W. Horwitz, *S. Afr. J. Chem.*, 2000, **53** (3), 206-212, <http://journals.sabinet.co.za/sajchem/>, <http://ejour.sabinet.co.za/images/ejour/chem/chem_v53_n3_a4.pdf>.
[formerly: W. Horwitz, S. Afr. J. Chem., 2000, 53 (3), 4. (7pp.), <http://ejour.sabinet.co.za/images/ejour/chem/chem_v53_n3_a4.pdf>.]

Reporting Low-level Analytical Data

W. Horwitz*

Center for Food Safety and Applied Nutrition, HFS-500, Food and Drug Administration, Washington. DC 20204. USA

* To whom correspondence should be addressed; Fax:+91-1202-401-7740; e-mail:wxhor@aol.com

Received 5 July 2000; Accepted 26 July 2000

Abstract

Low level measurements - those near, at, or below limits of measurements (specification, quantification, detection) - should be reported as they appear: positive, negative, or zero, as the best estimate of the measured characteristic, usually concentration. The long-term mean of such poor estimates will often provide a surprisingly good estimate of the "true value" from the operation of the law of large numbers. This manner of reporting data near the limits of measurement can be independent of, and adaptable to, any set of agreed-upon definitions and parameters for the concept, including its uncertainty. This proposal is intended to help to standardize the method of reporting low-level analytical data, not to legitimize the data or any conclusions or actions resulting from their use or interpretation.

1. Introduction

The detection limit, determination limit, quantification limit, measurement limit, criterion of detection, and numerous related terms are characteristics of method performance and/or individual and multiple measurements. The important long-term parameters, such as the limit of detection or limit of quantification[1], are estimated by specific measurement statistics. Below this limit not only is the value highly uncertain but the presence of the analyte may be in doubt because a substantial fraction of the

measurements are in the region that overlaps zero. Nevertheless, an estimate of the concentration that may be present and its uncertainty is required if analytical chemistry is to perform its function of setting, monitoring, and enforcing safety, environmental, nutritional, and economic standards. Even worse from an interpretive point of view, governmental organizations are requiring estimates of population exposures to potential toxicants in the environment (e.g., polychlorinated aromatic compounds) and nutritional intakes of critical potentially deficient food components (e.g., folic acid, zinc, selenium) that require measurements below the limit of reliable measurements.

The development of a harmonized set of statistical and analytical conditions and vocabulary for the concept of limit of measurements is the subject of projects and activities within IUPAC and other standardization organizations. The subject has been extensively discussed in the literature[2,3]. However, the manner of reporting data near the limits of measurements can be independent of and adaptable to any set of agreed-upon definitions and parameters for the limits.

2. Alternatives

Some common practices for reporting low-level results include:

(1) Assigning a value of 0 to values whose reality is in doubt;

(2) Evading the issue by using deliberately ambiguous terms such as “less than” a measurement limit, however defined, or “not detected”;

(3) Assigning a fractional value such as ½, ⅓, or 1/sqr(2) of the measurement limit, however defined;

(4) Assuming a distribution of values suggested by the reported numerical values related to the test of interest, extrapolating this distribution into the region below the limit of measurement, and taking as the reported value a critical point equivalent to a 1-tail 1%, 5%, or 10% percentile point.

All of these and other practices attempt to compensate for the loss of information inherent in the highly uncertain reference point implied by the "limit of measurement” and related terms.

Any of these procedures may or may not be appropriate, depending upon the particular set of circumstances from which the data were obtained and the use to which

the data will be put. The assumptions made in reporting individual low-level results are usually invisible or unknown to the analyst or operator who makes the initial decision as to what value or conclusion is to be reported to the laboratory director for interpretation, action, or inaction. Sometimes, with automatic sampling and measurement instruments, computer programs and algorithms perform the calculations, make the decision, and send the conclusion to the laboratory director for action.

The first two procedures (1) and (2) are the simplest and are favoured by analysts. They accommodate the practical situation where the chemist suspects an analyte may be present but is not very positive about it. The matter may be disposed of by an unequivocal statement of "absent" or "not detected" when in doubt, or by a completely ambiguous but truthful statement of "less than" an arbitrary limit of measurement to which the analyst is willing to testify unequivocally. These statements permit the analyst to be "on both sides of the fence."

The difficulty with these two procedures is that they are inefficient and wasteful. Considerable resources have been expended in the examination of each test sample with negligible output. Any such output is necessarily ambiguous because a "less than" or "not detected" report cannot be taken as equivalent to "absent." It merely means that any potential signal cannot be distinguished from background. In presenting such results, the analyst has given a conclusion, not data. These statements cannot be handled statistically and therefore as data they must be discarded.

The assignment of an arbitrary factor (3) allows the analyst to assume an intermediate position - the analyte is not present in sufficient quantity to permit assignment of a specific value, yet it must be present. Therefore an intermediate result is presented somewhere in between, typically one-half of the estimated measurement limit. Although such an assignment is undoubtedly intended to provide a value halfway between the measurement limit and zero, practically the result given as half or some other fraction of the limit is in the same units as the limit. This results in a reported value in the same decade as the limit rather than as a value several decades lower than might have been intended or implied. This approach attempts to reach a compromise between optimistic and pessimistic values, but the effective assignment often desired is a value that would approximate the biological effect of the analyte. Such effects are usually assumed to decrease exponentially with decreasing concentration. If the

consequence of the assignment is to permit toxicologists to estimate biological effects at low level exposures, a linear extrapolation does not mimic the biological consequences of exponential dose-response curves (3).

The extrapolation of a distribution function into the unmeasurable region (4) assumes the existence of a specific population of interest having certain measurable characteristics that can be modelled by a distribution function extended into the "unmeasurable" region. The characteristic most frequently measured in chemical analysis is concentration, and the distributions most frequently assumed are normal or lognormal. Although analytical data (estimates) often appear to be lognormal, this may be an artifact of insufficient data or the frequent presence of outliers on the high side. Because of the lack of information about the variability of observations at low levels, it is impossible to make a goodness-of-fit test of the distribution. Therefore an assumption of normality for the parent population is often the only reasonable choice. A problem with this solution is that it requires enough data from the same population above the limit of measurement to fit a distribution to the estimates. It does not and cannot apply to the single data points obtained from routine examination of single random test portions of a laboratory sample.

3. Recommendation

Although it may be difficult to implement in practice, the solution with the least objectionable features is to report values as they are measured transformed to a concentration, despite the difficulties, whether the values are positive, negative, or zero. This may appear to be not much different from guessing, but this is the current practice anyway. Then, if the problem is to obtain the best estimate of a population average, the law of large numbers can be relied upon to provide the best estimate that the state of the art can provide. For single analyses, the best guess will be just as reliable as the censoring of values that exists at present, and in the long run the agglomeration of values will provide a practical view of the variability of measurements in the region where measurements are problematic.

This recommendation of reporting uncensored values as they are generated is also the preferred solution of the many theoretical treatments[4] of the limit of measurement problem from Gilbert and Kinnison[5] to Rocke and Lorenzato[6]. The

Analytical Methods Committee of the Royal Society of Chemistry of the United Kingdom recently reviewed the subject and arrived at the same conclusion[7].

The most frequent objection to this recommendation is the statement that concentrations cannot be negative. Although physically true, measurements must be treated as a statistical distribution of the intensities of signals that may be positive (e.g.,emission spectroscopy), negative (e.g., absorption spectroscopy), or zero (e.g., balancing electrical currents or light intensities). Electrochemists have no difficulties in working with positive and negative EMFs transformed to concentrations. A practical example of a potentially less than zero concentration occurs when chloroform preserved with alcohol is used as an extracting solvent: if the original chloroform is used as the zero absorbance background and the alcohol is removed along with the analyte during an aqueous extraction, the reagent blank analysis may show a lower (negative) scale reading (which may then be transformed to an apparent negative concentration for use as a correction factor) than the parent solvent. Furthermore, statistically, a truly zero blank can only be determined from the averaging of positive, negative, and zero concentrations; if negative values are censored, the blank will exhibit a positive bias.

Despite all warnings that these low-level values may be illusionary, that they may be based upon estimates taken from measurements that are not within the usual boundaries of statistical control (limiting mean, stable standard deviation), and that they may be subject to unknown and possibly high systematic errors and to random errors of a rnagnitude equal to the value itself, the exigencies of the situation may still require reporting of a "best estimate" accompanied by the uncertain uncertainty. This document is intended to provide uniform instructions for supplying such a poor "best estimate," when the supporting organization requires such an uncertain value and takes full responsibility for actions resulting from potential misuse of unsupportable scientific measurements. This proposal is intended to help to standardize the method of reporting low-level analytical data, not to legitimize the data or any conclusions or actions resulting from their use.

This proposal is illustrated as follows:

A recommendation to report values as they appear, including apparently negative values (the blank is greater than the measurement), may appear surprising because in reality concentrations cannot be negative. However, it is signals that are measured and

estimated concentrations that are obtained through the calibration function. Furthermore, a true zero signal would be expected to have an equal number of positive and negative measurements for a symmetrical, statistical distribution.

The following example based upon the American Society for Testing and Materials Designation D 4210-83 "Standard Practice for Intralaboratory Quality Control Procedures and a Discussion on Reporting Low-Level Data" illustrates the situation. Consider the following four different ways (measured values, heavily censored, replacement of "<3" by (½) x 3 and negative results censored) of reporting and interpreting a single set of data. Also note that any single value taken at random from any of the four columns, if used for the calculation of the total analyte content of the parent population, will provide an interpretation or value that will grossly deviate from the "best estimate".

	Measured values	**Heavily censored**	**Replacement of "<3" by (½) x 3**	**Negative results censored**
	2 µg	<3 µg	1.5 µg	2 µg
	-2	<3	1.5	0
	-1	<3	1.5	0
	4	4	4	4
	3	3	3	3
	-3	<3	1.5	0
	1	<3	1.5	1
	-1	<3	1.5	0
	0	<3	1.5	0
	2	<3	1.5	2
Mean	0.5	?	1.9	1.2
Std error	0.72	?	0.28	0.47

These data may be interpreted readily. The first column has confidence bounds for the mean that overlap zero and consequently the analyte may be absent; also note that the variability is greater than the mean, indicating a potentially indeterminate situation. Nevertheless, the 0.5 µg mean is the "best estimate" even though it is highly

uncertain. The second column may be rejected outright as uninterpretable. The arbitrary assignments of the third and fourth columns provide the highest means and the smaller standard errors, but only as a result of arbitrary, unsupportable adjustments.

References

1 L. A. Currie, *Pure and Appl. Chem.,* 1995, **67,** 1699-1723.

2 L. A. Currie. Editor, Detection in Analytical Chemistry, ACS Symposium Series 361, American Chemical Society, Washington DC (1988).

3 L. A. Currie and W. Horwitz, *Analusis*, 1994, **22,** M24-M26.

4 A. Goldstein, *Biostatistics an Introductory Text,* Macmillan Company, New York. (1965)

5 R. O. Gilbert and R. R. Kinnison, *Health Physics,* 1981, **40,** 377-390.

6 D. M. Rocke and S. Lorenzato, *Technometrics,* 1995, **37,** 176-184.

7 Analytical Methods Committee, *Analyst,* 1997, **122,** 495-497.