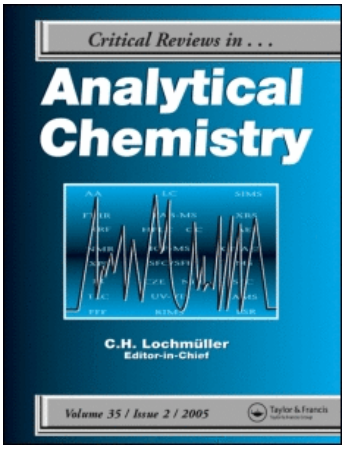


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# Qualitative Analysis Revisited

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# Qualitative Analysis Revisited

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**ABSTRACT:** A systematic approach to qualitative analysis at the down of the twenty-first century is presented. After a description of the most salient features of the binary yes/no response (types, quantitative connotations, properties and errors), the main types of qualitative analysis and the role played by standards and calibration are discussed. An overview of qualitative procedures based on classic and instrumental tools is provided. The significance of sample and analyte screening systems used to obtain binary responses is also discussed. Finally, the main present challenges of qualitative analysis are outlined.

**KEY WORDS**: binary response, qualitative analysis, chemical measurement process.



## I. INTRODUCTION

One of the main goals of Analytical Chemistry[1] is to ensure consistency of the true chemical information delivered by the laboratory with that actually contained in the objects and systems that are subjected to analysis, and also the analytical information delivered with that requested by the "client" in the context of the analytical problem.[2] Both are schematically depicted in Figure 1. They represent the basic and applied sides of this discipline.

Careful examination of the analytical information typically requested at present reveals that qualitative responses account for a substantial portion. Private and government bodies, toxicological institutes, industrial firms, inspection services, courts of justice, national and international trade companies, etc., are increasingly interested in obtaining general answers based simply on binary yes/no responses rather than on detailed, discriminate chemical information. Thus, an environmental body may be interested mainly in knowing whether a seawater is contaminated by hydrocarbons as per EC legislation rather than in compiling a long list of aliphatic and aromatic hydrocarbons including their individual concentrations and uncertainties. The divorce between the information requested and that delivered can be avoided by developing responsive analytical systems such as screening systems[3] and sensors[4] to obtain global responses and by revitalizing qualitative analytical principles (the approach subject addressed in this article).

It is interesting to note that the traditional qualitative bias of classic chemical analysis, reflected in the substantial portion of the Analytical Chemistry curriculum it has usually been allocated, has declined in the last few decades at the expense of instrumental analytical techniques the qualitative analytical potential of which is under exploited. At present, qualitative responses to yes/no questions such as "does the sample contain a banned additive?", "does this pepper contain any pesticide?", "did this athlete take any drugs?", or "has this animal been illegally treated with anabolics?" are

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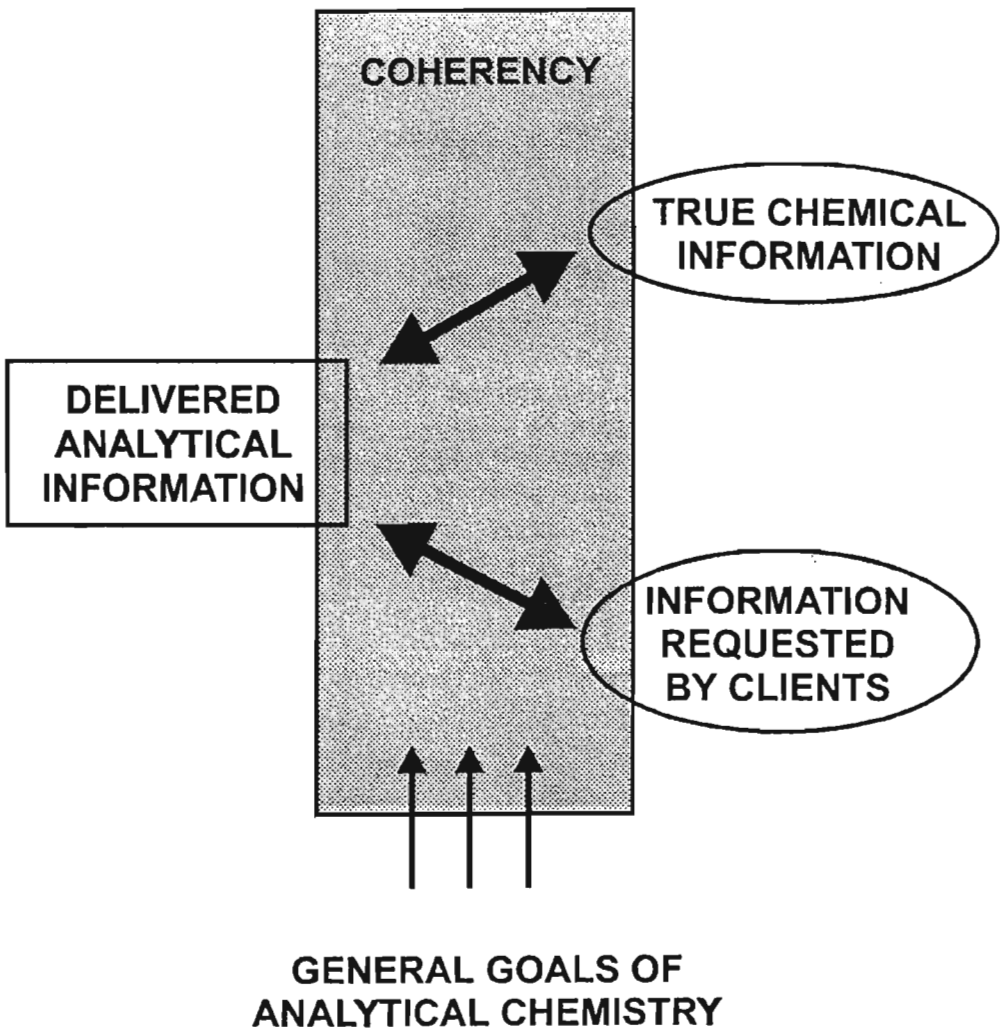


**FIGURE 1.** Main goals of basic and applied Analytical Chemistry relying on consistency of the information delivered with both the true and requested information.

extremely relevant with a view to fulfilling one of the main objectives of Analytical Chemistry[5] (see Figure 1).

## II. QUALITATIVE CHEMICAL INFORMATION

Qualitative chemical information possesses the following essential features:

1. It is based on the binary yes/no response;
2. It has relevant quantitative connotations that cannot be avoided;
3. It can be characterized from classic analytical properties, but more practical approaches are required for this purpose;
4. It is not systematically supported by metrological standards and guides, which are strongly biased to physical measurements, where qualitative responses are not as relevant as in chemical analysis.

All these features are discussed in this article, which is primarily intended to emphasize various well-known concepts and facts that, however, are rarely dealt with in a systematic, modern manner.

## III. THE BINARY RESPONSE

The output of a chemical measuring process (CMP) used to derive qualitative chemical information is either yes or no (i.e., binary information). This section describes the different types of binary responses one can obtain from qualitative analyses, their quantitative connotations, analytical attributes, and the errors potentially involved.

### A. Types of Binary Response

The apparent simplicity of a yes/no response can be misleading. In fact, as can be seen from Figure 2, the information content of such an answer can vary widely. The most simple possible binary response is the identification of an analyte in a sample as the answer to two complementary questions, namely, "is this substance the analyte?" and "is it (the analyte) in the sample?". This answer, which in fact is only one, is completed by those to the other questions asked in Figure 2. In deriving the qualitative information sought, one may need to consider a concentration limit or threshold imposed by the client or legislation. The actual question thus addressed will be something like "is the concentration of the analyte (e.g., a toxin, a pollutant) above the preset threshold?". The binary response to this question will obviously have more quantitative connotations than stated in the most simple possible form.

There is a growing need to obtain discriminate qualitative information about the different forms in which an analyte can oc-

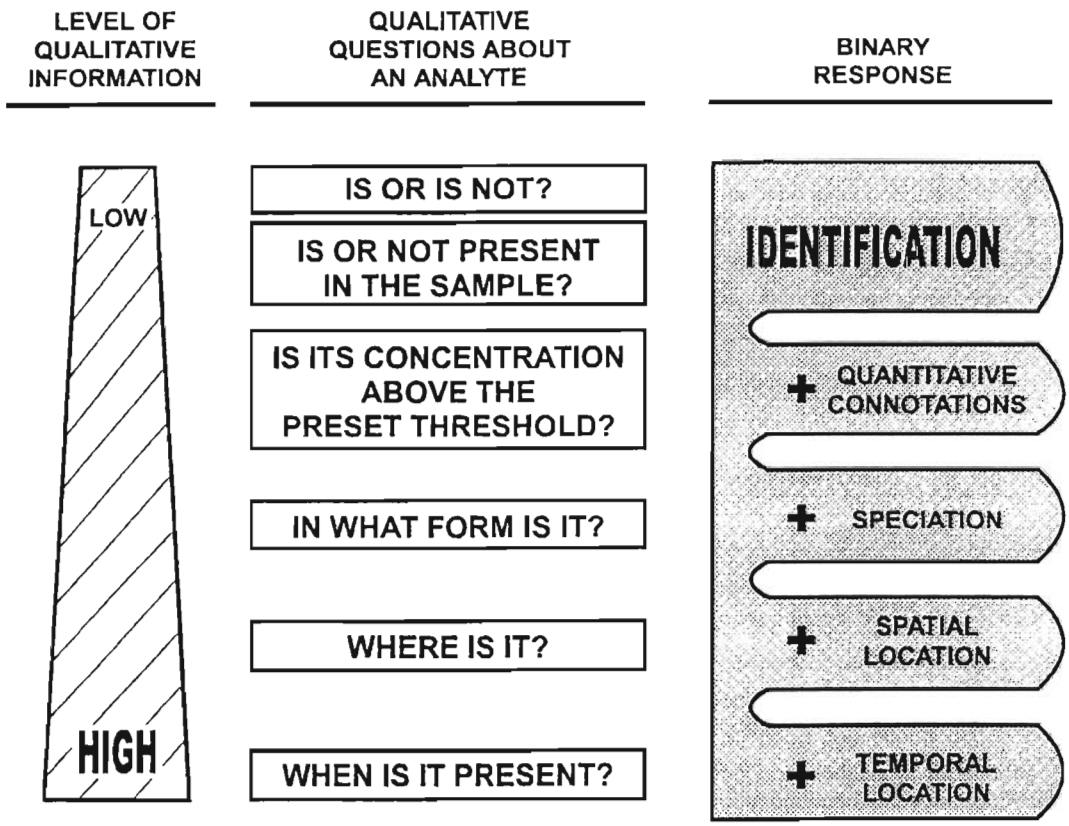


**FIGURE 2.** Types of binary responses ranked by information content, dependent on the questions posed by the information requested. The simplest response (identification or not) is a prerequisite for the others. The questions can also refer to a family of analytes. (Adapted from Reference 5, with permission from Springer Iberica).

cur in a given type of sample. As a result, the so-called "speciation" involves both the qualitative detection of different species and the determination of the concentration of each. Speciation is related not only to metals in the environment but also to other analytical problems including determinations of free and bound calcium in cells or the proportion of enantiomers of an active molecule in pharmaceuticals. The question "in what form is the analyte?" thus must be answered with a multiple binary response (one per species potentially present) and hence involves chemical discrimination. This binary response relies on the presence of the analyte, i.e. on a yes answer to the first type of question: "is it present?".

Some analytical problems require expanding the most simple binary response with temporal (e.g., answering the question "when?" for dynamic objects from which the samples are withdrawn) or spatial discrimination (i.e., answering the question "where?" for heterogeneous objects such as those involved in surface analyses). Consequently, even in its most simple possible form, the binary yes/no response can be chemically, spatially, and temporally different from case to case.



## B. Quantitative Connotations

Qualitative information invariably possesses some quantitative connotations, essentially to obtain the former one compares data (signals) produced in response to given concentrations or amounts of the analyte. To this end, one must use the references schematically depicted in Figure 3 placed on an imaginary concentration scale. Such references are as follows:

1. **The limit of detection,** $C_{DL}$, which is the concentration yielding a signal $X_{DL}$ that can be statistically discriminated from a blank signal, $\overline{X}_B$, and is expressed as

$$X_{DL} = \overline{X}_B + 3\sigma_B$$

where $\overline{X}_B$ is the mean for $n > 30$ signal blanks and $\sigma_B$ its standard deviation. This concentration is an internal reference inherent in the chemical measurement process. Sometimes, other references are used (e.g., $\overline{X}_B + 1.6\ \sigma_B$ as "practical limit of detection".[6] De Brabander et al.[7] describe the problems arising from different definitions of limit of detection in residue analysis.
2. **The cut-off concentration,** $C_C$, which is the concentration that produces a signal $X_C$ and is established on an particular basis by the analyst or the organism to which it depends in setting a given probability level to ensure the obtainment of a correct binary response. Sometimes the so-called "decision limit", defined as $\overline{X}_B + 6\ \sigma_B$, is used in this context.[8]
3. **The limiting concentration or threshold (alarm limit) concentration,** $C_L$, which is the highest or lowest level, established by the client or legislation, to be used in deciding whether the sample (or the object it represents) warrant assignation of a given attribute (e.g., toxic, contaminated, nutritionally fit, fat-free, decaffeinated).

It is interesting to note the sequence and distance between the references of Figure 3. Thus, the limit of detection, $C_{DL}$, must always be lower than the other two parameters — otherwise, detection (identification) will be impossible. Also, the cut-off concentration, $C_C$, must exceed the limit of detection as it involves a higher probability level that detection will be error free. Finally, any externally imposed limit or threshold, $C_L$, should be greater than $C_C$ — and inevitably greater than $C_{DL}$ as well— if

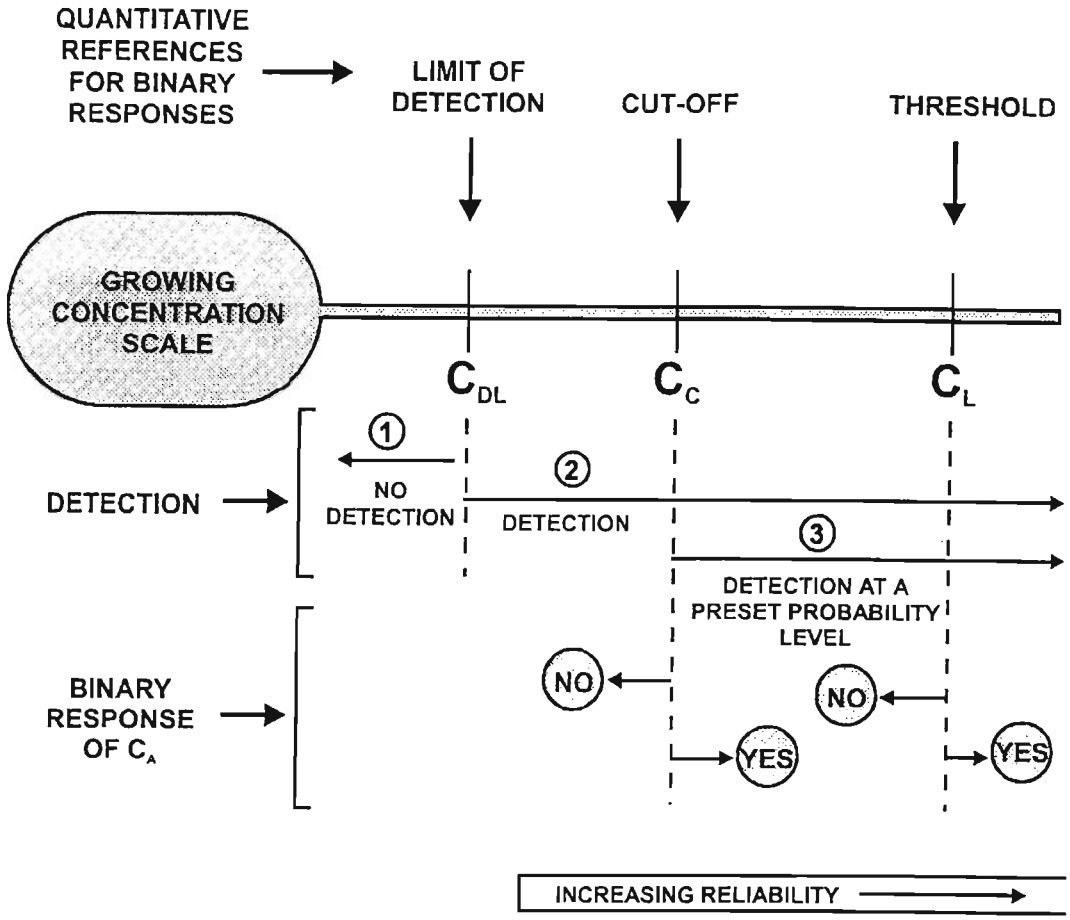


**FIGURE 3.** Quantitative references for the binary yes/no response. For details see text. $C_A$ analyte concentration. (Adapted from Reference 5, with permission from Springer Ibérica).



an error-free response is to be assured. The greater the difference [($C_C$ — $C_{DL}$) or ($C_L$ — $C_C$)] the more reliable is the binary response achieved.

The concentration of the target analyte, $C_A$, may lie in different zones of the imaginary scale of Figure 3. For the simplest binary question to have a reliable answer, $C_A$ must be greater than the limit of detection ($C_A > C_{DL}$), that is, $C_A$ must be in zone 2. With $C_A > C_C$ (zone 3 in the scale), there will be a given probability of the analyte being detected. Derivation of the binary yes/no response can rest on two different references, namely, an internal reference (the cut-off concentration, $C_C$) and an external one (the limiting concentration, $C_L$), with which the analyte concentration, $C_A$, is compared, being this one the most significant in practice.

One of the greatest weaknesses of qualitative analysis is the difficulty of converting raw data into a binary yes/no response (see Figure 4). Analytical laboratories evaluate crude analytical data on the basis of chemometric criteria (e.g., S/N ratios, differences between the signals provided by samples and reference materials, etc.); however, the binary response depends strongly on quality criteria imposed by the client. In each analytical field (environmental, food, veterinary, clinical) specific approaches exist that endown qualitative analysis with some subjective component. This becomes a "black hole" when no dia-

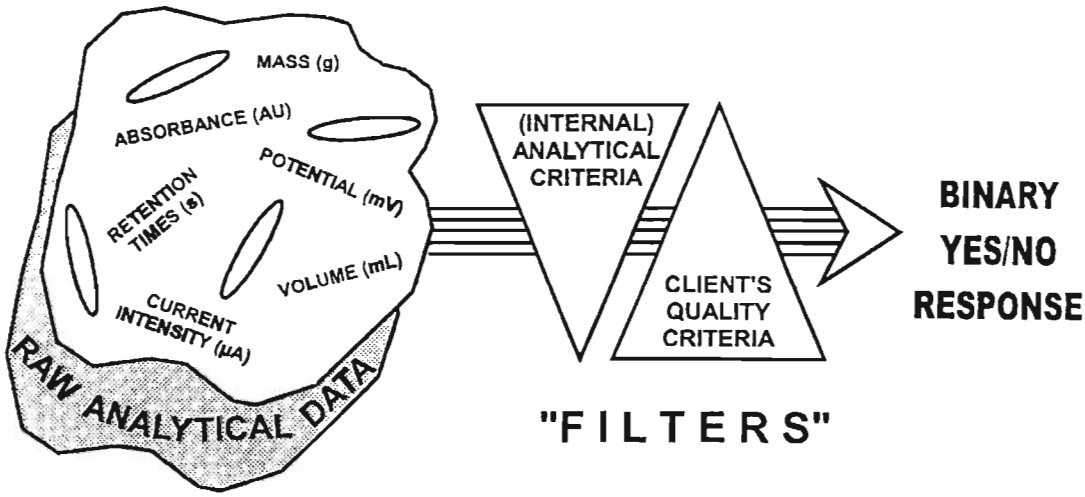


**FIGURE 4.** Schematic depiction of the "filters" used to convert crude analytical data into a reliable binary yes/no response.

log exists between the analytical chemist and the client.

## C. Analytical Properties

The three types of analytical properties, viz., capital (accuracy, representativeness), basic (precision, sensitivity, selectivity, proper sampling), and accessory (expeditiousness, cost-effectiveness, and personnel related factors), as well as their complementary and contradictory relationships,[9] can be systematically considered in qualitative analysis in much the same way as in quantitative analysis. However, a need to define a new capital property in this field as shown in Figure 5 exists.

It is rather difficult to use the accuracy and precision concepts because such in qualitative analysis as this capital and basic properties, respectively, are closely related. Their combination results in a new analytical property of the binary response called "reliability", which is defined as "*the proportion (percentage) of right yes or no answers provided by individual tests carried out on n aliquots of the same sample (reference material) to identify an analyte or a family of them*". This definition is consistent with the intrinsic nature of accuracy and precision and represents the positive side of the well-known errors in the binary response: false positives and negatives. The reliability of the binary response is not an independent property: it strongly depends on the basic characteristics of the CMP (sensitivity and selectivity); on the other hand, it is in contradiction with productivity-related properties such as cost-effectiveness and expeditiousness. In addition, it is markedly affected by the analyte concentration level, $C_A$, and by the quantitative references used for the binary responses. As a rule, the higher the analyte concentration, the higher is the reliability (see Figure 3). Selectivity in qualitative analysis can be determined from reliability, which in turn is estimated by analyzing mixtures of foreign species and the analyte in different ratios n times. The tolerated ratio is inferred when reliability (%) reaches a preset level (e.g., 95%).

Robustness, defined as the reliability against slight changes in the operating conditions, is a complementary analytical property of great relevance when biochemical or biological tools (e.g., immunoassays)[10-12] are used to obtain binary responses from screening systems. This is one of the most promising trends in qualitative analysis on account of its high selectivity and sensitivity; however, the low stability of biochemical, bio-

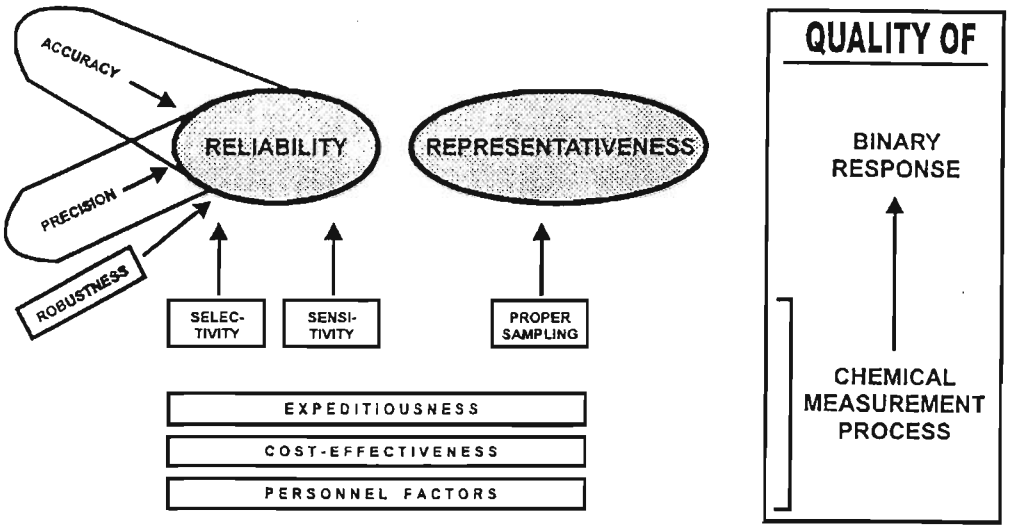


**FIGURE 5.** Analytical features of qualitative analysis that can be attributed to the binary response or to the chemical measurement process. For details see text.



logical, and immune reagents, and the strong influence of experimental variables, impose serious constraints in many cases. No doubt, this is one of the most relevant R+D topics in Analytical Chemistry.

## D. Errors: False Positives and False Negatives

The definition of the analytical property "reliability" in relation to the binary response contains an implicit statement of the errors made in Qualitative Analysis: the relative proportion (as a fraction of unity or a percentage) of wrong yes/no answers (e.g., of false positives and negatives). The proportion of errors is greater in the vicinity of the limit of detection, $C_{DL}$, which is consistent with the combination of the properties accuracy and precision in reliability. The notion of error usually employed in this context encompasses both systematic (determinate) and random (indeterminate) errors; however, the latter obviously will be more relevant when the analyte concentration is near the limit of detection.

As noted earlier, the errors contained in qualitative information are specifically called "false positives" and "false negatives", which, based on statistical principles, correspond to errors of the first kind ($\alpha$, resulting from rejection of a true hypothesis) and errors of the second kind ($\beta$, made in holding a false hypothesis as true), respectively.[8]

Table 1 provides schematic definitions of errors in the binary response based on comparisons of the analyte concentration, $C_A$, with the reference concentrations of Figure 3. A **false positive** arises when the signal for a sample containing the analyte at a level below the reference concentrations (false hypothesis) yields a yes response even though the sample is in fact a blank (i.e., it results from acceptance as positive of samples that are not such but blanks). On the other hand, a **false negative** results from the signal for a sample containing the analyte at a level above the reference concentrations (true hypothesis) being deemed a blank and a no response thus being assumed; therefore, it is made in rejecting a signal for a sample containing the analyte in the mistaken belief that it is a blank (i.e., that it does not contain the analyte).

The relative concentration of the analyte, $C_A$, in the quantitative references of Figure 3 affects not only the reliability but also the

**TABLE 1 Quantitative Definition of Errors in Qualitative Analysis**

| Quantitative References | Relative Concentrations | Binary response | | Errors |
|---|---|---|---|---|
| | | Correct | Incorrect | |
| Cut-off | $C_A < C_C$ | NO | YES | False positive |
| | $C_A > C_C$ | YES | NO | False negative |
| Threshold limit | $C_A < C_L$ | NO | YES | False positive |
| | $C_A > C_L$ | YES | NO | False negative |

type of error made. As a rule, if $C_A$ is high, then false negatives are usual; if it is low, false positives are to be expected. This relationship was demonstrated with an urine screening systems for benzodiazepines.[13]

The implications of these errors depend on the particular analytical problem. As a rule, the results of screening tests and systems are confirmed by using a conventional CMP when any error made can have a significant social or economic impact. False negatives are especially serious when detecting or identifying a toxic chemical or chemical family as no confirmation step is usually taken.

## IV. TYPES OF QUALITATIVE ANALYSIS

A comprehensive picture of qualitative analysis can be acquired by systematically considering various classifications based on purpose, the characteristics of the chemical measurement process involved and the dimensions of the information produced.

The target of a qualitative analysis can be a single species, which will produce individual binary responses (e.g., in the identification of clembuterol in beef), or several species belonging to the same chemical group or family to which a global index or response is assigned (e.g., in the identification of hydrocarbons in water).

Qualitative analysis can also be classified according to various aspects of the CMP used to derive the binary response. Thus:

1. The analytical techniques involved in qualitative CMPs used either the human senses (classic analysis) or instruments (instrumental analysis).
2. The signals provided by the analytical techniques used in a qualitative CMP can be produced by the analyte itself or the product of a chemical, enzymatic, or immune reaction, for example. This substep of the CMP boosts the sensitivity and selectivity of the identification. For example, the bluish color of the cupric ammine, $Cu(NH_3)_4^{2+}$, is too light to be easily detected and can be masked by other, stronger colors. The addition of a ligand (cuproine) to form a bright red, soluble chelate ($CuL_2^+$) dramatically increases the sensitivity and selectivity of the identification, which thus is made much more reliable.
3. The need to obtain an acceptably reliable binary response has led to includ-

ing a separation method in many qualitative CMPs. Classic qualitative analysis uses non-chromatographic methodologies such as precipitation, liquid-liquid extraction or ion exchange. On the other hand, instrumental qualitative analysis usually employs chromatographic approaches [gas (GC), liquid (LC) and supercritical fluid chromatography (SFC)] involving the use of a detector (instrument) to continuously monitoring the signal produced by the eluent that emerges from the chromatographic column.

4. Qualitative CMPs can be conducted manually (e.g., by visually inspecting the formation of a precipitate and/or its color, by comparing IR spectra), semiautomatically (e.g., when locating the retention time for an analyte in a chromatogram with the aid of an electronic integrator or computer) or fully automatically (e.g., in spectral searches of computer libraries).[14,15]

The reliability of the binary response additionally depends on the dimensions of the information supplied by the CMP, that is, the identification points used to provide the yes/no response. Some instruments can provide signals for one, two, three or more parameters. The more raw data (parameter values and signals) are available and the better discriminated they are the more reliable will be the identification. Thus, classic qualitative analysis uses a multidetection system (the human senses and brain) and one, two or more signals for identification (e.g., the formation of a precipitate, this and the precipitate color, the previous two and the precipitate texture, etc.). On the other hand, the identification of a metal ion present in trace amounts in water entails using atomic absorption spectrometry: a signal at a preset wavelength (i.e., an instrumental parameter). A fluorescent analyte (or its reaction product) is identified fluorimetrically, that is, from a fluorescence intensity signal obtained at two different instrumental parameters (the excitation and emission wavelengths). The body of spectra provided by instrumental techniques (IR spectroscopy, mass spectrometry, nuclear magnetic resonance) for a given species — or a suitable combination of the information thus gathered — makes a powerful, highly reliable identification tool on account of the many signals and instrumental parameters it encompasses.

## V. METROLOGY OF THE BINARY RESPONSE

Are the standards involved in a screening test for the identification of pesticides in human milk? Which is the standard in the identification of $Cd^{2+}$ using sulphide in an $NH_4^+$-$NH_3$ buffer and $CN^-$ as masking agent? Is it possible to implement chemical analyses without (measurement) references? In fact, identifying involves comparing one or more signals arising from three different aliquots subjected to the analytical process (see Figure 6), namely, (1) a standard containing the analyte; (2) a blank resembling the sample in composition but containing no analyte; and (3) a sample, which may or may not contain the analyte.

Measurement standards are quite well described and understood in quantitative analysis but less systematically considered in qualitative tests, even though they share the same crucial importance. Metrology in chemistry relies on traceability,[16,17] assurance of which entails proper use of quality standards (certified and uncertified reference materials). There is a need to strengthen this unique side of metrology in chemistry taking into account the difference between the two most frequently used types of standard here: equipment and method calibration.[18] *Equipment calibration*, based on standards not containing the analyte, is done to ensure correct functioning of the identification in-

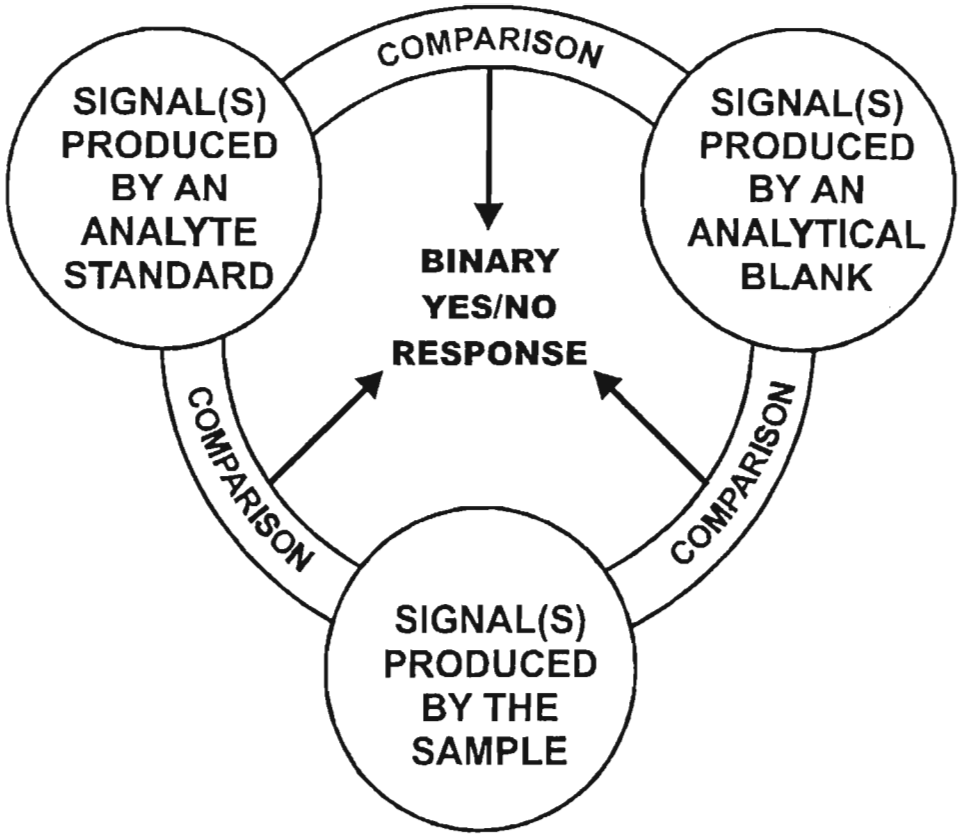


**FIGURE 6.** Triple comparison of raw analytical data involved in the production of a binary response in qualitative analysis.



strument. Thus, a polyethylene film (a reference material, RM) is typically used to calibrate IR absorption spectrophotometers. The film spectrum should coincide with that of the RM; otherwise, the instrument must be readjusted. A solid fluorophore (e.g., rhodamine) dispersed in a transparent plastic block is employed to check that the two monochromators of a fluorimeter operate to specification.

*Method calibration* uses standards containing the analyte to establish an unambiguous relationship between physico-chemical properties of the analyte (or a reaction product) and the signals provided by a pre-calibrated instrument under specific operating conditions. The identification involved in qualitative analyses relies on standards that are used in two different ways for method calibration:

1. Calibration based on the relationship between the signal and properties of the analyte (or its product). Such is the case with identification in classic qualitative analysis: the product (a gas or solid) of a chemical reaction is previously identified by the operator using a standard of the pure analyte. Once the features (color, odor, texture) of the product have been recorded by the brain, the identification test is performed on a sample aliquot; whether the new product is identical with that previously obtained from the standards is decided on by the operator. In instrumental qualitative analysis, the standard provides two data sets (instrument parameters and/or signals) that are compared to each other. The greater the number of data used and the more similar, the more reliable is the determination. Comparisons can be made manually or with the aid of a computer; the latter allows the sample spectrum to be automatically

checked against those for a wide range of standards included in a so-called "spectral library". The identification can be made even more reliable by using a derivative (first, second, etc.) of the original signal; this expands the initially available information with new bands and diminishes background noise.

2. Calibration based on the behavior of the analyte (or standard) in a dynamic instrumental system that produces signals of temporal or spatial dimension. Thus, in a column chromatographic system (capillary electrophoresis and liquid, gas or supercritical fluid chromatography), the analyte is identified from its retention time; by contrast, in planar chromatography and classic electrophoresis, identification relies on the distance travelled (migrated) by the analyte.

## VI. CLASSIC QUALITATIVE ANALYSIS

Classic qualitative analysis uses the human senses (mainly sight and smell) to detect the presence of an analyte; the analyte is subjected to a chemical (acid-base, complex formation, precipitation, redox, condensation, etc.), biochemical, or immune reaction that yields a product that is identified from a well-defined change (e.g., the formation of a gas, color, or precipitate).

Identification in classic qualitative analysis thus relies on the comparisons shown in Figure 6. Comparisons can also rely on the use of a reference scale, from which the operator can read semiquantitative information. Such is the case with pH, active chlorine, and glucose measurements in fluids, pool water, and urine, respectively, provided by reagent strips; the color taken by the strip allows one not only to identify the presence of the analyte but also to obtain an estimate of its concentration.

The limited capacity of the human senses and brain to detect small changes, the low discrimination among signals, and the scarce variety of the information that can be derived severely restrict the identification scope of classic qualitative analysis relative to instrumental analysis. As a result, reliability in this context strongly depends on the sensitivity and selectivity of the particular CMP used and, ultimately, on the chemical reaction(s) it involves. Boosting these two analytical properties — primarily with the aid of separation techniques — has been a permanent challenge to classic qualitative analysis.

The qualitative CMP of choice differs widely depending on whether a single analyte (e.g., clembuterol in beef for human consumption), a compound family (e.g., atmospheric aromatic hydrocarbons), a small group of species (e.g., pesticides in oranges), or a wide range of analytes (e.g., metals and non-metals in a soil) is to be identified. The CMP for a classic qualitative analysis is also dictated by the nature of the analytes involved (inorganic, organic, biochemical). On the other hand, the complexity of the qualitative analysis strongly depends on how deep is the available knowledge about them. Based on this criterion, samples can be classified into three main groups, namely, "white", "grey", and "black".[19] In fact, some "black" samples (i.e., samples of absolutely unknown composition) contain scores of analytes at very different concentration levels; the identification of all is the most complicated situation.

There are three generic approaches to the identification of analytes in complex mixtures (samples), namely,

1. Direct individual identifications of each analyte or family using straightforward testing. The book by Jungreis[20] is representative of this situation. Selectivity and sensitivity must be high in each test.

2. Individual identifications following systematic separation (e.g., by precipitation, liquid-liquid extraction, ion exchange) to obtain spatially discriminated species or reduced groups of them. The $H_2S$ scheme of Fresenius[21] is one typical example in inorganic qualitative analysis, as is the book by Cheronis et al.[22] in organic analysis.
3. Individual identifications of each analyte in different sample aliquots, which may be subjected to a simple separation process in a preset operational sequence. The Charlot scheme is one typical example.

The reagents typically used in qualitative chemical analysis can be classified into three main categories, namely,

1. Identification reagents, which give a reaction the externally apparent effect of which can be readily detected by human senses. The selectivity of the binary response increases in the following sequence of reagent types inorganic < organic < biochemical < immune. These reagents can be used to identify analytes of widely variable nature.
2. Group reagents, which are intended to effect the separation of the analytes contained in the sample into small groups in such a way that mutual interferences in the identification tests can be minimized or avoided. One additional advantage of this approach is that the sensitivity is indirectly increased through preconcentration.
3. Masking reagents, which are added to the reaction identification medium in order to avoid interferences from other species potentially present in the original sample or in an isolated group of analytes.

## VII. INSTRUMENTAL QUALITATIVE ANALYSIS

In instrumental qualitative analysis, physico-chemical properties of the analyte or its reaction product are converted into signals that can be measured by optical, electroanalytical, thermal, magnetic, or radiochemical instruments with a view to their identification. As noted above, the difference between instrumental and classic qualitative analysis is that the latter uses the human body as "instrument". The substantially increased identification power of available equipment obviously makes instrumental qualitative analysis much more reliable and widely applicable.

The probability of obtaining yes/no as the binary response depends on the degree of consistency between the signals produced, their number, and how well discriminated. The use of a single signal (e.g., absorbance) obtained at a single instrumental parameter value (e.g., wavelength) obviously provides less reliable qualitative identification than multiple signals recorded at many different instrumental parameter values (e.g., the bands in an IR absorption spectrum). Molecular absorption spectra are much broader and general than are atomic absorption spectra; the latter contain much better resolved signals and hence enable much more reliable identification. Not all instruments are equally capable of providing reliable identifications; in fact, reliability in this context depends on the selectivity and the amount of information content of the responses they provide. Instrumental analytical techniques can be ranked in the three broad categories of Figure 7 in this respect — the ranking, however, can obviously have some exceptions.

The instruments in **Group 1** provide a very general response (i.e., one shared by many analytes). Such is the case with the mass measured by a balance or a piezoelectric sensor. This type of information therefore is useless for qualitative analyses unless altered

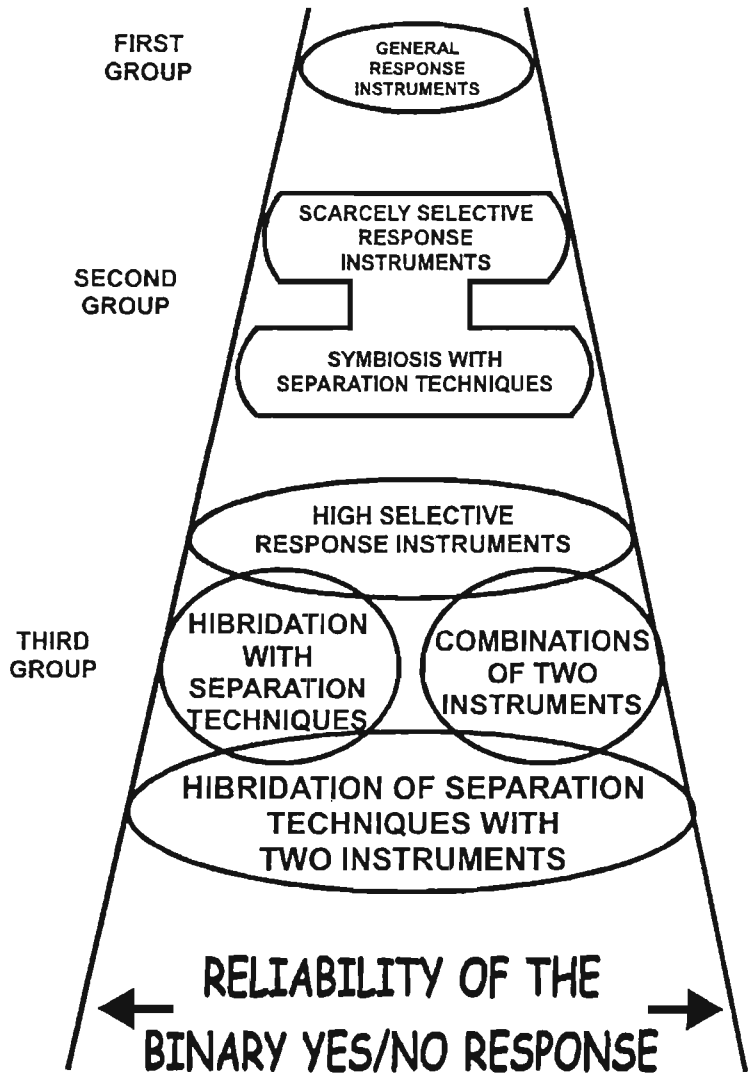


**FIGURE 7.** Classification of instrumental techniques according to reliability in the identification of the analytes. For details see text. (Adapted from Reference 5, with permission from Springer Ibérica).

in some way to increase its selectivity (e.g., in thermogravimetries, which provide mass-temperature two-dimensional information, and in sensing with piezoelectric sensors coated with selective sorbent materials).

The instruments in **Group 2** give a scarcely selective response (i.e., one that can be subject to may interferences from sample components other than the analyte). One case in point is UV-visible absorption spectroscopy (photometry), where virtually every species exhibits absorption of incident light. The selectivity of this technique can be improved by derivatizing the analytes to products with differential spectral features. Alternatively, more selective techniques such as fluorimetry ensure higher reliability (fluorescence is a much more uncommon property than in molecular absorption). Even greater selectivity can be achieved from on-line combinations of instruments in this group with continuous column chromatographic separation techniques; the poor selectivity of the instrument is offset by the high selectivity of the continuous separation, which isolates the analytes within dynamic zones.

Finally, the instruments in **Group 3** provide highly selective information (e.g., that

of atomic absorption and emission spectroscopies) or information containing many well-resolved signals obtained at multiple instrumental parameter values (e.g., those of IR spectroscopy or mass spectrometry). The use of this type of instrument as a detector in chromatographic techniques has given rise to so-called "hyphenated techniques", which provide significantly increased reliability in the identification. Reliability can also be substantially improved by the joint use of information provided by one instrument of Group 2 and other of Group 3 (or two Group 3 instruments). One typical example is the highly reliable (>99%) identification of analytes in a sample from its IR and mass spectra. However, the highest level of reliability is provided by the combination of a separation technique and two or more instruments of Group 2 or, better, Group 3 (e.g., the gas chromatography-mass spectrometry-IR spectroscopy tandem).

A complementary view of the classification shown in Figure 7 can be obtained if the instruments are divided into two main groups according to the dependence of the signal with time. In static systems, the blank and standard are inserted into the instrument to obtain a time-independent analytical signal. This information is usually two-dimensional (a signal as a function of one instrumental parameter) but can occasionally be three-dimensional (a signal as a function of two instrumental parameters). How reliable the identification is will depend directly on how well the information profile of the analyte is resolved from those for other species in the sample (i.e., on the group to which the instrumental technique belongs). Such is the case of UV-visible and infrared molecular spectroscopies, atomic emission and absorption spectroscopies, ion-selective electrodes, stripping voltammetry, among others.

Dynamic systems provide time-dependent signals. Discrimination among species in the same sample and hence their reliable individual identification thus relies on time as a parameter. As a rule, the qualitative information required is derived from the x-axis of a signal-time two-dimensional plot. The dynamics inherent in the instrumental system may arise from (a) the instrumental technique itself (**instrumental kinetics**), (b) a chemical reaction the development of which is monitored (**chemical kinetics**) or (c) the use of a separation technique (e.g., chromatography) coupled on-line to a Group 2 or Group 3 instrument (**physical kinetics**). Only the last is considered here on account of its strong practical implications.

The ability of separation techniques to physically isolate the components of a mixture (sample) is used for group separation in classic qualitative analysis. Such an ability can be substantially enhanced by on-line coupling to an instrument. Once case in point is the chromatography-capillary electrophoresis couple. As can be seen from Figure 7, the information content of use for reliable identifications with Group 2 and 3 instruments can be increased by using a chromatographic or capillary electrophoretic separation technique. With these instrumental assemblies, each analyte is identified in terms of its "retention time", $t_R$, which is the time (on the x-axis of the chromatogram or electropherogram) corresponding to the top of the analyte peak. This process can be performed in various ways, depending on the type of reference (standard) used, namely,

1. By comparison with the $t_R$ value for an analyte standard previously inserted into the system instead of the sample. However, the value provided by the standard is usually scarcely reliable because it depends strongly on the operating conditions (pressure, temperature, flow-rate of the mobile phase, voltage), small changes in which may considerably alter the dynamic behavior of a given species in the standard and sample. For this reason, direct comparisons are inadvisable.

2. By using the internal standard procedure, which involves adding a standard of a species other than the analyte to both the samples and the ordinary analyte standards used. The retention times thus obtained are either normalized of referred to the internal standard. In this way, the distorting influence of isolated fluctuations in the experimental conditions (e.g., temperature, pressure, flow-rate), which have crucial effects on the measured parameter (the retention time), is minimized.
3. By adding a standard of the analyte to the sample in order to facilitate its identification. Two chromatographic runs are performed, using the sample in one and the sample plus standard in the other. If any peak increases in height as a result, then the analyte is the specie contained in the added standard.
4. By using a Group 3 technique (e.g., IR spectroscopy, mass spectrometry), which provides whole spectra for each chromatographic peak and facilitates highly reliable identification.

## VIII. SAMPLE AND ANALYTE SCREENING SYSTEMS

Screening systems play and will play an important role in qualitative analysis. Notwithstanding the absence of clear-cut, the consideration of the domains where this term is usually employed makes possible the establishment of three categorically different features in such screening systems. The acceptations discussed in this section are summarized in Figure 8.

*Sample screening systems* refer to expeditious, reliable analytical methodologies intended to identify and select a group of samples from a starting set, samples which will contain one or more analytes above a preset concentration level (e.g., screening of urine samples, soils screening, or fruit and vegetable screening).[3] These straightforward, responsive analytical systems allow those samples to be "filtered out". One other term frequently used in connection with sample screening systems is "pre-screening", which involves estimating the concentrations of analytes in a sample prior to their chromato-

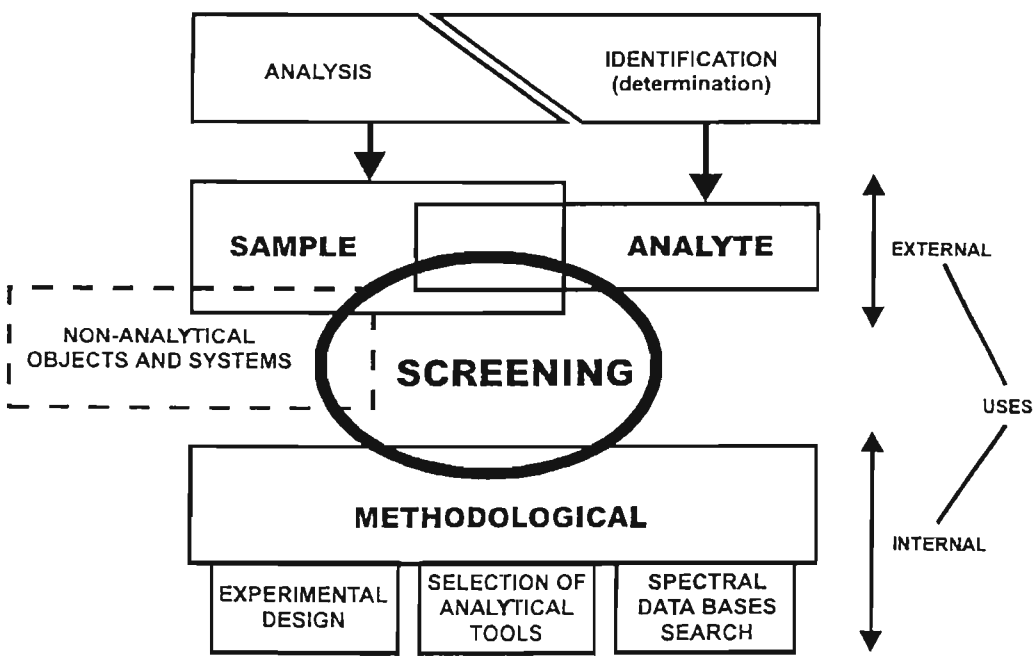


**FIGURE 8.** General uses of the word "screening" in Analytical Chemistry. For details see text.

graphic determination. In this context, the word screening is also used to designate the process by which the objects and systems related with the analytical problem addressed are selected; it also entails screening the samples. Such systems are called object/systems screening systems. In this regard, there are literature references to "patient screening", "routine forensic screening", "environmental screening", or "screening for occupational exposure to pesticides".

*Analyte screening systems* involve identifying one or more analytes in a given type of sample or system and is used more frequently to refer to methodologies intended for both the identification of analytes in complex samples and multideterminations. These systems use conventional sample treatments and/or powerful identification techniques [e.g., Fourier transform-infrared spectroscopy [FT-IR], inductively coupled plasma-mass spectrometry [ICP-MS], nuclear magnetic resonance [NMR]), occasionally coupled to a chromatographic (GC, LC, SFC) system. Based on the hierarchical distinction among analysis, determination and measurement, sample screening systems are closer to "analysis", whereas analyte screening systems resemble "determination" (identification) more closely. In any case, the two acceptations are separated by a wide interface (see Figure 8). Worth special note here is the use of "screening" as applied to combinatorial chemistry. The aim of combinatorial chemistry is to generate a large number of structurally distinct molecules (so-called "libraries") in a short time. The pharmaceutical industry has fostered the use of combinatorial chemistry in response to the growing need for high-throughput screening, which is an effective solution with a view to expediting the process of drug discovery.

*Methodological screening systems* encompass other acceptations that are inherent in Analytical Chemistry and widely varied in nature. Such is the case with the initial step of the "experimental design", in which the factors involved in the analytical system are selected and their relative importance established. There are also references where the word screening is associated to different components of the equipment needed to derive the final response (e.g., "screening electrode", "screening reagent", "screening gradient", "screening column", or even "interference screening"). This designation has also been used to describe the systematic selection of analytical tools (e.g., "screening of electrode material for a carbon monoxide sensor") or screening for spectral databases.

## CONCLUDING REMARKS

The main aim of this article is to emphasize the significance of qualitative analysis to today's and tomorrow's Analytical Chemistry. The growing importance of the binary response in many analytical problems calls for a systematic approach to qualitative analysis based on developments in classic qualitative analysis and taking advantage of the potential of modern instrumental techniques and their symbiosis.

The main current challenges of qualitative analysis are as follows:

1. There is a need to strengthening the metrological approach to qualitative chemical analysis, never previously considered in a systematic manner. The traceability and uncertainty concepts must be adapted and specific developments (standards, guides) developed.
2. The binary yes/no response and its quantitative connotations require practical chemometric support rather than the typical statistical approaches used in this context, which are very interesting but distant from bench level.
3. The development of measurement standards and their proper use (equipment and method calibration) is a qualitative analytical target the impact of which

has never to date been systematically considered. R+D efforts must be adapted to the characteristics of qualitative analysis. In some cases (e.g., with global indexes) finding proper standards constitutes a rather difficult problem.

4. There is a need to define a widely accepted quality parameter to globally characterize the results of qualitative analysis. "Reliability", a combination of accuracy and precision, is our proposal. It is very simple and practical.
5. The development of robust analytical tools and processes to obtain raw data that can be easily converted into binary responses with a high reliability is one of the most promising current research lines in Analytical Chemistry.
6. It is necessary to educate clients and officials of public bodies about how to properly request chemical information. It is simply inadequate to deliver a figure (e.g., 0.1 ppb of $Pb^{++}$ in water) as the threshold limit. Those involved must be aware of the importance of uncertainties, how difficult it is to convert raw data into binary responses, etc. If this facet of the analytical problem is essential in chemical analysis, it is crucial with a view to obtaining binary responses.



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