5ml per run
	LC-MS	Drugs	Acetonitrile	Multicomponent (7) determination in only 8 min and 4ml per run
	LC-MS	Pesticide	Methanol	Multicomponent (10) determination in only 10 min and 3ml per run
	µ CE-MS	Drugs	Acetonitrile/ Methanol	Multicomponent (4) determination in only 1
	µ CE	Phenolic compound	Acetonitrile/ Methanol	Micromachine capillary electrophoresis chip with a thin-film amperometric detector
	NIR	Pesticide	Acetonitrile	
Recovery of reagents	Cyclic FIA-uv/vis	Lead	Arsenazo III	Cation exchange column to regenerate the reagent and retain toxic ions
	FIA-FTIR	Propyphenazone and caffeine		Distillation unit on-line recycling of the $CHCl_3$
On-line	Decontamination of wastes	FIA-uv/vis	Formetanate	PAP/KIO_4
	Detoxification TiO_2 and uv radiation			
Multi-component HG-AFS	Hg		Deactivation heavy metal matrix of $Fe(OH)_3$	
Reagent free methodologies	FT-Raman	Iprodione		Direct measurement in glass vials
	FT-Raman	Sweeteners		Direct measurement in glass vials
	NIR	Pesticides		Direct measurement in glass vials
	NIR	Peroxide value		Direct measurement in oil
	PAS	Mancozeb		Direct measurement of solid pesticide
	Sample matrix assisted PI-CVC-AFS	Hg	uv radiation	Sample matrix reduce Hg ions to Hg (0)

FIA: Flow Injection Analysis; UV: Ultraviolet; SPE: Sequential Injection Analysis; µFA: Micro Flow Analysis; HG-AFS: Hydride Generation Atomic Fluorescence Spectrometry; PAP: p-aminophenol; MB: Methylene Blue; FTIR: Fourier Transform Infrared; HIFU: High Intensity Focused Ultrasound; SPS: Solid phase spectrometry; NIR: Near Infrared; PAS: Photoacoustic spectroscopy; PI-CVC-AFS: Photo Induced Cold Vapor generation-Atomic Fluorescence Spectroscopy

Table 2: Some green alternatives, obtained from papers in which one of the objectives was to make analytical methods greener[3]

Sr.No	Extraction method	Analyte	Matrix	Solvent	Amount solvent per sample
1	MAE	Triazines	Soil	Water	30ml
		Phenols	Soil	POLE: Water (5:95)	8ml
2	SFE	Pesticide Residues	Plants	CO_2/n-hexane	1ml
		Pesticide Residues	Strawberries	CO_2/acetone	10ml
3	ASE	Estrogens	Soil	Acetone	
		Carotenoids	Food	Methanol/ethyl acetate/light petroleum	

4	SPME	Phenols Volatile organic compounds	Water Snow	Acetonitrile: Water (70:30) Thermal Desorption	70µl
5	SDME	Aniline Derivatives	Water	Benzyl alcohol: Ethyl acetate (80:20)	150µl
6	LLME	Phenoxy Herbicides	Bovine milk	DS: Sample+ HCl (0.5M) OS: 1-Octanol AS: 0.1M NaOH	AS: 7 µl
		Aniline Derivatives	Water	DS: Sample + NaOH (pH=13) OS: Benzyl alcohol: Ethyl acetate (80:20) AS: HCl (pH=2)	AS: 3 µl
7	MASE	Pesticide Residues	Juice	DS: Sample+ NaCl(Saturated) AS: Cyclo-hexane	AS: 800 µl
8	Micelle Mediated Extraction	Trichlorfon	Cabbage	SDS: 0.1M	200ml
9	Modification Of Surfaces	Copper	Water	HCl 0.1N	10ml
10	SBSE	Pesticide Residue	Juice	Thermal Decomposition	-

MAE-Microwave assisted extraction; SFE-Supercritical Fluid Extraction; SPME-Solid Phase Micro Extraction; SBSE-Stir-bar Sorptive Extraction; SDME-Single Drop Micro Extraction; LLLME-Liquid Liquid Liquid Microextraction; MASE-Membrane Assisted Solvent Extraction; AS: Acceptor Solvent; DS: Donor solvent; PHB-Poly-3-hydroxy-butyrate; POLE: Polyoxyethylene-10-lauryl ether; OS: Organic Solvent;

Predictive tool for chemical process on larger scale

Atom economy

This parameter is a ratio of the molecular weight of the target molecule to the sum total of the molecular weights of all the substances produced in the stoichiometric equation for the reaction involved. The main use of this parameter is to adopt reaction sequences in a way that transformations with low atom economy are limited to minimum. Cyclo additives are examples of 100% atom economy.

Environmental Factor (E-factor)

This factor is the ratio of the weight of generated waste to the total weight of the end product. It is useful tool for rapid evaluation of processes based on generated waste.

Environmental Quotient (EQ)

The E-factor is multiplied by environmentally hazardous quotient Q. For example, a Q-value of 1 can be attributed to NaCl, while heavy metals can be assigned a value between 100-1000 on the basis of their toxicity.

Effective mass yield

It is defined as the percentage of the mass of desired product relative to the mass of all non-benign material used in synthesis.

Mass intensity

It is defined as the ratio of the total mass used in process and the mass of the end product. It takes into account the yield, stoichiometry, solvent, and the reagents used in synthesis.

Process Profile

It takes into account all important factors involved in large scale production. These are:

(a)Raw material cost (b) Yield (c)Throughput Time (d) Throughput Volume (e) Number of steps in synthetic sequence (f) Special equipment requirements g) Reproducibility h) Tolerance to abuse (i) Linearity of sequence (j) Environmental Abuse potential (k) Potential occupational health and safety hazards

Metrices for Green Analytical Chemistry

National Environmental Method Index (NEMI)[1]

It results in a very simple to read pictogram stating if hazardous or corrosive reagents are used or procedure generates significant amount of waste.
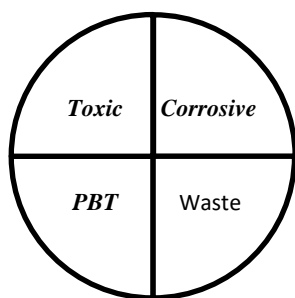
PBT – A chemical is listed as persistent, bio accumulative and Toxic. A toxic chemical is listed on the TRI or RCRA's D, F, P or U lists.
A method is "less green" if: Corrosive: pH is < 2 or >12 or if >1% concentrated mineral acids or bases are used. Waste: > 50 gm total waste or the ratio of work up materials to solid sample >1. Waste: > 50 gm total waste or the ratio of work up materials to Liquid sample >0.2

Disadvantage of this method is that the result of the analysis is qualitative only, it does not carry out any information about the quantity of hazards.

Analytical Eco-Scale: [10]

- The tool uses a scale from 0 to 100 with 0 representing a totally failed reaction (0% yield) and 100 representing the ideal reaction which is defined as follows: Compound A (substrate) undergoes a reaction with inexpensive compounds B to give the desired compound C in 100% yield at room temperature with a minimal risk for the operator and a minimal risk to the environment.

- 6 general parameters which influence the quality of reaction conditions are analyzed (table-3). Within each of these parameters, individual penalty points of various relative weights are assigned that takes into account all possible situations when setting up an organic chemistry experiment. The penalty points are cumulative for all components of the preparation. In order to simplify the EcoScale design, the usual differentiation between solvents (usually present in >10 equivalent) reagents, auxiliary or co-reagents and catalysts (usually present in <0.1 equivalent) is not made.

Sr. No	Parameter	Penalty points
**Table-3 Penalty points to calculate EcoScale[11]**	
1	Yield	$(100-\%yield)/2$
2	Price of reaction component (to obtain 10 mmol of end product)	
	Inexpensive (<$10)	0
	Expensive (>$10 and <$50)	3
	Very expensive (>$50)	5
3	Safety$_a$	
	N (dangerous for environment)	5
	T (toxic)	5
	F (highly flammable)	5
	E (explosive)	10
	F+ (extremely flammable)	10
	T+ (extremely toxic)	10
4	Technical setup	
	Common setup	0
	Instruments for controlled addition of chemicals $_b$	1
	Unconventional activation techniques $_c$	2
	Pressure equipment >1 atm $_d$	3
	Any additional special glassware	1
	(Inert) gas atmosphere	1
	Glove box	3
5	Temperature/Time	
	Room temperature <1hour	0
	Room temperature <24hour	1
	Heating <1hour	2

		Heating >1hour	3
		Cooling to 0℃	4
		Cooling < 0℃	5
6		Workup and purification	
		None	0
		Cooling to room temperature	0
		Adding solvent	0
		Simple filtration	0
		Removal of solvent with bp <150℃	0
		Crystallization and filtration	1
		Removal of solvent with bp >150℃	2
		Solid phase extraction	2
		Distillation	3
		Sublimation	3
		Liquid-Liquid extraction$_e$	3
		Classical Chromatography	10

$_a$Based on the hazard warning symbols. $_b$Dropping funnel, Syringe pump, gas pressure regulator etc. $_c$Microwave irradiation, ultrasound or photochemical activation etc. If applicable the process includes drying with desiccant and filtration of desiccant

Calculation of Eco-scale

An ideal reaction has the EcoScale value of 100. The EcoScale score for a particular preparation of product in a high purity state (>98%) is calculated by lowering the maximum value of 100 by any applicable penalty points.

Eco-Scale = 100 – Sum of individual penalty

Disadvantage of this method:

a) The score does not carry any information about the structure of the hazard.

b) The assessment procedure considers hazard in semi-quantitative way.

HPLC-EAT (High Performance Liquid Chromatography Environmental Assessment Tool) [12]

It sums the safety, health and environmental impact of all solvents used in chromatography method and gives a final score, which reflects the overall greenness of the method based on type and amount of solvent used. The lower the score, the greener is the method. The score is calculated according to the following equation:

HPLC-AT= $S_1m_1+H_1m_1+E_1m_1+S_2m_2+H_2m_2+E_2m_2+$……. $+S_nm_n+H_nm_n+E_nm_n$

Where S,H,E are safety, health and environment factors respectively (calculated according to Koller et al*) for n number of solvents, and m is the mass of the solvent(s)

HPLC-EAT can calculate the volumes of different component of mobile phase even if it is mixture of three organic solvents in both isocratic and gradient programs.

Chemometrics [13]

Chemo metric is the science of extracting information for chemical system by data driven method. It is applied to solve both descriptive and predictive problems in experimental natural sciences especially in chemistry. In descriptive applications, properties of chemical systems are modeled with the intend of learning the underlying relationships and structure of the system (i.e., model understanding and identification). In predictive application, properties of chemical system are modeled with the intend of predicting new properties or behavior or interest.

Techniques in chemometrics

Multivariate calibration

The objective of multivariate calibration is to develop models which can be used to predict properties of interest based on measured properties of the chemical system such as pressure, flow, temperature, infrared, Raman, NMR, spectra and mass spectra.

Classification of Multivariate calibration techniques:

i. Classical method: The models are solved such that they are optional in describing the measured analytical responses (eg: spectra) and can therefore be considered optimal descriptors.
ii. Inverse: models are solved to be optimal in predicting the properties of interest (eg: concentration).

Advantage of this method

- Fast, cheap, or non-destructive analytical measurements (such as optical spectroscopy) can be

used to estimate sample properties which would otherwise require time-consuming, expensive or destructive testing (such as LC-MS)

- Multivariate calibration allows for accurate quantitative analysis in the presence of heavy interferences by other analyte

Multivariate curve resolution

It seeks to deconstruct data sets with limited or absent reference information and system knowledge. For example, a data set comprising fluorescence spectra from a series of samples each containing multiple fluorophores, multivariate curve resolution methods can be used to extract the fluorescence spectra of the individual fluorophores, along with their relative concentration in each of the samples, essentially unmixing the total fluorescence spectrum into the contributions from the individual components.

Multicriteria Decision Analysis

It allows the ranking of analytical procedures, according to their greenness.

Following are the methods of MCDA:[14]

Multi Attribute Utility Theory (MAUT)

It is a performance aggregation-based approach which requires the identification of utility functions and weights for each attribute that can then be assembled in a unique synthesizing criterion with thw additive and multiplicative aggregations being the most widely being applied.

Analytical Hierarchy Process (AHP)

It was introduced by Saaty with the aim of evaluating tangible and intangible criteria in relative terms by means of an absolute scale. It requires firstly the identification of a set of alternatives and a hierarchy of evaluation criteria (value tree) followed by pairwise comparison to evaluate alternative performance on criteria (scoring) and criteria among themselves (weighting). All the weights/alternatives are compared in respect to the criteria by asking the DM his preference on a scale from 1 to 9 with 1 indicating equal preferences and 9 absolute preference, Intermediate values are used to express increasing preference / performance for one weight/alternative.

Elimination and Choice Expressing the Reality (ELECTRE)

This method was developed by Bernard Roy, in order to account for heterogenous criteria whose aggregation in a common scale is difficult to prevent compensation behavior and to account for differences in term of preferences, leading in this way to introduction of thresholds.

Preference Ranking Organization Method for Enrichment of Evaluation (PROMETHEE)

This method was developed by J.P.Brans and is based on a set of prerequisites (i) The extend of difference between the performance of two alternatives must be accounted for; (ii) The scales of the criteria are irrelevant as comparisons as performed on a pairwise base; (iii) Three cases are possible; alternative a is preferred to alternative b; alternative a and alternative b are indifferent; alternative a and alternative b are comparable (iv) The method should be easily understandable by the decision maker. (v) Weights must be assigned in a flexible manner.

Dominance based Rough Set Approach

It was introduced by Greco and Slowinski. It can handle classification, choice, and ranking problems.

It is based on information table whose rows are defined as alternatives, while the columns are divided into condition attributes; namely the criteria that are needed to assess the alternatives and decision attribute, which represent an overall evaluation of the alternative.

Lifecycle analysis (LCA) [15]

It is systematic method for analyzing the environmental aspects of a product, process or service through a "cradle to grave" approach. In this approach, a product is examined from when and how their raw materials are acquired, to its production, use, and finally destruction. Thus, it allows a comprehensive understanding of the overall environmental effect of the process, allowing the analyst to recognize problems and solutions that a single – issue approach does not readily identify.

The following steps should be considered in order to develop LCA:(a) Goal, definition and scope (b)

Lifecycle inventory analysis (LCI) (c) Lifecycle impact assessment (d) Lifecycle interpretation.

The focus on a product system in Life Cycle Assessment has some important implications for the nature of the impacts, which can be modelled in LCA:

- The product system is extended in time and space, and the emission inventory is often aggregated in a form which restricts knowledge about the geographical location of the individual emission.
- The LCI (Life Cycle Impact) results are also typically unaccomplished by information about the temporal course of the emission or the resulting concentration in the receiving environment.
- The functional unit of the LCA refers to the assessment of an often rather small unit. The emissions to air, water or soil in the inventory are determined as the functional unit's proportional share of the full emission from each process. The LCIA (Life Cycle Impact Analysis) thus has to operate on mass loads representing a share of the full emission output from the process.

CONCLUSION

The use of Green Analytical Chemistry methods has proved to be a smart strategy to provide environmental and economic benefits so we would like to propose the term "Sustainable Analytical Procedures", for these methods.

Green Analytical Chemistry would be very beneficial for both Humans and also for the environment. Following are the strategies that could be applied to make analytical methods greener.

- Use of chemometrics and statistics for the reduction of number of samples.
- Decrease in the use of hazardous reagents or their replacement with some plant extracts or other natural reagents.
- Miniaturization of methods to decrease the risk to the operator and environmental hazard.

REFERENCES

1. Lawrence H. Keith, Liz U. Gron and Jennifer L. Young's, Green Analytical Methodologies, Chem, Rev, 107, 2007, 2695–2708

2. Anastas P.T, Green Chemistry and the Role of Analytical Methodology Development, Crit. Rev. Anal. Chem. 29, 1999, 167.

3. Armenta S, Garrigues S, Guardia M. de la, "Green Analytical Chemistry", Trends in Analytical Chemistry, Vol. 27, 2008, 6.

4. Settheeworrarit T, Hartwell S.K, Lapanatnoppakhun S, Jakmunee J, Christian G.D, Grudpan K, Exploitting guava leaf extract as an alternative natural reagent for flow injection determination of iron, Talanta, 68, 2005 262.

5. Manera M, Miro M, Estela J.M, Cerda V, Green alternatives for sample preparation and determination of phenolic pollutants in water, Anal. Chim. Acta 582, 2007, 41.

6. Melchert W.R, Rocha F.R.P, Determination of Nitrite and Nitrate in Water Samples by an Automated Hydrodynamic Sequential Injection Method, Talanta, 65, 2005, 461.

7. Simonet B.M, Grases F, March J.G, J. Fresenius, Determination of phosphate in urine by sequential injection analysis, Anal. Chem, 369, 2001, 96.

8. Vidotti E.C, Costa W.F, Oliveira C.C, Development of green chromatographic method for determination of colorants in food samples, Talanta, 68 [48], 2006, 516.

9. Salvador A, Chisvert A, Determination of uv filters worldwide authorized in sunscreens by high performance liquid chromatography. Use of cyclodextrins as mobile phase, Chromatogr J, A 921, 2001, 207.

10. Agnieszka Gałuszka, Piotr Konieczka, Zdzisław M. Migaszewski, Jacek Namies´nik, Analytical Eco-Scale for Assessing the Greenness of Analytical Procedures, Trends in Analytical Chemistry, Vol. 37, 2012.

11. Aken Koen Van, Strekowski Lucjan, Patiny Luc, Eco-scale, a semi-quantitative tool to select an organic preparation based on economical and ecological parameters, Beilstein Journal of Organic Chemistry, 2(3), 2006.

12. Gaber Yasser, T¨ornvall Ulrika, Kumar M. A, Amine Magdy Ali and Kaula Rajni Hatti, HPLC-EAT (Environmental Assessment Tool): A tool for profiling safety, health and environmental impacts of liquid chromatography methods, Green Chem, 2011, 13, 2021.

13. Kumar Naveen, Rawal Ravindra K, Talanta, volume 123, 2014, 186-199

14. Cinelli Marco, Coles Stuart R, Kirwan Kerry, Analysis of the potentials of multi criteria decision making analysis methods to conduct sustainability assessment, Ecological Indicators, 46, 2014, 138-148.

15. Finnveden Goran, Hauschild Michael Z, Ekvall Tomas, Guinee Jeroen, Heijungs Reinout, Hellweg Stefanie, Koehler Annette, Pennington David, Suh Sangwon, Journal of Environmental Management 91, 2009, 1-21

Source of Support: Nil, **Conflict of Interest:** None.