

USE OF TOLERANCES IN THE
DETERMINATION OF ACTIVE INGREDIENT
CONTENT IN SPECIFICATIONS FOR PLANT
PROTECTION PRODUCTS

(Adopted on March 3rd Meeting 2005, ECPA – SEG)

CONTENTS

PREFACE

SUMMARY

INTRODUCTION

FORMAT OF SPECIFICATIONS

QUALITY CONTROL

STATISTICAL CONSIDERATIONS

PRODUCTS CONTROL

ACCEPTANCE OR REFUSAL OF A PRODUCT IN CASE OF DISPUTE

APPENDICES

REFERENCES

USE OF TOLERANCES IN THE DETERMINATION OF ACTIVE INGREDIENT CONTENT IN SPECIFICATIONS FOR PLANT PROTECTION PRODUCTS

PREFACE

CropLife International is the trade association of the worldwide plant science industry.

To facilitate trade in plant protection products specifications for products are used to satisfy customers and official control laboratories on the quality of a pesticide product and to act as a means of quality control for the manufacturer. The active ingredient content of a product is obviously an important component of any specification and analytical methods are available for the determination of active ingredient. However, the conditions under which methods of analysis are undertaken will vary from laboratory to laboratory and it is therefore necessary to apply appropriate tolerances to the results obtained.

This monograph has been prepared by CropLife International to provide guidance for analysts and includes worked examples in determining whether a product complies with a specification or not.

SUMMARY

This monograph summarises the definitions used to specify the active ingredient content of plant protection products and recommends the adoption of the following statement proposed by FAO [Reference 1]:

The active ingredient content of technical materials should be expressed as:

"The [ISO common name] content shall be declared (not less than ... g/kg) and, when determined, the mean measured content shall not be lower than the declared content."

The active ingredient content of technical concentrates and formulated pesticides should be expressed as:

"The [ISO common name] content shall be declared (g/kg or g/l at $20 \pm 2^\circ\text{C}$,) and, when determined, the mean measured content shall not differ from that declared by more than the following tolerances:"

Table 1: Tolerances defined in the FAO/WHO manual

Declared content in g/kg or g/l at $20 \pm 2^\circ\text{C}$	Tolerance
up to 25	$\pm 15\%$ of the declared content for "homogeneous" formulations (EC, SC, SL, etc.), or $\pm 25\%$ for "heterogeneous" formulations (GR, WG, etc.)
above 25 up to 100	$\pm 10\%$ of the declared content
above 100 up to 250	$\pm 6\%$ of the declared content
above 250 up to 500	$\pm 5\%$ of the declared content
above 500	± 25 g/kg or g/l
Note In each range the upper limit is included	

Compliance of a consignment of a technical or formulated product with any specification of this type is based on chemical analysis and, owing to the occurrence of both random and systematic errors, the result obtained by the manufacturer and customer will invariably differ. Analytical methods therefore include a statement on the expected precision of results, but such statements can lead to confusion unless their significance is fully understood. This monograph defines precision in terms of both repeatability, that is, within-laboratory variations, and reproducibility, that is, between laboratory variations. The statistical criteria for the acceptance or rejection of results obtained within or between laboratories are described and illustrated by

worked examples. The approach used is in line with those recommended by accepted national and International Standards Authorities, e.g. DIN/ISO.

INTRODUCTION

Use of tolerances in the determination of active ingredient content in specifications for plant protection products

The expression of tolerances for the active ingredient content of plant protection products is a matter of agreement between the parties concerned and, in principle, can be expressed in different ways, provided that technical and statistical considerations have been taken into account. In practice, however, the different methods used to express tolerances can lead to confusion and thus it is desirable to devise a standard approach as guidance to interested parties.

Compliance of a product with the active ingredient clause of its specification is based on chemical analysis and the correct statistical interpretation of the data is therefore of fundamental importance. Again, it is desirable to standardise the statistical approach employed.

This monograph, which is in line with the recommendations of accepted national and International Standards Authorities, e.g. DIN/ISO 5725 presents CropLife International's guidance for both the expression of tolerance and the statistical evaluation of analytical data needed to confirm compliance with a given specification.

FORMAT OF SPECIFICATIONS

As mentioned previously, the active ingredient content of a product is determined analytically for purposes of quality control. Owing to the occurrence of random error, identical values are normally not obtained on repeating the determination, the variation being a measure of the method's precision. In addition to these purely random errors, analytical results can obtain a positive or negative bias and this will

affect the accuracy of the determination. For these reasons, the true active ingredient content of a sample cannot be determined exactly.

In order to minimize the effects of random error and bias, it is essential that the parties concerned agree to use the same analytical method and, where feasible, the same analytical reference standards traceable to identical primary reference materials. It is then possible to introduce the term “defined true value“. This is the figure which the mean of single results obtained in m different laboratories approaches, when m approaches infinity.

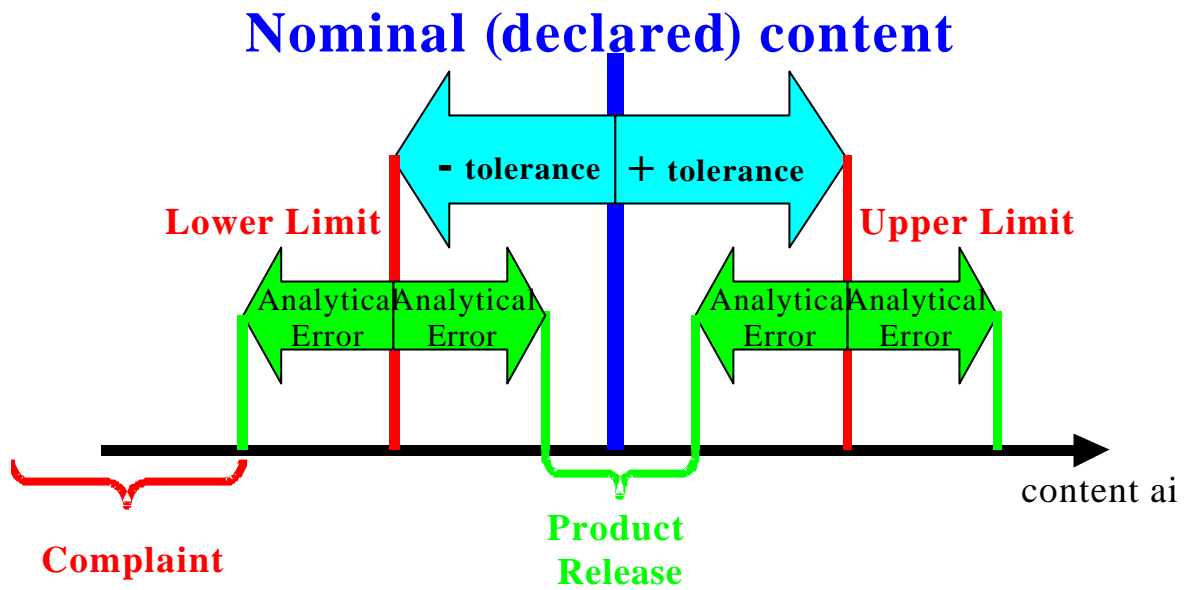
With a finite number of analyses, however, the “defined true value“ cannot be determined exactly and it is therefore not possible to declare an exact active ingredient content for a product. It is, nevertheless, possible to define a range which includes the “defined true value“ with a mathematically defined degree of probability.

From this it follows that the limits of the declared range must be taken as the limits for the defined true value.

Thus everyone concerned with the manufacture or control of plant protection products has to incorporate an allowance for analytical error in their tolerance clause (see Figure 1):

- a) The manufacturer must guarantee that the defined true value is within the declared limits. This means that the limits for internal production control should normally be set narrower than the guaranteed limits by the amount of analytical error.
- b) The customer or any official control laboratory can complain about inferior quality only in those cases in which analytical results are outside the guaranteed range by more than the amount of this analytical error.

Figure 1 : Setting of tolerances for the analytical errors of manufacturer and customer formulated products and technical concentrates



1.1 Technical Active Ingredients (TC)

For technical active ingredients it is usual for only minimum content, rather than tolerance range, to be declared in specifications.

The minimum a.i. content is usually assigned a minimum value based on multi-batch analysis of manufacturing grade material. All batches of technical grade material must comply with this minimum a.i. content. A batch or consignment is released if the mean analytical value is greater than this minimum value.

Thus paragraph 3.3.2 of the FAO-Specifications reads:

*The active ingredient content of technical materials should be expressed as:
"The [ISO common name] content shall be declared (not less than ... g/kg) and, when determined, the mean measured content shall not be lower than the declared content."*

Adoption of this sentence for general use in product specifications is also recommended by this monograph.

1.2. Formulations and technical concentrates

For technical concentrates and formulations both an upper and a lower limit are declared in specifications. FAO manual gives the following recommendation:

*The active ingredient content of technical concentrates and formulated pesticides should be expressed as:
"The [ISO common name] content shall be declared (g/kg or g/l at $20 \pm 2^\circ\text{C}$,) and, when determined, the mean measured content shall not differ from that declared by more than the following tolerances:" – see Table 1 above for tolerance range examples*

It is possible to look at the tolerance range of formulated products in two different ways:

a) In the formulation manufacturing process, a technical material is used whose content is not exactly known because of analytical error described previously. Furthermore, there is a manufacturing error which covers all measuring and weighing errors of all components used plus any inhomogeneity of the product. This manufacturing error is unavoidable even when using good technical equipment.

b) The a.i. content of a formulation is controlled by chemical analysis of the final product manufactured. The analytical error of the method used for product analysis can therefore be used to determine the minimum width of the tolerance range

There may be justifiable reasons, especially for innovative products or products with very low concentrations of active ingredient, to define tolerances specifically for the product by using either of methods a) or b) and to declare them in a product specification. However as a general rule the recommendation of this monograph is to simplify the process by making use of the tolerances defined by those given in the FAO / WHO manual (Table 1). These tolerances described in the FAO/WHO manual are presently used widely in industry as a standard.

It is important, to note that the manufacturing aim point or target value for a formulated product is always the declared content and that this target needs to be maintained over the duration of entire production campaign(s).

2. STATISTICAL CONSIDERATIONS

2.1 Definitions

Repeatability r is a quantitative term for the size of random errors which occur, if one qualified person in one laboratory using one set of equipment analyses the same sample several times, independently and under standardized conditions.

Repeatability is defined as that difference between 2 single results obtained in the described way, which under statistical conditions is exceeded only in one of 20 cases (i.e. 95% confidence). For a large number of single determinations, it is calculated according to formula (2.1.1).

$$2.1.1 \quad r = 1.96s_r\sqrt{2} \text{ !Syntaxfehler, 2}$$

s_r = standard deviation under repeatability conditions

The factor 1.96 increases for small numbers of single determinations. For 10 determinations it is 2.26

Reproducibility R is a quantitative term for the size of random errors which occur, if different persons in different laboratories using different sets of equipment analyse the same sample once by application of the same analytical procedure.

Reproducibility is defined as that difference between 2 single results obtained in the described way, which under statistical conditions is exceeded only in one of 20 cases (i.e. 95% confidence). For a large number of single determinations, it is calculated according to formula (2.1.2).

$$2.1.2 \quad R = 1.96 s_R \sqrt{2}$$

s_R = standard deviation under reproducibility conditions

Before R can be calculated the results of the different laboratories must be checked carefully for biases and/or outliers using CIPAC guidance documents. (Reference 2)

3.2 Criteria for the acceptance of analytical results obtained in 1 laboratory

DIN/ISO 5725-6 (Reference 3) recommends the following procedure:

If 2 single results are obtained by independent repetition (repeatability conditions) of the prescribed procedure, and the difference between these values is less than or equal to r, the mean result should be accepted.

If the difference is greater than r, both results must be considered as suspect. It is then necessary to obtain 2 additional test results. If the range ($x_{\max} - x_{\min}$) of the four results is less than the critical range at the 95% probability level $CR_{0.95}(4)$, then the arithmetic mean of the four test results should be reported as the final quoted result.

$$CR_{0.95}(n) = f(n) s_r$$

Values for the factor f(n) for different number of analytical results can be taken from Table 1 in appendix 1.

If the range for the four results is greater than the critical range $CR_{0.95}(4)$, DIN/ISO5725 recommends to report the median as final result. However, since in this case method performance is significantly less than achievable precision s_r defined by the data from the method validation, this monograph recommends to discard these

values and to repeat the determination after a careful analysis of the reason behind the method failure.

PRODUCTS CONTROL

4.1 From the manufacturer's viewpoint

When a manufacturer controls the quality of his product, he may consider the product as complying with a given specification, if the difference between the analytical result and the limit of the range given in the product specification is greater than his analytical error.

4.2 From the customer or official control laboratory's viewpoint

These parties also have to allow for their analytical errors. The rejection of a product as non compliant with its specification is only justified, if the analytical result is outside of the specified range by more than the control laboratories analytical error.

In both cases the determination of the analytical error and the needed level of certainty (confidence level) is crucial.

This monograph recommends the following procedure:

A level of 50% of the tolerance allowed by the FAO specification is set as the general range of analytical error. This corresponds very well with the range that results from twice the repeatability standard deviation of CIPAC collaborative studies. (see Appendix 2). However, if either party has information, that its analytical error is on a different level, it may as an alternative set a range of $2 \times s_r$ as analytical error, taking s_r from its own data on the validation of the analytical method.

5. ACCEPTANCE OR REFUSAL OF A PRODUCT IN CASE OF DISPUTE

A case of dispute is every case in which supplier and customer, after checking back their respective results, cannot agree on the quality of a product. Here, the following procedure according to DIN/ISO5725-6 should be followed:

Both laboratories get in contact and check the analytical method, as well as the equipment, for any deviations from standard condition, after which the analysis (above) is repeated. Special care should be given to the identity of reference substances (analytical standards) used in the determination and to sampling procedures. It is urgently recommended, that both laboratories agree on the use of analytical standards that can be traced to the same primary reference substance, i.e. from the same supplier and – if possible – from the same batch. Similarly sampling procedures should be compared and if possible analytical samples exchanged between laboratories. Experience has shown differences in the reference substances and the analytical samples as – after deviations in the analytical method - the second most significant sources of disputed results.

APPENDICES

Appendix 1

Table 1 – Critical range factors, $f(n)$

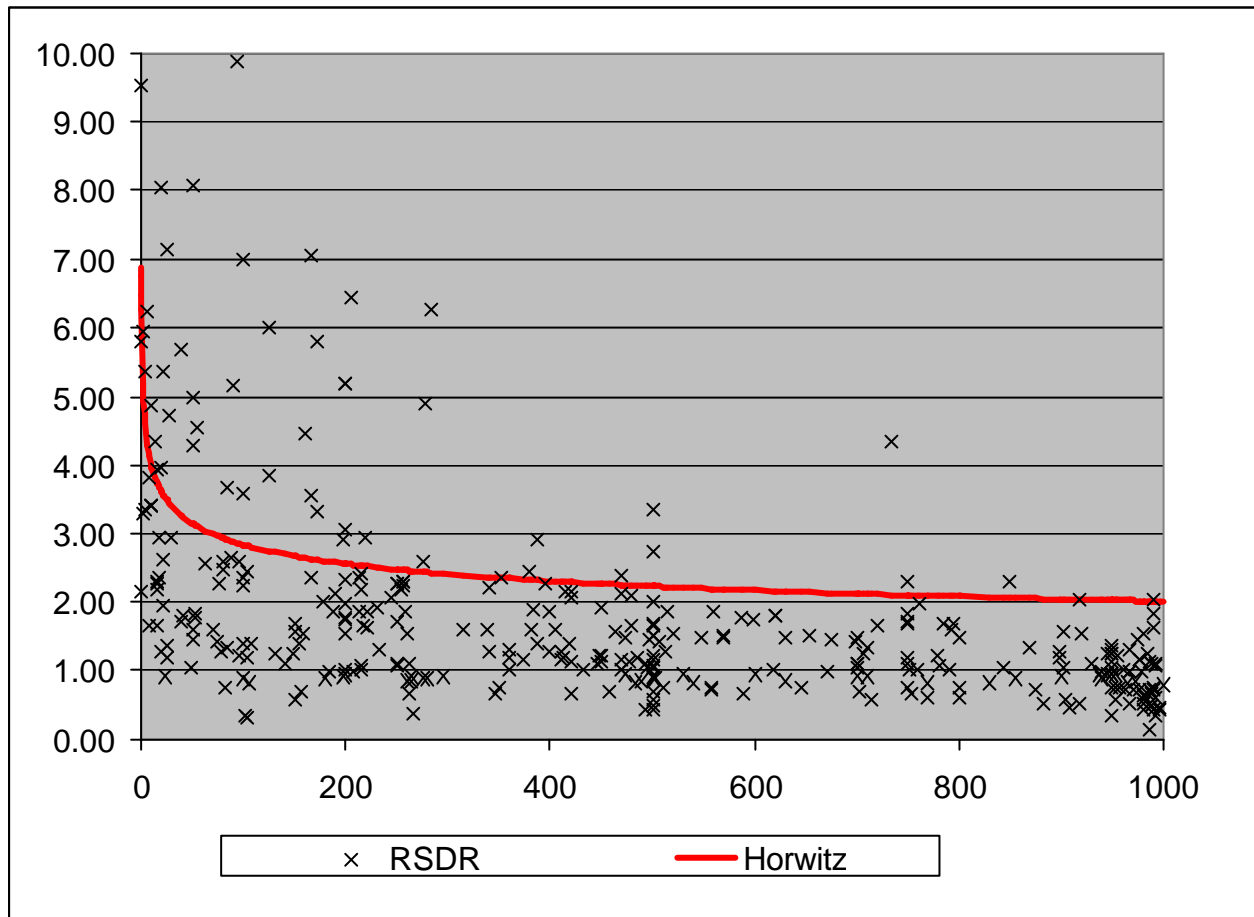
<i>n</i>	<i>f(n)</i>	<i>n</i>	<i>f(n)</i>	<i>n</i>	<i>f(n)</i>
2	2.8	17	4.9	32	5.3
3	3.3	18	4.9	33	5.4
4	3.6	19	5.0	34	5.4
5	3.9	20	5.0	35	5.4
6	4.0	21	5.0	36	5.4
7	4.2	22	5.1	37	5.4
8	4.3	23	5.1	38	5.5
9	4.4	24	5.1	39	5.5
10	4.5	25	5.2	40	5.5
11	4.6	26	5.2	45	5.6
12	4.6	27	5.2	50	5.6
13	4.7	28	5.3	60	5.8
14	4.7	29	5.3	70	5.9
15	4.8	30	5.3	80	5.9
16	4.8	31	5.3	90	6.0
				100	6.1

NOTE: The critical range factor $f(n)$ is the 95% quantile of the distribution of $(x_{\max} - x_{\min})/s$ where x_{\max} and x_{\min} are the extreme values in a sample of size n from a normal distribution with a standard deviation s .

Appendix 2

Comparison of the Horwitz value with historical CIPAC collaborative method data

Plot of Experimental CIPAC RSD_R versus Active ingredient content



REFERENCES

1. Manual on Development and Use of FAO and WHO Specifications for Pesticides. First Edition Rome 2002
2. CIPAC Guidelines for Collaborative Study Procedures for Assessment of Performance of Analytical Methods, CIPAC 3426, section 7.1.3 “outliers”.
3. ISO 5725-6, Accuracy (trueness and precision) of measurement methods and results – part 6, use in practice of accuracy values. 1994-12-15
4. Boyer, K.W. Horwitz, W and Albert, R Analytical Chemistry 57, 454-9, (1985).