Analytical chemistry at the interface between metrology and problem solving

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The constant need to harmonize theory and practice in analytical chemistry requires the continued evolution of metrology in chemistry. In this contribution, we highlight conflicts that arise from the diverging foci of conventional metrology and analytical problem solving and put them into context with the role of analytical chemistry as a scientific discipline that is embedded in society and is producing (bio)chemical information. We suggest strategies that allow harmonization of the intrinsic and the extrinsic aspects of analytical chemistry that are seen in metrology and analytical problem solving, respectively. Facing the constraints of analytical measurements, which may result from limitation in time, financial or instrumental resources among others, we propose to define quality compromises in each situation where analytical information is required. Based on the adapted quality compromises, there is a need to adopt intrinsic and extrinsic aspects of the analytical process under investigation. This undertaking aims to assure high integral quality of analytical results in a given context.

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1. Introduction

Analytical chemistry deals with the development and application of instrumentation and methodology capable of providing information on the chemical composition of matter in space and time [1]. This information is increasingly being asked for in our modern society for a variety of different purposes, such as rapid decision-making in intensive-care units and quality assurance of high-value products to mention just two quite different examples. Analytical chemistry may thus be perceived as a response to an existing need for information. As a consequence, its importance, role and tasks must be defined in the context where the need for information arises.

The result of chemical analysis is frequently expressed in terms of concentration, which is a metrologically sound unit, as it is based on the SI units mole and meter. Apart from concentration, other ways of reporting analytical results are common practice, too (e.g., using global indices and binary responses). In a favourable case, the results are also accompanied by a stated uncertainty at a given confidence level. However, these numbers referring to concentrations, indices, or arbitrary parameters are truly useful only if they can be readily converted into answers qualified to solve the problem that initially motivated the analysis. When recognising this claim, two aspects of chemical information become obvious. First, there is acknowledgement that knowledge of the concentration of the analyte under investigation or the magnitude of a given parameter/index in a particular sample at a given point in time is indeed appropriate for decision-making and thus will solve a given problem. Second, the validity of the analysis procedure adopted must be assured to achieve confidence and comparability, and thus validity, of the result obtained.

The latter issue, frequently considered as the basic facet or intrinsic aspect of analytical sciences, has been dealt with systematically in recent decades mostly within metrological bodies. The basic initial idea was to develop analytical measurement concepts and techniques that would allow establishment of an unbroken chain of comparison with, as little as possible, known uncertainties to stated references. In the ideal case the ultimate reference is the mole, the SI unit of chemical measurement.

This strategy seems to be practicable in a thought experiment when the required information is a concentration of a well-

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defined chemical identity. However, this is impractical or even impossible in many cases, especially when dealing with so-called empirical or method-defined parameters, where the value obtained for the measurand depends on the method in use. Furthermore, because of limitations in cost and time, deviations from high metrological standards are frequently required to solve a given problem in time or with the available budget.

The increasing use of direct spectroscopic techniques of analysis to determine concentrations of defined analytes but also to infer physical [2], (bio)chemical as well as (bio)medical [3,4] properties of a given sample is a good example to highlight the fact that, in chemical measurements, metrological concepts beyond concentrations, calibration curves and detection limits are urgently needed. For example, analysis of dried blood samples by mid-infrared spectroscopy allows quantitative determination of glucose [5–7], but it also allows detection of disease, as was shown in the detection of scrapie infection in hamsters [8] or ante-mortem detection of BSE in cattle [9]. Whereas the determination of glucose can readily be supported with existing concepts of metrology in chemistry, the situation is less clear when it comes to disease detection. In the latter case, the information on disease is contained in the overall chemical composition of the sample, which is reflected in its infrared spectrum. Using modern data analysis techniques, known as chemometrics, it is possible to correlate the spectra directly with disease, thereby bypassing classical, quantitative analysis. In such a situation, it may not be necessary to define an ''analyte'', the presence of which can be judged in terms of concentration in order to provide an answer whether or not the disease is detected. It would be an obvious mistake to invent an analyte only to satisfy a metrological concept. It is much more appropriate to expand current metrology in chemistry to cover such peculiarities of (bio)chemical measurements that also include binary responses, as shown in the example of disease detection given above.

Currently, there is still a tendency in analytical chemistry to deal separately with the basic facets (metrologically oriented or intrinsic) as well as the applied facets (problem solving oriented or extrinsic). The importance of the fitness for purpose of analytical measurements is frequently addressed and has even been topic of a dedicated Eurachem guide [10]. However, in our opinion, these important contributions lack applied facets relating to the problem-solving aspect of analytical measurements. Whereas for conventional metrological issues, the elements required for analysis are defined along with the related performance characteristics, these characteristics are missing for important practical issues, such as time and cost constraints. Metrology in chemistry continues to develop and, in the recent CITAC/Eurachem guide to quality in analytical measurements [11], these constraints are explicitly stated as part of the analytical requirements, which need to be agreed upon with the customers who request analytical chemical information.

Nevertheless, the separate treatment of basic and applied facets still prevails and gives rise to conflicts of different kinds during the production and the exploitation of the chemical information that is gathered. However, a truly unifying approach could lead to important synergies and thus strengthen the significance of analytical chemistry as the scientific discipline that delivers assured (bio)chemical information.

There are many examples of conflicts. Uncertainty associated with an analytical result is well understood and applied among metrology specialists, but many clients establish a direct relationship between uncertainty and doubt about the reliability of the result. This misunderstanding occurs frequently (e.g., in courts of justice when analytical chemical information is required on topics such as ethanol in blood of people involved in traffic accidents, or the presence or the concentration of veterinary drugs in meat or drugs in sports). The results provided by portable glucosimeters have an associated uncertainty of $\pm$10–20% and the artificial control solutions has a ''certified'' value in the range 90–140 mg/dL of glucose. Both aspects are rather unusual from a strict metrological point of view, but glucosimeters are very efficient at identifying the health problem. Furthermore, the most frequent types of (bio)chemical information required in rapid decision-making (such as total indices and method-defined parameters, as obtained by empirical methods along with their conversion to a yes/no result, or even methods that directly deliver a binary response) are hardly considered in metrological guidelines. In the ISO 17025:1999 standard, they are not considered at all, and that causes serious practical problems during accreditation processes.

Furthermore, the existence of such ''black holes'' in chemical metrology makes it difficult to add an uncertainty interval to a yes/no binary response of a qualitative test, or to select a proper measurement standard for calibration of a method for the determination of total hydrocarbons in waters when faced with the fact that there are more than 12 million potential analytes.

However, there are also many examples where state-of-the-art chemical metrology is key in assuring the worth and the quality of a given product. This is the case in added-value materials, where the price strongly depends on a few tenths of a few hundredths of a percent of analytes. As such specifications are often given in concentration units, high-quality metrological support can be achieved by mimicking physical metrology as far as possible. There is an obvious need for solid metrological support in modern research, especially in bioanalysis, in particular proteomics, where vast quantities of data are produced every day without almost no quality control.

2. Metrology in chemistry

Metrology is the science of measurements in which analytical chemistry holds a special position because of the complexity of chemical and biochemical measurements [12–15]. The chemical connotations of metrology are still under development, which explains why there are divergent approaches to this topic [16,17]. Analytical chemists engaged in R&D frequently consider metrology an unscientific, bothersome aspect that is not worth considering systematically. As a consequence, they contribute little to the development of solid concepts for metrology in chemistry. Among chemists belonging to metrological bodies, there can be discerned a strong desire to handle metrology in chemistry with the same approach that was successfully developed for physical measurements. They advocate that written standards and guides should be common to all types of measurements. Finally, chemists at the bench level frequently consider metrology as too theoretical and far removed from their daily work. However, usually they are made aware of the need to apply metrology when they establish quality assurance systems in their laboratories in order to achieve accreditation.

Metrology in chemistry is an essential foundation of analytical chemistry. Everyone directly or indirectly concerned with (bio)chemical information should consider it fundamental. Metrology in chemistry needs specific developments tailored to the peculiarities of (bio)chemical measurements because direct extrapolations from general metrology, which is still heavily biased towards physical measurements, can lead to incomplete or even wrong approaches. These developments are necessary to approach metrology in chemistry in a truly meaningful way [12,13].

Differences between physical and (bio)chemical measurements are evident for various reasons. Examples are the different impact of samples and sampling, the complexity of measurement processes, the availability of proper measurement standards, the two types of calibration procedures, the uncertainty calculation [14], the last reference in the traceability chain, and the existence of well-supported laboratory networks. These peculiarities cause conceptual and practical difficulties that are not fully comprehended by classical metrologists and are therefore subject to argument [18,19].

It is interesting to note that the metrological side of analytical chemistry was not systematically considered and exploited until 15–20 years ago. The metrological approach has already added great value to analytical sciences and has shaped the way that we deal with chemical information today. This evolution from the classical approach to one that is metrology guided is reflected in the replacement of accuracy with the conceptually richer approach of traceability [20] along with the replacement of precision by uncertainty [21]. That further expands the classical concept, as precision and uncertainty now have the support of accuracy and traceability, respectively.

Further important developments are:

- the move from the use of official, standard methods as written references to the use of more reliable concepts, such as primary, traceable and validated methods;
- the shift from a general interest in all steps of the analytical processes to more emphasis on measurements;
- the change from a general interest in analytical quality to the systematic implementation of quality assurance systems involving internal and external quality control; and, finally,
- the switch from little consideration of the work done by other laboratories to frequent participation in interlaboratory exercises (e.g., proficiency testing schemes) with the aims of achieving comparability and harmonization.

In summary, the metrological approach to handle chemical information is essential for the future of analytical chemistry. Unfortunately, metrology in chemistry has many weak points when compared to metrology in physics. Metrology in chemistry therefore needs to evolve to consider the peculiarities of (bio)chemical measurements. Our p[principal] message in this article is that, for this undertaken to be truly successfully, it is essential to put more emphasis on the applied facet (problem solving) of analytical chemistry.

3. Analytical problem solving

An analytical result with high metrological qualification (i.e. low uncertainty and traceable) can be of poor quality if it is not representative [22] (i.e. it is not consistent with the information needed by clients to make decisions). For this reason, it is essential to consider systematically the so-called analytical problem [23,24], which can be defined in several complementary ways, namely:

(a) the interface between analysts and clients who require (bio)chemical information;
(b) the frame to ensure consistency between requested and required analytical information [25]; and,
(c) an essential element of integral analytical quality.

During analytical problem solving, all analytical properties and their complementary, often contradictory, relationships must be considered. The analytical properties consist of the classical (e.g., accuracy, precision, sensitivity and selectivity) and the productivity related (e.g., speed, cost-effectiveness and risk) [26]. However, more communication among those involved in the analytical problem-solving process (clients and analysts) is required. This can be visualized by the need to break down traditional boundaries (e.g., laboratory walls and libraries) of classical chemical analysis.

The process of analytical problems solving is a five-stage procedure:

1. It is necessary to identify and confirm the (bio)chemical information needs of clients to make well-founded and timely decisions. This very first stage must be considered the principal bottle-neck of the whole approach.
2. Then, information needs should be transformed into the targeted analytical chemical information by specifying samples, analytes expected, and qualitative or quantitative results and by establishing quality compromises.
3. The analytical strategy should be planned by selecting a specific analytical process. Quality compromises must also be considered at this stage.
4. Monitoring (validation) of the results provided by the selected analytical process should use as criteria the outputs of the first two stages. If this check is satisfactory, the process is finished and the problem is solved.
5. If there are discrepancies, corrective actions must be undertaken and may involve a partial or complete change in the analytical strategy.

4. Achieving integral analytical quality by establishing quality compromises

The consideration of practical aspects of analytical problem solving in metrology opens up the possibility of establishing so-called quality compromises in a crystal clear way and thus achieving integral analytical quality. This integral analytical quality may be seen as the capability of analytical chemistry to provide chemical information under the constraints of available technology, information, time and money. Quality compromises may be viewed as the needle of a balance that has metrological quality and analytical problem solving in its two pans. By establishing quality compromises, the inclination of the needle is determined together with the client. The art of analytical chemists may now be visualized in selecting the measures needed to adjust the intrinsic (metrological) and extrinsic (problem solving) aspects of their work to achieve results that fit the established quality compromises (Fig. 1) (e.g., timely (bio)chemical information with 10% uncertainty would be better than information with 0.1% uncertainty but delivered too late to make a correct, profitable decision). These quality compromises should be clearly stated in

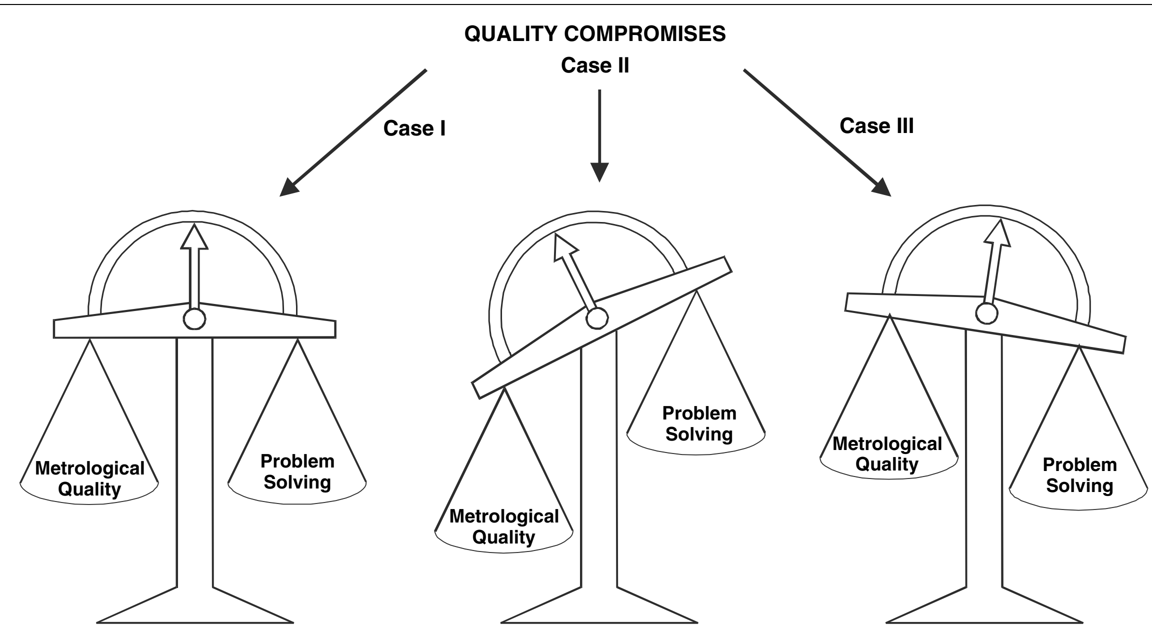

Figure 1. The definition of quality compromises establishes an appropriate balance between metrological quality and problem solving. These quality compromises need to be defined for each situation where analytical chemical information is produced.

documents of analytical quality systems as well as in contracts between the laboratory organization and its clients. The quality compromises realize the necessary harmonization between the basic (intrinsic) and applied (extrinsic) facets of analytical chemistry.

5. Sources of conflicts between metrology and analytical problem solving

Several sources of potential conflicts between metrology and analytical problem solving can be identified (Fig. 2). The first source of conflicts between state-of-the-art metrology and analytical problem solving arises from the contradictory relationships between the basic analytical properties (e.g., accuracy, precision and traceability) and the so-called productivity-related properties (e.g., speed, cost-effectiveness and risk). The basic ones come within the frame of state-of-the-art metrology, whereas the productivity-related properties are taken into account in the analytical problem solving approach outlined above.

A second source of conflicts is the different impact of the generic analytical references being measurement standards and written standards and the client's information needs. Measurement standards and written standards dominate, whereas the client's information needs are ordinarily missed. Metrology relies basically on generic analytical references and measurement standards, whereas the client's information needs have to be given priority to solve analytical problems. Written standards have a similar importance in both approaches.

The third source of conflicts is associated with the intrinsic and the extrinsic aspects of analytical excellence. Coincidence between the delivered and the required information is the key objective of analytical problem solving. However, coincidence between the delivered information and the referential information (e.g., a certified reference material) is the main focus of state-of-the-art metrology. The divergent direction of these two tendencies is an excellent example of the opposed foci of current metrology and analytical problem solving.

Finally, the fourth generic conflict arises from the two paradigms of the routine analytical laboratory: compliance with guides and standards (for example, the ISO 17025 standard, for accreditation purposes); and, client satisfaction. Both are required to assure laboratory activities and to maintain or even increase its competitiveness. Metrology in these applications still mainly relates to compliance with standards, whereas analytical problem solving has as its main goal client satisfaction.

6. From conflicts to synergies

Now, conventional metrology in chemistry [10–12] faces several important practical limitations. It is in general far removed from daily analytical work because it is not consistent with the (bio)chemical information really needed to make decisions. The most relevant weaknesses of current ability of analytical chemistry in problem solving [24,25] are insufficient definition of the client's information demands, the constraints on the activities of analysts arising from their traditions and their education and attitude, the difficulties in adopting quality compromises and the scarce metrological support for increasingly unconventional (bio)chemical results, such as yes/no binary responses and total indices. To transform these conflicts into synergies, the way that the intrinsic and the extrinsic aspects are dealt with within metrology in chemistry needs to change.

Metrology in chemistry needs to become more flexible and really capable of effectively supporting analytical problem solving. This implies systematic consideration of

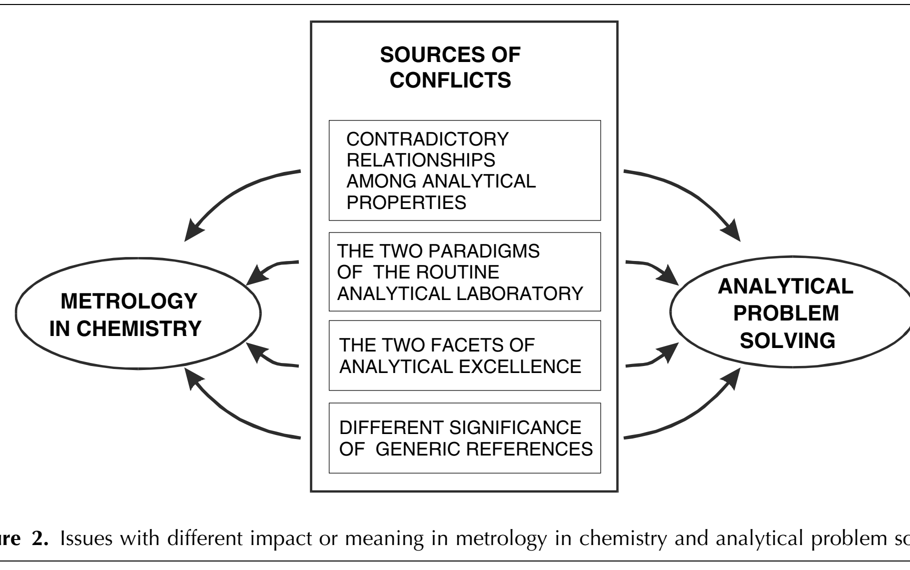

Figure 2. Issues with different impact or meaning in metrology in chemistry and analytical problem solving.

the client's information needs as a crucial reference in addition to classical metrological ones, such as are measurement and written standards. A framework of basic metrological principles needs to be established that is capable of accommodating any analytical activity independent of the format of information that they provide (e.g., concentrations, indices, or binary responses). Accreditation processes should be more quantitatively oriented. Conventional qualitative (visual and documental assessment) approaches should essentially be complemented by direct evaluation of the quality of results. This could be achieved by analysis of blind CRMs or regular participation in proficiency testing schemes. Finally, some efforts should be made to facilitate the client-analyst-auditor dialogue. For example, the misinterpretation of uncertainty, when the use of a ''reliability interval'' or a ''confidence interval'', which have the same scientific and technical meaning, would be more convenient to facilitate client-analyst relationships, according to Thomas [27]. The argument among most established metrologists that clients should be ''educated'' can be complemented by the client-centred approach: analysts and metrologists need to be close to practical reality and ''educated'' in this respect. It is also essential to persuade accredited calibration laboratories to have certified instruments for (bio)chemical measurements. Such certification is a regular activity in physical measurements but quite unusual in metrology in chemistry, despite the intrinsic difficulty of calibrating atomic spectrometers, chromatographs and instrument combinations (e.g., LC–MS, CE–MS, GC–MS, GC–MS–FTIR) in an orthodox way. Finally, it is of great relevance to change the attitude of scientists engaged in analytical R&D, who should take into account metrological principles and practice as a substantial part of their contributions. It would be a great error to consider that metrological support of the ''products'' of analytical R&D should be implemented by ''others'' because, in that way, important input and expertise in practical work would be wasted.

However, during analytical problem solving, crucial metrological characteristics (e.g., traceability and uncertainty) and the principles and practice of quality-assurance systems should be considered systematically, because they have inherent advantages as compared to classical properties (e.g., accuracy and precision). There is a need to increase the importance of measurement standards because there are only few CRMs available. Furthermore, there is a need to distinguish between instrument/apparatus and method calibration.

It would also be very convenient to introduce accepted confidence intervals (uncertainties) in the thresholds imposed by legislation and clients. It is well known that the simple comparison between two figures (that provided by the laboratory and the threshold limit) is not chemometrically correct; it is necessary to compare data and their respective uncertainty intervals at the same probability level. It is recognized that introduction of confidence intervals in legislation would require major changes that are unlikely today. However, discussion of these issues is considered fruitful in the context of the necessary continued evolution of metrology in chemistry. Furthermore, it will help to increase awareness of the importance of analytical chemistry as a scientific discipline in many aspects of our modern information society.

The mutual adaptation of metrology in chemistry and analytical problem solving processes is already reflected in the ISO 17025:1999 standard [28], but rarely exploited. The management and technical requirements of a laboratory are ordinarily considered separately; we do not consider that appropriate. For example, the link between ''service to client'' (management requirement 4.7 of ISO 17025) and the fitness for purpose concept of ''method validation'' (technical requirement 5.4 of ISO 17025) is a good start for looking for synergies between metrology in chemistry and analytical problem solving.

7. Black holes in state-of-the-art metrology in chemistry

One of the proposed changes in current metrology in chemistry is its adaptation to the peculiarities of (bio)chemical measurements. Some ''black holes'' should be eliminated (e.g., sampling, which now may be considered a ''grey hole'', as it is in ISO 17025 standard, or calibration of routine analytical instruments because their complexity). Improvements are required in the availability of proper measurement standards (e.g., CRMs for bioanalytical methods) and in marketing of the analytical reports by emphasizing positive rather than negative connotations. Finally, a metrological support is needed for types of chemical information other than concentration (e.g., binary yes/no responses, total indices and method-defined parameters). Most of them have already been commented on above. We next deal briefly with the need for metrological support for these types of analytical information.

Qualitative analysis and the binary information it provides are not considered in the technical requirements of ISO 17025 standard [28], which is totally oriented towards quantitative measurements. There is a need to adapt classical metrological principles to the peculiarities of test methods and yes/no responses. The analytical properties, accuracy and precision cannot be applied, so a new property, termed reliability (the opposite of false positives and false negatives) was proposed recently [29,30]. In addition, guidelines on how to manage the different definitions of sensitivity and selectivity in the chemical and the medical fields in order to avoid misunderstandings are urgently needed. Traceability should be approached by using a chain of comparisons based on reference or primary methods of increasing metrological quality. This is usual practice where ''confirmatory'' quantitative methods are associated with test methods. However, the conventional uncertainty approach cannot be applied. In qualitative analysis, the use of an ''unreliability'' interval of amount (concentration, parameter, indices) of the target analyte(s) or sample properties where the errors are produced at a fixed probability level is suggested as a substitute for the classical concept. Several of these new approaches appear in the results of a recently finished European project that aimed to contribute actively to the evolution of metrology needed in chemistry [29,30].

A total index [31] is a measurand that describes in analytical figures (e.g., binary responses (presence/absence) or arbitrary quantities) or in concentration units a group of chemical compounds that can range from millions (e.g., hydrocarbons in waters) to few (e.g., mercury species in a sediment) that share one or several features, such as similar nature or structure (e.g., total fat in foods), similar operational behaviour (e.g., chemical oxygen demand of waters) or observed properties (e.g., bitterness in beer). The lack of metrological support for total indices is remarkable, when one considers how frequently they are used.

There is a need to adapt metrological principles and practices to the peculiarities of total indices in two complementary directions:

- To develop new approaches to measurement standards, in which consensus and universal acceptance are the main cornerstones. In addition to the classical (chemical) measurement standards, the standard can be the method itself when the total index is a method-defined parameter obtained from empirical methods, such as cold-water extract of flour or bitterness in beers. The latter is only an arbitrary parameter that is established and useful.
- To develop atypical calibration systems based on a single measurement standard that represents the group of compounds (e.g., phenol in the total phenol index determination) a representative mixture of standards (e.g., benzene, cyclohexane and *n*-octane in the total hydrocarbon index determination) or even avoid measurement standards (e.g., total fatty acids in cream by gravimetry).

8. Final remarks

Analytical chemistry is under pressure from two opposing driving forces relating to its intrinsic and extrinsic aspects, namely metrology and problem solving. In this area of conflict, analytical chemists need to face the constant challenge of establishing quality compromises that may differ from situation to situation. Analytical chemistry as an information-delivering scientific discipline can be treated responsibly only when its realisation in our society is understood. There are high expectations with regard to the problem-solving capability of this scientific discipline; analytical chemists need to face these on a daily basis. To meet these, both aspects of analytical chemistry need to be considered when performing an analysis. It is the aim of metrology to provide rules and guidelines for performing and reporting the results of analysis, so that real, useful answers are obtained to meet the information needs of clients. In this context, reliability of results and client satisfaction are interwoven and therefore need to be discussed jointly.

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