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DEFINITION AND CLASSIFICATION OF INTERFERENCES IN ANALYTICAL PROCEDURES

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Definition and classification of interferences in analytical procedures

Abstract - Based on a survey of various alternatives found in the litera-
ture a definition of interference is presented and recommendations are
given for the classification of interferences in analytical procedures. It
is recommended that the usage of the term interference will be restricted
to the effects caused by concomitants in the sample. Several examples are
given.

INTRODUCTION

The comparison of different analytical procedures calls for a well-defined set of terms and
quantities that characterize the merits of the various procedures. Such quantities are, for
instance, precision (standard deviation), bias (systematic error), limit of detection, sensi-
tivity, range of linear response, but also costs of an analysis, effort and time needed to
obtain the analytical result. These aspects are sometimes summarized as 'performance charac-
teristics'. Since analytical results may be affected by the presence of concomitants in the
sample, it is also desirable to introduce unambiguous terms describing these influences. It
is within this context that Commission V.1 has started a discussion on concepts such as se-
lectivity, specificity and interference. As a result of this discussion recommendations for
the usage of selective, selectivity and related terms in analytical chemistry have been es-
tablished [1]. From all publications dealing with this subject it is evident that selectivi-
ty cannot be discussed without introducing the term interference; both are closely interre-
lated. It was therefore logical that den Boef and Hulanicki [1] started their discussion on
selectivity with a small section on interference, but ending with the comment that the pro-
blem of classification of interferences is still in discussion and will be dealt with in a
future publication.

The present article gives a definition and some recommendations for the classification of
interferences.

DEFINITION

Analytical procedures yield results of which their value and accuracy generally depend on
both the overall sample composition, the instruments used (the term instruments has to be
understood in a broad sence, ranging from simple equipment like pipettes to the most complex
measuring device) and the operator. Thus, errors in the analytical results may be of chemi-
cal, physical, instrumental but also from human origin.

Although there appears to be no universally accepted definition of the term interference, in
most cases explicit reference is made to the sample and, in particular, to substances accom-
panying the analyte. Purely instrumental factors causing errors are, in general, not classi-
fied as interferences. The reason might be that appropriate analytical procedures should
provide for the avoidance, elimination or correction of such errors.

It is desirable that a definition of the term interference should also include an indication
of the type and magnitude of error that is produced. Wilson [2] has presented a good summary
of various views on systematic errors. The general tendency in such papers is to restrict
the term interference to systematic errors. Only Maurice and Buijs [3] have suggested that
variation in random errors should also be included. According to Wilson it is not advisable,
however, to include two types of error in one definition; moreover, seldom does a substance
cause an increased random error without generating a systematic error. Therefore, it was
logically concluded that there is virtually no need to extend the concept of interferences
to include increased random errors.
It has to be realized, however, that in those circumstances where concomitants cause an in-
crease in random errors without affecting the accuracy, e.g. in producing increased back-
ground noise, the change in the standard deviation does have implications for the level at
which an interfering effect can be observed with a certain degree of confidence. This is true
for both quantitative and qualitative analysis.

Once it is accepted that the definition of interference should only refer to systematic errors, a decision has to be taken about the threshold value that has to be exceeded before an interference is accepted as such. Three options have been put forward in the literature (see e.g. [2]):
An interfering substance is one that causes a systematic error .....
- ..... greater than some arbitrarily-chosen percentage of the determinand concentration.
- ..... greater than a value that is equal to the standard deviation multiplied by a numerical factor which depends on the confidence limit desired
- ..... of any magnitude.

The first two options can lead to some ambiguity, in particular, if the magnitude of the systematic error or the precision of the results depends on the concentration level of the analyte. On the other hand acceptance of the third option, in which no *a priori* specification of the magnitude of the error is adopted, has the practical disadvantage that almost all concomitants have to be considered as potential interferents. This latter disadvantage gives favour to the first two options, the more so as the ambiguity can be eliminated, by properly stating the application range and by specifying the relevant standard deviation. Which of the two options is to be preferred is to some extent a matter of personal choice, but it also depends on the use that is to be made of the concept of interference. For the selection of a suitable analytical procedure for a well-defined analytical problem the first option has some advantages. It relates interferences directly to the sample, besides, results for such analyses are normally also given on a relative, or percentual basis. If, however, emphasis is laid upon the general characterisation of analytical procedures as such, the preferred definition is the one based on the standard deviation of an unequivocally defined set of analytical results (e.g. data obtained within a laboratory, with the same instrument, on the same day), i.e. the second option is to be preferred.

So far the discussion has tacitly focussed on quantitative analytical procedures. The question might be raised whether the definition should also be applicable to qualitative analyses. However, it is difficult to quantify the magnitude of the systematic error in such cases; for instance, for identification reactions the result is true (positive) or false (zero or negative). A solution for this problem is to define interference in a more general way and to specify it subsequently for quantitative analysis.
Based on these considerations the following definition is proposed:

> *"An interfering substance in analytical procedures is one that, at the given concentration, causes a systematic error in the analytical result. In the case of a quantitative determination this error has to be greater than a value given by the standard deviation of an unequivocally defined set of results obtained with the analytical procedure, multiplied by a numerical value which depends on the level of confidence desired".*

By considerations similar to those used in defining the limit of detection, it is strongly recommended to adopt a value of 3 for this numerical factor as well (this corresponds to a confidence level of 99,86% for a one-sided Gaussian distribution) [4].

To conclude this section on the definition of interferences, it has to be emphasized that the term always refers to the total analytical procedure, starting from decomposition and preparation of the sample to the evaluation of the data. The applicable concentration range should be clearly stated.

CLASSIFICATION

Interferences can be classified according to various principles, for instance:
a) to the properties that are decisive for the mechanism of interference, i.e. physical or chemical interferences [4]. Examples are interferences because of limited spectral resolution of interferent and analyte signals and those due to chemical interaction with the same reagent as the analyte, respectively.
b) to the effect the interferent may have on different elements or compounds that have to be analyzed in the sample, e.g. specific or non-specific interferences [4];
c) to the relation between the effect and the concentration of the analyte, i.e. independent of or proportional to the analyte concentration [1]. An illustrative example, based on the work of Benedetti-Pichler [5], is discussed by Kolthoff et al. [6]. It refers to the precipitation of aluminium as the hydroxide by the addition of ammonia. A constant error was observed as long as a constant volume of ammonia was used owing to the presence of silica which was coprecipitated, whereas with very pure ammonia a much lower but proportional error remained due to the presence of water that stayed behind in the residue even after prolonged ignition.
d) to the kind of mechanism that is involved, i.e. the interfering substance contributes to the result or signal by a mechanism similar to that of the analyte 'SM-interference' and the result or signal is influenced by the interferent by means of a different mechanism 'DM-interference' [1]. Examples will be given in the next sections.

The various aspects on which a classification could be based do not necessarily exclude each other. In fact, each interferent can be classified in a N-dimensional "classification space" where N is the number of aspects taken into consideration. However, this is not a very practical approach; it is much more useful to select only those aspects that give most information about measures to be taken to avoid, eliminate or at least reduce errors.

In a classification based on a) one easily runs into problems in defining precisely what are chemical and what physical aspects. Moreover, although it is always desirable to have some information about the origin of interferences, this particular knowledge gives in most cases little or no specific information how to eliminate the interference. The possibility b) is often not very relevant because, in general, analytical procedures aim at the determination of specified analytes. Classification according to c) is closely related to d). Both may give an indication how one can correct for the effect of the interferent. E.g., if the error is proportional to the analyte concentration, the calibration problem can be solved by the standard addition method or by multivariate calibration techniques [7].

Thus it is concluded that a subdivision into SM- and DM-interferences offers the best basis for classification.

SM-INTERFERENCE is interference by a substance that contributes to the result or signal by a mechanism similar to that of the analyte and which by the given procedure (including the apparatus used) cannot be distinguished from the signal generated by the analyte. This type of interference leads to a systematic error, the magnitude of which is, in general, not dependent on the concentration of the analyte but, of course, is dependent on the concentration of the interferent. With regard to recommendations to adapt procedures in order to eliminate these interferences, it makes sense to distinguish between the interferences that are inherent to the basic procedure and those that are partly due to a limited resolution of the instrument used. An example of an interference inherent to the basic procedure is the spectrophotometric determination of chloride by means of the displacement of thiocyanate from its mercury(II)-complex in the presence of iron(III)-ions. The absorbance of the red iron(III) thiocyanate complex(es) is measured. All ions capable of bringing about a similar displacement reaction, such as other halide ions, will interfere.

In some cases this type of interference can be overcome by the use of masking agents. For example, in the spectrophotometric determination of beryllium as its sulphosalicylate complex aluminium interferes but the complexation of aluminium with the sulphosalicylate ion can be prevented by the addition of EDTA [8]. Similarly, the interference of lead ions in the polarographic determination of thallium (I) can be eliminated by shifting the lead reduction wave to more negative potentials by the addition of EDTA. These two examples show interferences that can be eliminated by chemical means but not by improving the instrumental performance. The second type of interference, that due to limited resolution of the instrument, occurs in the case of atomic spectrometry where, due to a too large band width, the atomic line of an analyte is not completely resolved from an interfering line. Another example may be the colour reaction of an analyte with an organic ligand where both analyte and interferent produce a coloured product that absorbs in the same wavelength region. Although there may be a considerable degree of overlap of the spectra of the two compounds, which will obscure the straightforward determination of the analyte, an increase of the instrumental resolution may reveal structural details in the spectra which may allow the distinction between analyte and interferent.

A third category of SM-interference is the one in which computational methods can be used to get rid of the influence of interferents on the final result. Often used methods comprise multivariate calibration (e.g. see review by Beebe and Kowalski [7]) and deconvolution procedures. Examples of the latter procedure are the correction for peak overlap in X-ray analyses [9] and the calculation of the contribution of the individual components in the case of overlapping chromatographic peaks [10].

In order to differentiate between these three types of SM-interferences the following subdivision is proposed:

* interferences that can be eliminated by means of chemical adaptations of the analytical procedure {SM[chem]};
* interferences that can be eliminated by instrumental improvements {SM[instr]};
* interferences that can be corrected by computational methods {SM[comp]}.

Some interferences can be classified in more than one category. In atomic spectrometry the influence of one element on the determination of another element can often be eliminated either by improving the resolution of the instrument or by the use of computational methods as indicated above. Examples can even be found where an interference can be placed in all three categories. This can be the case with the overlap of chromatographic peaks. Here the composition of mobile or stationary phase can be varied, and the column parameters can be changed in order to get a better resolution, but also mathematical procedures for calculating the individual contributions to the total signal can be employed.

DM-INTERFERENCE is an interference in which the relevant analytical signal is affected by a process based on a different mechanism. For example, in atomic flame absorption spectrometry accompanying components may cause the conversion of the analyte to non-dissociating species. In general, DM-interference leads to a systematic error which depends on the concentration of the analyte: the signal is reproducibly suppressed or enhanced to a certain extent. Hence, the sensitivity is affected and, in several cases, its linearity. It is possible to correct for changes in the sensitivity by the application of standard addition techniques. Sometimes, however, the degree of interference is dependent on the interferent as well. The previously mentioned method of multivariate analysis [7] may solve the problem in such a situation. DM-interferences can also be subdivided into interferences that can be eliminated by changes in the chemical procedure, the instrumental conditions or by means of computational methods. So, in the flame atomic absorption example given above the formation of non-dissociating species may be prevented or reduced by the addition of an excess of another compound ('releaser') or by raising the flame temperature.

All effects caused by concomitants can be summarized under the term *matrix effects*. In some cases the influence of concomitants cannot be ascribed to some single components in particular. Then the terms "overall matrix effect", "global matrix effect" or "non-specific interference" are appropriate. Examples are the influence on the potential of ion-selective electrodes caused by variations of the ionic strength, or the viscosity in the delivery of aliquots of reagents or titrants. The effect of this type of interferences can be eliminated by deliberately adding a large excess of indifferent salt or some viscosity regulating substance, respectively.
Note: In general, instrumental noise which is independent of the sample is not considered as interference!

CONCLUSIONS

It is recommended to restrict the usage of the term interference to effects caused by concomitants present in the original sample or added inadvertently during the analytical procedure and the systematic errors they cause, and to refrain from purely instrumental disturbances. Although it is possible to discuss a more detailed classification for a particular technique such as analytical flame spectroscopy [4], it is not useful to attempt to include all possible cases in one general scheme. Therefore, only a limited number of categories of interferences are suggested. In the description of analytical procedures the possible interferences should be clearly stated, and the kind of interference should be mentioned as well as the magnitude of the error in relation to the concentration of the interferent.

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