METRICA
METRology Institutional CAtalog

ISTITUTO NAZIONALE DI RICERCA METROLOGICA
Repository Istituzionale

Risk of false decision on conformity of a multicomponent material when test results of the components' content are correlated

This is the author's submitted version of the contribution published as:

Original
Risk of false decision on conformity of a multicomponent material when test results of the components' content are correlated / Kuselman, Ilya; Pennecchi, Francesca R; da Silva, Ricardo J N B; Hibbert, D Brynn. - In: TALANTA. - ISSN 0039-9140. - 174:(2017), pp. 789-796-796. [10.1016/j.talanta.2017.06.073]

Availability:
This version is available at: 11696/57080 since: 2020-11-26T15:32:48Z

Publisher:
Elsevier

Published
DOI:10.1016/j.talanta.2017.06.073

Terms of use:

This article is made available under terms and conditions as specified in the corresponding bibliographic description in the repository

Publisher copyright

(Article begins on next page)

28 December 2024

Elsevier Editorial System(tm) for Talanta
Manuscript Draft

Manuscript Number:

Title: Risk of false decision on conformity of a multicomponent material when test results of the components' content are correlated

Article Type: Research Paper

Keywords: Conformity assessment
Multicomponent material
Measurement uncertainty
Risk of false decision
Correlated test results
Case study

Corresponding Author: Dr. Ilya Kuselman, D.Sc.

Corresponding Author's Institution: Independent Consultant on Metrology

First Author: Ilya Kuselman, D.Sc.

Order of Authors: Ilya Kuselman, D.Sc.; Francesca R Pennecchi, PhD; Ricardo J. N. B. da Silva, Prof. ; D. Brynn Hibbert, Prof.

Abstract: The probability of a false decision on conformity of a multicomponent material due to measurement uncertainty is discussed when test results are correlated. Specification limits of the components' content of such a material generate a multivariate specification interval/domain. When true values of components' content and corresponding test results are modelled by multivariate distributions (e.g. by multivariate normal distributions), a total global risk of a false decision on the material conformity can be evaluated based on calculation of integrals of their joint probability density function. A total specific risk can be evaluated as the joint posterior cumulative function of true values of a specific batch or lot lying outside the multivariate specification domain, when the vector of test results, obtained for the lot, is inside this domain. It was shown, using a case study of four components under control in a drug, that the correlation influence on the risk value is not easily predictable. To assess this influence, the evaluated total risk values were compared with those calculated for independent test results and also with those assuming much stronger correlation than that observed. While the observed statistically significant correlation did not lead to a visible difference in the total risk values in comparison to the independent test results, the stronger correlation among the variables caused either the total risk decreasing or its increasing, depending on the actual values of the test results.

Opposed Reviewers:

Cover letter

Professor Jean-Michel Kauffmann,

Talanta, Editor 21 May, 2017

Dear Prof. Kauffmann,

Please find attached the manuscript by Ilya Kuselman, Francesca R. Pennecchi, Ricardo J.N.B. da Silva and D. Brynn Hibbert, titled "Risk of false decision on conformity of a multicomponent material when test results of the components' content are correlated", which we would like to publish in Talanta in continuation of our position paper (Talanta 164 (2017) 189-195).

Novelty Statement: A statistical procedure is developed for evaluation of a total risk (due to measurement uncertainty) of a false decision on conformity of a multi-component material when test results of the components' content are correlated. Correlation among test results complicates conformity assessment. In a case study of correlated test results for four components under control in a drug, it is shown that strong correlation may lead either to decreasing or increasing of the total risk, depending on the actual test results.

This research is supported in part by the International Union of Pure and Applied Chemistry (IUPAC Project 2016-007-1-500).

Declaration of interest: There is no any actual or potential conflict of interest of any author.

Submission declaration and verification: The work described has not been published previously, it is not also under consideration for publication elsewhere. The publication in Talanta is approved by all the authors.

Best regards,

Dr. Ilya Kuselman,
the manuscript corresponding author,
ilya.kuselman@gmail.com
ilya.kuselman@bezeqint.net

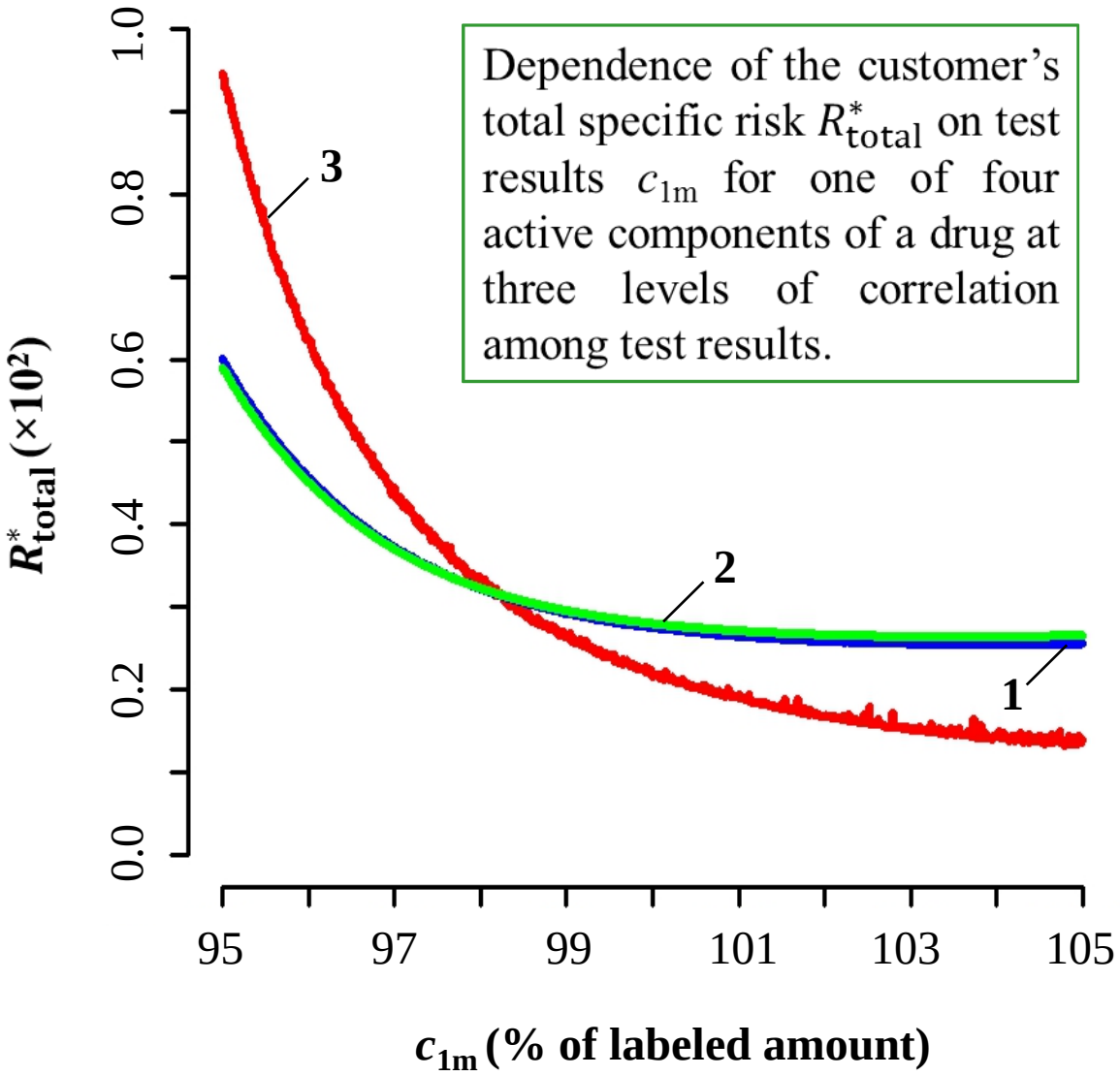
Novelty Statement

A statistical procedure is developed for evaluation of a total risk (due to measurement uncertainty) of a false decision on conformity of a multi-component material when test results of the components' content are correlated. Correlation among test results complicates conformity assessment. In a case study of correlated test results for four components under control in a drug, it is shown that strong correlation may lead either to decreasing or increasing of the total risk, depending on the actual test results.

HIGHLIGHTS

- Correlation among test results of a multicomponent material complicates its conformity assessment.
- A statistical procedure for evaluation of a total risk of false decision on the drug conformity is developed.
- A case of correlated test results for four components under control in a drug is studied.
- Strong correlation may lead either to decreasing or increasing of the total risk, depending on the actual test results.

*Graphical Abstract (for review)



*Manuscript
Click here to view linked References

Risk of false decision on conformity of a multicomponent material when test results of the components' content are correlated

Ilya Kuselman[a,*], Francesca R. Pennecchi[b], Ricardo J. N. B. da Silva[c], D. Brynn Hibbert[d]

[a] *Independent Consultant on Metrology, 4/6 Yarehim St., 7176419 Modiin, Israel*

[b] *Istituto Nazionale di Ricerca Metrologica (INRIM), Strada delle Cacce 91, 10135 Turin, Italy*

[c] *Centro de Química Estrutural, Faculdade de Ciências da Universidade de Lisboa, Edifício C8, Campo Grande, 1749-016 Lisboa, Portugal*

[d] *School of Chemistry, UNSW Sydney, Sydney NSW 2052, Australia*

---

* Corresponding author. Tel.: +972-50-6240466

E-mail address: ilya.kuselman@bezeqint.net (I. Kuselman)

4/6 Yarehim St., Modiin, 7176419 Israel

Abstract The probability of a false decision on conformity of a multicomponent material due to measurement uncertainty is discussed when test results are correlated. Specification limits of the components' content of such a material generate a multivariate specification interval/domain. When true values of components' content and corresponding test results are modelled by multivariate distributions (e.g. by multivariate normal distributions), a total global risk of a false decision on the material conformity can be evaluated based on calculation of integrals of their joint probability density function. A total specific risk can be evaluated as the joint posterior cumulative function of true values of a specific batch or lot lying outside the multivariate specification domain, when the vector of test results, obtained for the lot, is inside this domain. It was shown, using a case study of four components under control in a drug, that the correlation influence on the risk value is not easily predictable. To assess this influence, the evaluated total risk values were compared with those calculated for independent test results and also with those assuming much stronger correlation than that observed. While the observed statistically significant correlation did not lead to a visible difference in the total risk values in comparison to the independent test results, the stronger correlation among the variables caused either the total risk decreasing or its increasing, depending on the actual values of the test results.

Keywords:

Conformity assessment
Multicomponent material
Measurement uncertainty
Risk of false decision
Correlated test results
Case study

1. Introduction

Risk of false decision on conformity of a multicomponent material due to measurement uncertainty was recently discussed in the position paper of the IUPAC task group [1]. There are several kinds of such risk. The probability of accepting a batch or lot of the material, when it should have been rejected, is named 'consumer's risk', whereas the probability of falsely rejecting the lot is the 'producer's risk'. For a specified lot, they are referred to as the 'specific consumer's risk' and the 'specific producer's risk', R_{ci}^{*}, for *i*-th particular component of the material under control, $i = 1, 2, \ldots, n$, respectively. The risks of incorrect conformity assessment of a lot randomly drawn from a statistical population of such lots are the 'global consumer's risk' and the 'global producer's risk', R_{ci}, for *i*-th particular component, since they characterize the material production globally [2]. Even if conformity assessment for each *i*-th component of a material is successful (i.e. the particular specific R_{ci}^{*} or global R_{ci} risks are small enough), the total probability of a false decision concerning the material as a whole (the total specific R_{total}^{*} or global R_{total} risks) might still be significant. A scheme summarizing the terminology used here is shown in Fig. 1.

Fig. 1

A model of the total risk for the case of independent quantities has been formulated on the basis of the law of total probability [3]. Using this model, the total risk can be evaluated as a combination of the particular risks of conformity assessment of the material components. For a more complicated task, i.e. for an increased number of components of the material under control, the total risk increases. Examples for three and four components ($n = 3$ and 4, respectively) are given below in the Appendix. General expressions for evaluating the total global consumer's risk

for any number n of the material components are also provided [1]. The counterpart models for the total producer's risk are easily obtainable as well.

However, the problem is that the assumption of independence of true values of each component content c_i from other(s) and independence of corresponding measurement/test results $c_{i\mathrm{m}}$ is not always acceptable. Correlation of true values may be caused by stoichiometry of native compounds, or by technological conditions in production of materials, etc. In their turn, test results may be correlated because of correlation of true values, and/or due to systematic effects in the measurement/test process, common for two or more analytes.

The task of evaluating the total risks for correlated quantities is detailed in the present paper, based on a case study of test results of NyQuil tablets. This cold/flu medication contains four active components: 1) acetaminophen (APAP) as a pain reliever and fever reducer; 2) dextromethorphan hydrobromide (DEX) as a cough suppressant; 3) doxylamine succinate (DOX) as an antihistamine and hypnotic; and 4) phenylephrine hydrochloride (PE) as a nasal decongestant [4]. However, there are publications which have claimed that the last component (PE) is no more effective than placebo [5]. Therefore, the case study is performed for both scenarios: when particular risks of conformity assessment of four and thee only (without PE) components contribute to the total risks. To assess influence of the correlation of the test results on the evaluated total risk values, they are compared with those calculated for independent test results by formulas (A.1) – (A.4) shown in the Appendix, and also with the values obtained supposing much stronger correlation than that observed.

2. Experimental

2.1. Specification and acceptance limits

The assay test lower and upper specification limits, lsl_i and usl_i, for the product release for each active component i = 1, 2, 3, 4 are 95.0 - 105.0 % of the labeled amount l_i, respectively. The labeled amounts are the following: l_1 = 325 mg for APAP, l_2 = 10 mg for DEX, l_3 = 6.25 mg for DOX, and l_4 = 5 mg for PE, per tablet (775 mg on average). The acceptance limits of test results coincide with the specification limits in this study.

2.2. Test method

2.2.1. Sample preparation

A sample of the tablets is weighted, dissolved in solution of phosphoric acid and acetonitrile in water on a magnetic stirrer plate, and then centrifuged. An aliquot is transferred into an autosampler vial for determination of the low-dose active components – DEX, DOX and PE. Another diluted aliquot is used for determination of the high-dose active component – APAP.

2.2.2. Standard solution preparation

The stock standard solution containing the four active components, in concentrations higher than those in the sample solutions, is prepared from the USP reference standards [6], produced also by Merck [7].

The working standard solution is prepared from the stock standard solution by dilution to bring the analyte concentrations to the values as in the sample solutions. Two independent working standards solutions are prepared according to the USP <621> chromatography

requirements [8]: one for quantitation of the analyte content, and the second one for the system suitability control.

2.2.3. Separation, quantification and calculation

Separation and quantification of the analytes are performed using HPLC System with diode-array ultra violet detector (DAD-UV) or multichannel detector and column (C18) heater. Blank solution used is phosphoric acid and acetonitrile in water in concentrations as in a sample solution. After injection of the blank solution, the first working standard solution is injected five times, followed by injection of the second working standard solution for determination of system suitability by USP <621>. Then the sample solutions are injected. At least one additional injection of first working standard solution is performed after every 6 sample injections and at the end of the sample sequence.

All replicates of the first working standard solution (at least 6) are averaged and used for calculation of a test result $c_{i\mathrm{m}}$:

$$c_{i\mathrm{m}} = \frac{A_{i\mathrm{s}}}{A_{i\mathrm{ws}}} \frac{(\gamma_i f) V_\mathrm{s} D_\mathrm{s}}{n_\mathrm{t} l_i} \times 100\ \%, \qquad (1)$$

where $A_{i\mathrm{s}}$ is the *i*-th component/analyte peak area of the sample solution; $A_{i\mathrm{ws}}$ - the averaged *i*-th analyte peak area of the first working standard solution; γ_i - the *i*-th analyte mass concentration in the first working standard solution (the analyte mass, mg, per volume, mL, taking into account its dilution factor); f = 1 is the concentration factor, not changing the test result value, but indicating a comparison of the first and the second working standards, used below in section 2.3 for the measurement uncertainty evaluation according to the Eurachem/CITAC Guide [9]; V_s and

D_s are the sample volume, mL, and its dilution factor, respectively; n_t is the number of tablets in the sample (the sample mass divided by the tablet average mass). A test result c_{im} is expressed in % of labeled amount l_i.

2.3. Measurement uncertainty

The test method requirement is that the relative standard deviation, RSD, of the analyte peak area for all injections/replicates of the first working standard solution (6 or more) will be 2.5 % or less. The same RSD ≤ 2.5 % should hold also for a single analyte peak area of a sample solution. The relative standard deviation of the averaged peak area is $RSD_{avg} \leq 2.5\ \%/\sqrt{6}$ = 1.0 %. Therefore, the relative standard measurement uncertainty, u_r, of the ratio of the analyte peak area of the sample solution and the averaged peak area of the first working standard solution, A_{is}/A_{iws}, is $u_r \leq \sqrt{(2.5\ \%)^2 + (1.0\ \%)^2}$ = 2.7 %.

By another requirement of the test method, the relative difference between the averaged normalized (to the analyte concentrations) peak areas obtained for the two working standard solutions must be 2.0 % or less. This condition is a limitation on the error which may affect preparation of the first working standard solution, shown in formula (1) as factor *f*. Its contribution to the measurement uncertainty, evaluated as the standard deviation of a rectangular distribution [9], is $u_{ws} \leq 2.0\ \%/\left(2\sqrt{3}\right)$ = 0.6 % for any component.

Contributions from other uncertainty sources, such as purity of USP reference standards, weights, volumes and dilutions, are negligible here in comparison to u_r and u_{ws}. Therefore, the relative combined standard uncertainty of a test result c_{im} for each active component is $u_{rel} \leq \sqrt{u_r^2 + u_{ws}^2} = \sqrt{(2.7\ \%)^2 + (0.6\ \%)^2}$ = 2.8 %. Such measurement uncertainty is typical for

HPLC [10-12]. However, note that in this study 2.8 % is the target relative measurement uncertainty [13], whereas the actual measurement uncertainty may be lower.

3. Results and discussion

3.1. Global distributions of the components' content values

A total of $N = 105$ lots of the medication produced and released at the same factory during a year were tested in the same laboratory belonging to the factory. Histograms of the test results c_{im} are shown in Fig. 2 for: a) APAP, $i = 1$; b) DEX, $i = 2$; c) DOX, $i = 3$; and d) PE, $i = 4$. Mean, m_i, and standard deviation, s_i, values of the test results are presented in Table 1.

Fig. 2

Note that the s_i values are smaller than the target measurement uncertainty $u_i = (u_{rel}/100\ \%)\, c_{im} = 0.028\, c_{im}$, % of labeled amount, in spite of the fact that the lot-to-lot variation of test results is formed by variation of the production/technological factors and the measurement uncertainty. The reason is that each released lot has passed not only assay determination, but also tests of uniformity of dosage units by USP <905>, dissolution by USP <711> [8] and some others. Any out-of-specification and/or out-of-trend test result investigation pointing out a production problem prevents the lot release. As a result, s_i values are minimized in this way and the lot-to-lot (empirical) distributions of test results are truncated by the specification limits.

Table 1

Goodness-of-fit of the empirical and theoretical normal distributions with unknown parameters was tested by the Kolmogorov-Smirnov criterion [14]. Empirical criterion values, i.e. values of the maximal absolute difference, D_i, between empirical and theoretical cumulative

distribution functions, calculated using R software [15] are shown in Table 1. The critical values for $N = 105$ test results were approximated as $D_{crit} = 0.895/(\sqrt{N} - 0.01 + 0.85/\sqrt{N}) = 0.087$ for confidence level $P = 0.95$ and as $D_{crit} = 1.035/(\sqrt{N} - 0.01 + 0.85/\sqrt{N}) = 0.101$ for $P = 0.99$ [16]. When an empirical criterion value is greater than the critical one, then the null hypothesis about goodness-of-fit of the empirical and theoretical distributions at the chosen level of confidence P should be rejected. One can see from Table 1 that the empirical value of the criterion is equal for DEX to the critical value D_{crit} for $P = 0.95$, but exceeded it for other components. However, there is no empirical value exceeding D_{crit} for $P = 0.99$. Therefore, the null hypothesis is not rejected at that confidence level.

3.2. Correlation

Linear correlation among the test results for different components was estimated by the Pearson's correlation coefficients r_{ij}, $i \neq j = 1, 2, 3, 4$, reported in Table 2. The two-sided critical values of the coefficient r_{crit} for $N - 2 = 103$ degrees of freedom are 0.195 for the level of confidence $P = 0.95$, and 0.254 for $P = 0.99$ [17, 18]. Therefore, only the test results for APAP are independent of the others, since $r_{1j} < r_{crit}$ for each j and for both the confidence levels. The test results for the low-dose active components – DEX, DOX and PE – are correlated significantly. There is no indication for systematic errors which could cause correlation in the chemical analysis/testing. Random chemical analytical factors contributing to measurement uncertainty are able only to decrease the correlation as any noise. Probably the root cause is in the technological conditions. However, the reason of the observed correlation is not important in framework of this study, since correlation should be taken into account irrespective of its origin.

3.3. Prior and likelihood functions

Since 'producer' in this study is the factory (pharmaceutical company), the probability density functions, pdfs, of theoretical normal distributions with means $\mu_i = m_i$ and standard deviations $\sigma_i = s_i$, shown in Fig. 2, are used as pdfs approximating the global distributions of the true components' content values c_i in the lots, i.e. as prior pdfs.

'Consumer' here is fuzzy: they are people who may catch cold or get sick with the flu. Their interests are defended by regulatory authorities supported by official medicines control laboratories controlling the quality of marketed medicinal products [19, 20]. The following evaluation of the consumer's risks is performed for a case when tablets from a lot, released already by the producer for a market, are tested by such a control laboratory (external for the producer). The laboratory uses the same test method for assay as discussed above. Therefore, pdfs of normal distributions with measurement result $c_{i\mathrm{m}}$ as mean and standard deviation $u_i = 0.028\ c_{i\mathrm{m}}$, % of labeled amount, are used as the likelihood functions.

3.4. Treatment of the correlated data

Principal component analysis (PCA) is the oldest widely-used technique of multivariate analysis. The idea of PCA is to reduce the dimensionality of a data set in which there are a number of interrelated variables, retaining as much as possible the variation of the initial data [21]. PCA was applied, for example, in the EURAMET guide for a bivariate study of skin cream friction and adhesion [22]. However, for a larger number of variables PCA is sensitive to the

scaling of the data, and there is no consensus which scale is the best to obtain optimal results. Another problem is that converting the original correlated variables c_i and c_{im} into fewer orthogonal/uncorrelated 'principal components' complicates the drug conformity assessment, since the 'principal components' and their specification limits can not be expressed in % of labeled amount.

In the current study, the true content values of the four components are jointly described by a multivariate prior normal pdf, and the likelihood function of their test results is also modelled by a multivariate normal distribution. Therefore, the joint posterior function is a multivariate normal pdf, as well [23].

The prior covariance matrix is the following:

$$S_{\mathrm{c}} = \begin{pmatrix} 1.8769 & 0.1495 & 0.1798 & 0.2958 \\ 0.1495 & 1.0404 & 0.3331 & 0.5027 \\ 0.1798 & 0.3331 & 1.1025 & 0.6905 \\ 0.2958 & 0.5027 & 0.6905 & 1.4884 \end{pmatrix},$$

where the diagonal elements are variances $\sigma_i^2 = s_i^2$ (Table 1), while others - covariances $cov_{ij} = r_{ij} \cdot \sigma_i \cdot \sigma_j$, $i \neq j$ (r_{ij} as in Table 2).

If the "noise" of the random chemical analytical factors contributing to measurement uncertainty in a control laboratory is negligible, the correlation among the test results is the same as shown in Table 2. Then, the likelihood covariance matrix for test results c_{im} equal to the prior means $\mu_i = m_i$ (Table 1), for example, is:

$$S_{\mathrm{cm}} = \begin{pmatrix} 7.7120 & 0.8129 & 0.9655 & 1.3617 \\ 0.8129 & 7.4835 & 2.3662 & 3.0617 \\ 0.9655 & 2.3662 & 7.7353 & 4.1530 \\ 1.3617 & 3.0617 & 4.1530 & 7.6747 \end{pmatrix},$$

where the diagonal elements are variances $u_i^2 = (0.028\, c_{im})^2$; and the covariances are $cov_{ij} = r_{ij} \cdot u_i \cdot u_j,\ i \neq j$.

For comparison with the case of uncorrelated data, the covariance matrices were transformed into corresponding diagonal ones, setting correlation coefficient values equal to zero. Another chosen point for comparison was the case of much stronger correlation than that observed, assuming correlation coefficients $r_{ij} = 0.7$. Thus, three points on the correlation scale ($r_{ij} = 0$, r_{ij} as in Table 2, and $r_{ij} = 0.7$) are addressed.

The joint posterior function was calculated as a multivariate normal pdf having the following parameters [23]:

$$S_{\text{post}} = (S_{\text{c}}^{-1} + n_{\text{rep}}\, S_{\text{cm}}^{-1})^{-1} \text{ and } \boldsymbol{c}_{\text{post}} = S_{\text{post}}(S_{\text{c}}^{-1}\boldsymbol{c} + n_{\text{rep}}\, S_{\text{cm}}^{-1}\, \overline{\boldsymbol{c}_{\text{m}}})^{-1}, \quad (2)$$

where S_{post} and $\boldsymbol{c}_{\text{post}}$ are the posterior covariance matrix and the vector of the posterior means, respectively; $\boldsymbol{c}$ is the vector of the prior mean values [μ_1, μ_2, μ_3, μ_4]; $\overline{\boldsymbol{c}_{\text{m}}}$ is the vector of the arithmetic means of replicate measurement/test results; and n_{rep} is the number of such replicates (in this study, for a single test result $n_{\text{rep}} = 1$, $\overline{\boldsymbol{c}_{\text{m}}} = \boldsymbol{c}_{\text{m}} = [c_{1\text{m}}, c_{2\text{m}}, c_{3\text{m}}, c_{4\text{m}}]$).

The use of such a posterior pdf was validated, in the case of independent quantities, by evaluation of the risks of false decisions with formulas (A.1) – (A.4). For an additional validation, calculation of the parameters of the posterior multivariate normal distribution was performed also by Markov Chain Monte Carlo (MCMC) simulations of the posterior distribution, using Metropolis-Hasting algorithm [23] and Cholesky decomposition of the

covariance matrix in MS Excel ambient [24]. Both the developed R code and Excel spreadsheet program can be sent upon request to the corresponding author.

3.5. Global risks

According to the framework developed in ref. [1], the total global consumer's risk R_{total} is the probability of the following event:

$$\mathrm{C} \cap \mathrm{B} = (\mathrm{C} \cap \mathrm{B}_1) \cup (\mathrm{C} \cap \mathrm{B}_2) \cup (\mathrm{C} \cap \mathrm{B}_3) \cup (\mathrm{C} \cap \mathrm{B}_4)\,, \tag{3}$$

where $\mathrm{C} = \mathrm{C}_1 \cap \mathrm{C}_2 \cap \mathrm{C}_3 \cap \mathrm{C}_4$ is the event occurring when all the test results $c_{i\text{m}}$ are in their acceptance intervals simultaneously, and $\mathrm{B} = \mathrm{B}_1 \cup \mathrm{B}_2 \cup \mathrm{B}_3 \cup \mathrm{B}_4$ is the event occurring when at least one of the true values of the components' content c_i is outside its specification interval. Therefore, R_{total} can be considered as the following:

$$\begin{aligned} R_{\text{total}} = P(\mathrm{C} \cap \mathrm{B}) = {} & P(\mathrm{C} \cap \mathrm{B}_1) + P(\mathrm{C} \cap \mathrm{B}_2) + P(\mathrm{C} \cap \mathrm{B}_3) + P(\mathrm{C} \cap \mathrm{B}_4) - \\ & P(\mathrm{C} \cap \mathrm{B}_1 \cap \mathrm{B}_2) - P(\mathrm{C} \cap \mathrm{B}_1 \cap \mathrm{B}_3) - P(\mathrm{C} \cap \mathrm{B}_1 \cap \mathrm{B}_4) - P(\mathrm{C} \cap \mathrm{B}_2 \cap \mathrm{B}_3) - P(\mathrm{C} \cap \mathrm{B}_2 \cap \mathrm{B}_4) - \\ & P(\mathrm{C} \cap \mathrm{B}_3 \cap \mathrm{B}_4) + P(\mathrm{C} \cap \mathrm{B}_1 \cap \mathrm{B}_2 \cap \mathrm{B}_3) + P(\mathrm{C} \cap \mathrm{B}_1 \cap \mathrm{B}_2 \cap \mathrm{B}_4) + P(\mathrm{C} \cap \mathrm{B}_1 \cap \mathrm{B}_3 \cap \mathrm{B}_4) + \\ & P(\mathrm{C} \cap \mathrm{B}_2 \cap \mathrm{B}_3 \cap \mathrm{B}_4) - P(\mathrm{C} \cap \mathrm{B}_1 \cap \mathrm{B}_2 \cap \mathrm{B}_3 \cap \mathrm{B}_4). \end{aligned} \tag{4}$$

Each probability term in the expression (4) was calculated as a multiple integral of the product of the multivariate prior normal pdf (modelling events $\mathrm{B}_i \cap \mathrm{B}_j$, etc.) and the multivariate normal likelihood (modelling conditional event $\mathrm{C}|[c_1, c_2, c_3, c_4]$), i.e. as the integral of the joint

distribution of true values and test results. Concerning the relevant integration limits, note that the test results spread in their multivariate acceptance interval (coinciding in this study with the specification interval/domain lsl_i - usl_i), whereas true values are outside the specification domain if probability of events B_i needed to be calculated. Otherwise, they spread on the whole range of real numbers leading to marginalization of the joint distribution with respect to those quantities.

The integration was performed in R ambient by application of the 'adaptIntegrate' function from the R package 'cubature' [25]. The numerical tolerance was set equal to 0.01, rather than the default value 0.00001, due to time issues in the calculation. The theoretical minus and plus infinity integration limits were substituted with more feasible values in the numerical evaluation of the integral, 70 % and 130 % of labeled amount, respectively, outside which any probability of a true components' content c_i and/or a test result value c_{im} for a released for a market medication is practically zero.

For diagonal matrices S_c and S_{cm}, defined above in section 3.4 for uncorrelated variables, $R_{total} = 0.19\times10^{-2}$. This value is equal to that calculated by formula (A.2). The observed correlation did not influence visibly the total risk: it is again $R_{total} = 0.19\times10^{-2}$, whereas for the correlation coefficients $r_{ij} = 0.7$ the calculated value is $R_{total} = 0.10\times10^{-2}$.

Practically the same risk values were obtained at all the levels of correlation when PE content was not taken into account, as well as by formula (A.1). That is apparently due to the minor contribution of the particular PE risk to the total probability.

3.6. Specific risks

The total specific risk R^*_{total} was evaluated, using the 'pmvnorm' function from the R package 'mvtnorm' [26], as the joint posterior cumulative function of true values c_i of a specific lot lying outside the multivariate specification domain, when the vector of test results $c_{i\text{m}}$, obtained for the lot, is inside this domain.

The dependences of the total specific risk R^*_{total} ($\times 10^2$) on test results $c_{i\text{m}}$ in the specification interval, 95-105 % of labeled amount, when test results for other active components $c_{j\text{m}}$, $j \neq i$, are equal to their prior pdf means $\mu_j = m_j$ (Table 1) are shown in Fig. 3. The plots are for: a) APAP, $c_{1\text{m}}$; b) DEX, $c_{2\text{m}}$; c) DOX, $c_{3\text{m}}$; and d) PE, $c_{4\text{m}}$. Line 1 is for the observed correlation among test results (Table 2); line 2 – for the case when there is no correlation (correlation coefficients $r_{ij} = 0$); line 3 – for a case when the correlation is much stronger than that observed ($r_{ij} = 0.7$). The "noise" in line 3 is due to the numerical errors in 'pmvnorm' function computing joint probability values for the strong correlation case. Fig. 3 shows that the correlation influence on the risk values is not easily predictable, especially when the correlation coefficients are different as in this study (Table 2). There is no significant difference between the risk values, if the test results are independent or correlated as observed (lines 2 and 3, respectively). However, when the correlation among the test results is stronger (lines 3), it may lead either to a decreasing of the total risk or to its increasing, depending on the actual values of the test results.

Fig. 3

One may expect that the risk values are increasing symmetrically when $c_{i\text{m}}$ are moving away from the midpoint of the specification interval (100 % of labeled amount) towards the specification limits (95 and 105 % of labeled amount), whereas that is not observed in Fig. 3. The reason is that all the prior means μ_i are shifted to the left side of the specification interval and the likelihood covariance matrix varies for different $c_{i\text{m}}$ values.

Note that results of calculations by formula (2) using the multivariate normal distributions for uncorrelated test results of content of three and four components (diagonal covariance matrices) coincide with those obtained by formulas (A.3) and (A.4), respectively. If PE is not taken into account, whereas independent c_{1m}, c_{2m} and c_{3m} values are equal to their prior pdf means μ_i (Table 1), the total risk is $R^*_{total} = 0.27\times10^{-2}$. Considering any possible c_{4m} values for PE in the specification interval for the same conditions on the other components (independent test results and $c_{im} = \mu_i$, i = 1, 2, 3), it was found that the minimal value of the total risk for all the four components is also, after rounding, $R^*_{total} = 0.27\times10^{-2}$. That is because of the minor contribution of the particular PE specific risk to R^*_{total}, as for the total global risk above. However, in general, R^*_{total} for the four components is greater than for three only components under control, i.e. increases with the number of the components under control, the fact observed in ref. [1] for denatured alcohols as well.

4. Conclusions

Correlation among test results of a multicomponent material complicates its conformity assessment. When true values of components' content and corresponding test results are modelled by multivariate distributions, for example normal pdfs (prior and likelihood, respectively), a total global risk of a false decision on the material conformity can be evaluated based on calculation of integrals of their joint pdf.

A total specific consumer's risk is evaluated as the joint posterior cumulative function of true values of a specific batch or lot lying outside the multivariate specification domain, when the

vector of test results, obtained for the lot, is inside this domain. The counterpart models for the total producer's risk are obtainable analogously.

It was shown, using a case study of four components under control in a drug, that the correlation influence on the total risk values is not easily predictable. In particular, when the correlation among the test results is strong, it may lead either to decreasing or increasing of the total risk, depending on the actual values of the test results.

Acknowledgement

This research was supported in part by the International Union of Pure and Applied Chemistry (IUPAC Project 2016-007-1-500).

Appendix. Total risk calculation for three and four components under control, when test results are uncorrelated.

For three components i = 1, 2, 3, assuming independent true values of each component's content c_i and independent corresponding measurement/test results $c_{i\mathrm{m}}$, the total global consumer's risk is:

$$R_{\mathrm{total}} = P(\mathrm{C}_2)P(\mathrm{C}_3)R_{c1} + P(\mathrm{C}_1)P(\mathrm{C}_3)R_{c2} + P(\mathrm{C}_1)P(\mathrm{C}_2)R_{c3} - P(\mathrm{C}_3)R_{c1}R_{c2} - P(\mathrm{C}_2)R_{c1}R_{c3} - P(\mathrm{C}_1)R_{c2}R_{c3} + R_{c1}R_{c2}R_{c3}, \quad \text{(A.1)}$$

where $P(\mathrm{C}_i)$ is the probability that the test result $c_{i\mathrm{m}}$ for component i is in its acceptance interval; R_{ci} is the particular global consumer's risk for the i-th component, i.e. the probability of false

conformance when the corresponding test result falls within its acceptance limits, whereas the true value is outside the tolerance/specification limits. For example, for particular risks R_{ci} = 0.05 and probabilities $P(\mathrm{C}_i)$ = 0.90 for all i, formula (A.1) gives $R_{\mathrm{total}} = 0.12$.

For four components i = 1, 2, 3, 4, under the same assumption of the independence of the true values c_i and the test results $c_{i\mathrm{m}}$, the total global consumer's risk is:

$$\begin{aligned} R_{\mathrm{total}} = {} & P(\mathrm{C}_2)P(\mathrm{C}_3)P(\mathrm{C}_4)R_{c1} + P(\mathrm{C}_1)P(\mathrm{C}_3)P(\mathrm{C}_4)R_{c2} + P(\mathrm{C}_1)P(\mathrm{C}_2)P(\mathrm{C}_4)R_{c3} + \\ & P(\mathrm{C}_1)P(\mathrm{C}_2)P(\mathrm{C}_3)R_{c4} - P(\mathrm{C}_3)P(\mathrm{C}_4)R_{c1}R_{c2} - P(\mathrm{C}_2)P(\mathrm{C}_4)R_{c1}R_{c3} - \\ & P(\mathrm{C}_2)P(\mathrm{C}_3)R_{c1}R_{c4} - P(\mathrm{C}_1)P(\mathrm{C}_4)R_{c2}R_{c3} - P(\mathrm{C}_1)P(\mathrm{C}_3)R_{c2}R_{c4} - \\ & P(\mathrm{C}_1)P(\mathrm{C}_2)R_{c3}R_{c4} + P(\mathrm{C}_4)R_{c1}R_{c2}R_{c3} + P(\mathrm{C}_3)R_{c1}R_{c2}R_{c4} + P(\mathrm{C}_2)R_{c1}R_{c3}R_{c4} + \\ & P(\mathrm{C}_1)R_{c2}R_{c3}R_{c4} - R_{c1}R_{c2}R_{c3}R_{c4}. \end{aligned} \quad \text{(A.2)}$$

For particular risks R_{ci} = 0.05 and probabilities $P(\mathrm{C}_i)$ = 0.90 for all i, one can obtain by formula (A.2) $R_{\mathrm{total}} = 0.13$.

Total specific consumer's risk for a given lot with three components i = 1, 2, 3 under control is:

$$R^*_{\mathrm{total}} = R^*_{c1} + R^*_{c2} + R^*_{c3} - R^*_{c1}R^*_{c2} - R^*_{c1}R^*_{c3} - R^*_{c2}R^*_{c3} + R^*_{c1}R^*_{c2}R^*_{c3}, \quad \text{(A.3)}$$

where R^*_{ci} is the particular specific consumer's risks for the i-th component. For example, when the particular specific risks are $R^*_{ci} = 0.05$, the total risk by formula (A.3) is $R^*_{\mathrm{total}} = 0.14$.

When four components i = 1, 2, 3, 4 are under control, the total specific customer's risk is:

$$R^*_{\text{total}} = R^*_{c1} + R^*_{c2} + R^*_{c3} + R^*_{c4} - R^*_{c1}R^*_{c2} - R^*_{c1}R^*_{c3} - R^*_{c1}R^*_{c4} - R^*_{c2}R^*_{c3} - R^*_{c2}R^*_{c4} - R^*_{c3}R^*_{c4} + R^*_{c1}R^*_{c2}R^*_{c3} + R^*_{c1}R^*_{c2}R^*_{c4} + R^*_{c1}R^*_{c3}R^*_{c4} + R^*_{c2}R^*_{c3}R^*_{c4} - R^*_{c1}R^*_{c2}R^*_{c3}R^*_{c4}. \quad \text{(A.4)}$$

For example, when the particular risks are again $R^*_{ci} = 0.05$, formula (A.4) gives $R^*_{\text{total}} = 0.19$ [1].

Note that these examples are for equal contributions of particular risks (R_{ci} and $P(\mathrm{C}_i)$, as well as R^*_{ci} values), for simplicity. When the contributions are not equal, the increase of the total risk with the number of components under control may be not assured for any test results, e.g. if one or more of the risk contributions are negligible.

References

[1] I. Kuselman, F. Pennecchi, R.J.N.B. da Silva, D.B. Hibbert, Conformity assessment of multicomponent materials or objects: Risk of false decisions due to measurement uncertainty – A case study of denatured alcohols, Talanta 164 (2017) 189-195.

[2] BIPM, IEC, IFCC, ILAC, ISO, IUPAC, IUPAP and OIML, Joint Committee for Guides in Metrology - JCGM 106, Evaluation of Measurement Data – The Role of Measurement Uncertainty in Conformity Assessment, 2012 (http://www.bipm.org/en/publications/guides/#gum).

[3] K. Baclawski, Introduction to Probability with R, Chapman & Hall/CRC Texts in Statistical Science, Boca Raton, 2008, ISBN 978-1-4200-6521-3.

[4] Drugs.com Overview: What is NyQuil Severe Cold & Flu (acetaminophen, dextromethorphan, doxylamine, and phenylephrine)? (https://www.drugs.com/mtm/nyquil-severe-cold-flu.html).

[5] L. Homewood, UF researchers question effectiveness of decongestant, University of Florida, news.ufl.edu, 07 (2006) (http://news.ufl.edu/archive/2006/07/uf-researchers-question-effectiveness-of-decongestant.html).

[6] United States Pharmacopeia (USP) Reference Standards Catalog (http://www.usp.org/reference-standards/reference-standards-catalog).

[7] Sigma-Aldrich/Merck Catalog. Acetaminophen USP Reference Standard (http://www.sigmaaldrich.com/catalog/product/usp/1003009?lang=en&region=IL).

[8] The United States Pharmacopeial Convention, United States Pharmacopeia (USP) 39 (2016).

[9] S.L.R. Ellison and A. Williams (Eds), Eurachem/CITAC Guide: Quantifying uncertainty in analytical measurement, 3rd edn., 2012 (https://www.eurachem.org/index.php/publications/guides).

[10] M.A.L. Traple, A.M. Saviano, F.L. Francisco, F.R. Lourenco, Measurement uncertainty in pharmaceutical analysis and its application (Review paper), J. of Pharmaceutical Analysis 4/1 (2014) 1-5.

[11] T. Tomic, N.U. Nasipak, S. Babic, Estimating measurement uncertainty in high-performance liquid chromatography methods, Accred. Qual. Assur. 17 (2012) 291-300.

[12] H.Z. Diawara, F. Gbaguidi, B. Evrard, J.Q. Leclercq, M. Moudachirou, B. Debrus, P. Hubert, E. Rozet, Validation, transfer and measurement uncertainty estimation of an HPLC-

UV method for the quantification of artemisinin in hydro alcoholic extracts of *Artemisia annua* L, J. of Pharmaceutical and Biomedical Analysis 56 (2011) 7-15.

[13] R.J.N.B. da Silva, A. Williams (Eds), Eurachem/CITAC Guide: Setting and using target uncertainty in chemical measurement, 1st ed., 2015 (https://www.eurachem.org/index.php/publications/guides).

[14] P.J. Kim and R.I. Jennrich, Tables of the exact sampling distribution of the two-sample Kolmogorov-Smirnov criterion, in: Harter, H. L., and Owen, D. B. (Eds.), Selected Tables in Mathematical Statistics, Vol. 1, Providence, Rhode Island: American Mathematical Society, 1973, pp. 80-129.

[15] The R project for statistical computing (https://www.r-project.org/).

[16] R.B. D'Agostino, M.A. Stephens (Eds), Goodness-of-feet techniques. Statistics: a series of textbooks and monographs, Marcel Dekker Inc, New York, 1986.

[17] D.B. Owen, Handbook of statistical tables, Addison-Wesley Publishing Company Inc, Massachusetts, 1962.

[18] R.E. Odeh, Critical values of the sample product-moment correlation coefficient in the bivariate normal distribution. Communications in Statistics - Simulation and Computation 11, 1982, pp. 1-26.

[19] Official Medicines Control Laboratory (OMCL) Networks (http://www.usp.org/global-health-programs/official-medicines-control-laboratory-omcl-networks).

[20] General European OMCL Network (GEON) (https://www.edqm.eu/en/general-european-omcl-network-geon).

[21] I.T. Jolliffe, Principal Component Analysis, 2nd edn,, Springer Series in Statistics, Springer, New York, 2002.

[22] L. Pendrill, H. Karlson, N. Fischer, S. Demeyer, A. Allard, EURAMET: A guide to decision-making and conformity assessment - A report of the EMRP joint project NEW04 "Novel mathematical and statistical approaches to uncertainty evaluation", 2015 (http://publikationer.extweb.sp.se/ViewDocument.aspx?RapportId=29488).

[23] A. Gelman, J.B. Carlin, S.H. Stern, D.B. Dunson, A. Vehtari, D.B. Rubin, Bayesian Data Analysis, 3d edn., Charman & Hall/CRC, Boca Raton, 2014.

[24] C. Zaiontz, Real statistics using Excel, Cholesky decomposition (http://www.real-statistics.com/linear-algebra-matrix-topics/cholesky-decomposition/).

[25] B. Narasimhan, S.G. Johnson, Package 'cubature'. Adaptive multivariate integration over hypercubes, 2016 (https://cran.r-project.org/web/packages/cubature/cubature.pdf).

[26] A. Genz, F. Bretz, T. Miwa, X. Mi, T. Hothorn, et al., Package 'mvtnorm', Multivariate normal and t distributions, 2016 (https://cran.r-project.org/web/packages/mvtnorm/mvtnorm.pdf).

Figure captions

Fig. 1. **Relationship among kinds of risk of false decision on conformity of a multicomponent material.** Specific risk refers to given lot, whereas global risk – to population of lots. Particular risk (specific R^*_{ci} or global R_{ci}) refers to *i*-th component of the material under control, $i = 1, 2, \ldots, n$; and total risk (specific R^*_{total} or global R_{total}) - to the material as a whole. These four kinds of risks are relevant as for the material producer as for its consumer: they are producer's risks and/or consumer' risks.

Fig. 2. **Global distributions of the components' content values.** Histograms of the test results $c_{i\mathrm{m}}$, and corresponding theoretical normal pdfs for true c_i values, both in % of labeled amounts, for: a) APAP, $i = 1$; b) DEX, $i = 2$; c) DOX, $i = 3$; and d) PE, $i = 4$.

Fig. 3. **Total specific risk in the specification interval.** Dependence of the consumer's total specific risk R^{*}_{total} ($\times 10^2$) on test results $c_{i\mathrm{m}}$ in the specification interval, 95-105 % of labeled amount, when test results for other active components $c_{j\mathrm{m}}$, $j \neq i$, are equal to their prior pdf mean (Table 1). The plots are for: a) APAP, $c_{1\mathrm{m}}$; b) DEX, $c_{2\mathrm{m}}$; c) DOX, $c_{3\mathrm{m}}$; and d) PE, $c_{4\mathrm{m}}$. Line 1 is for the observed correlation among the test results (Table 2); line 2 – for the case when there is no correlation (correlation coefficients $r_{ij} = 0$); line 3 – for a case when the correlation is much stronger than that observed ($r_{ij} = 0.7$).

Checklist

1. Cover Letter
2. Novelty Statement
3. Highlights
4. Manuscript
5. Figures
6. Checklist
7. List of Three Potential Reviewers

***List of Three Potential Reviewers**

Possible reviewers

1. Prof. Wolfhard Wegscheider, Faculty of General and Analytical Chemistry, University of Leoben, Austria, wolfhard.wegscheider@unileoben.ac.at
2. Dr. Markus Obkircher, Head of Reference Materials R&D, Sigma-Aldrich/Merck, Switzerland, markus.obkircher@sial.com
3. Dr. Della W.M. Sin, Government Chemist, Government Laboratory, Hong Kong, P. R. China, wmsin@govtlab.gov.hk
4. Dr. Anneli Kruve, Research Fellow, Institute of Chemistry, University of Tartu, Estonia, anneli.kruve@ut.ee

Table 1. Parameters of the global distributions

Component	Index	Parameter		
	i	m_i, %	s_i, %	D_i
APAP	1	99.18	1.37	0.099
DEX	2	97.70	1.02	0.087
DOX	3	99.33	1.05	0.088
PE	4	98.94	1.22	0.101

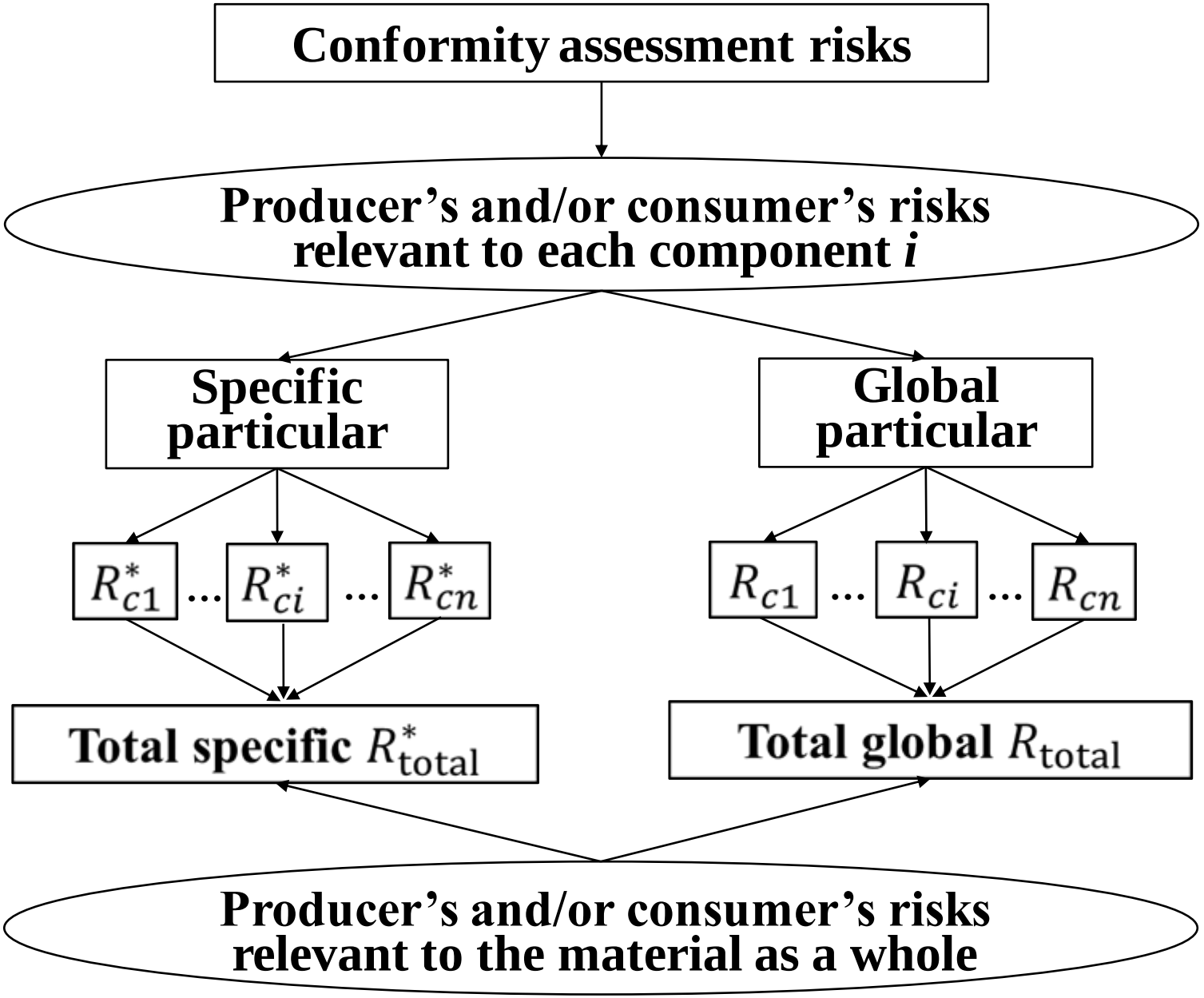
Note: m_i is the mean, and s_i - the standard deviation, both in % of labeled amount; D_i - the maximal absolute difference between empirical and theoretical cumulative distribution functions.

Table

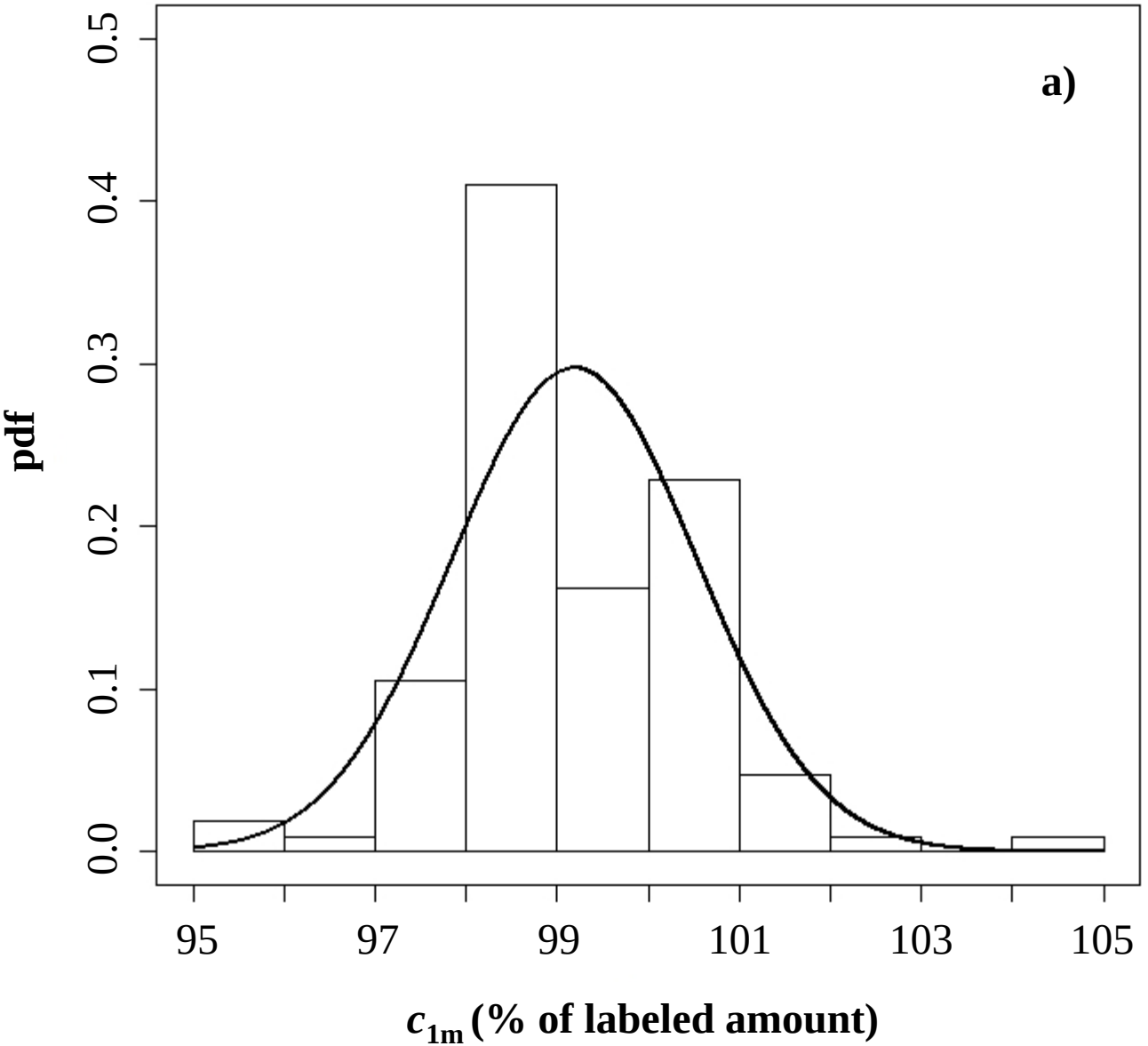
Table 2. Pearson's correlation coefficients of test results r_{ij}

Component	Index	APAP	DEX	DOX	PE
	i / *j*	1	2	3	4
APAP	1	1	0.107	0.125	0.177
DEX	2		1	0.311	0.404
DOX	3			1	0.539
PE	4				1

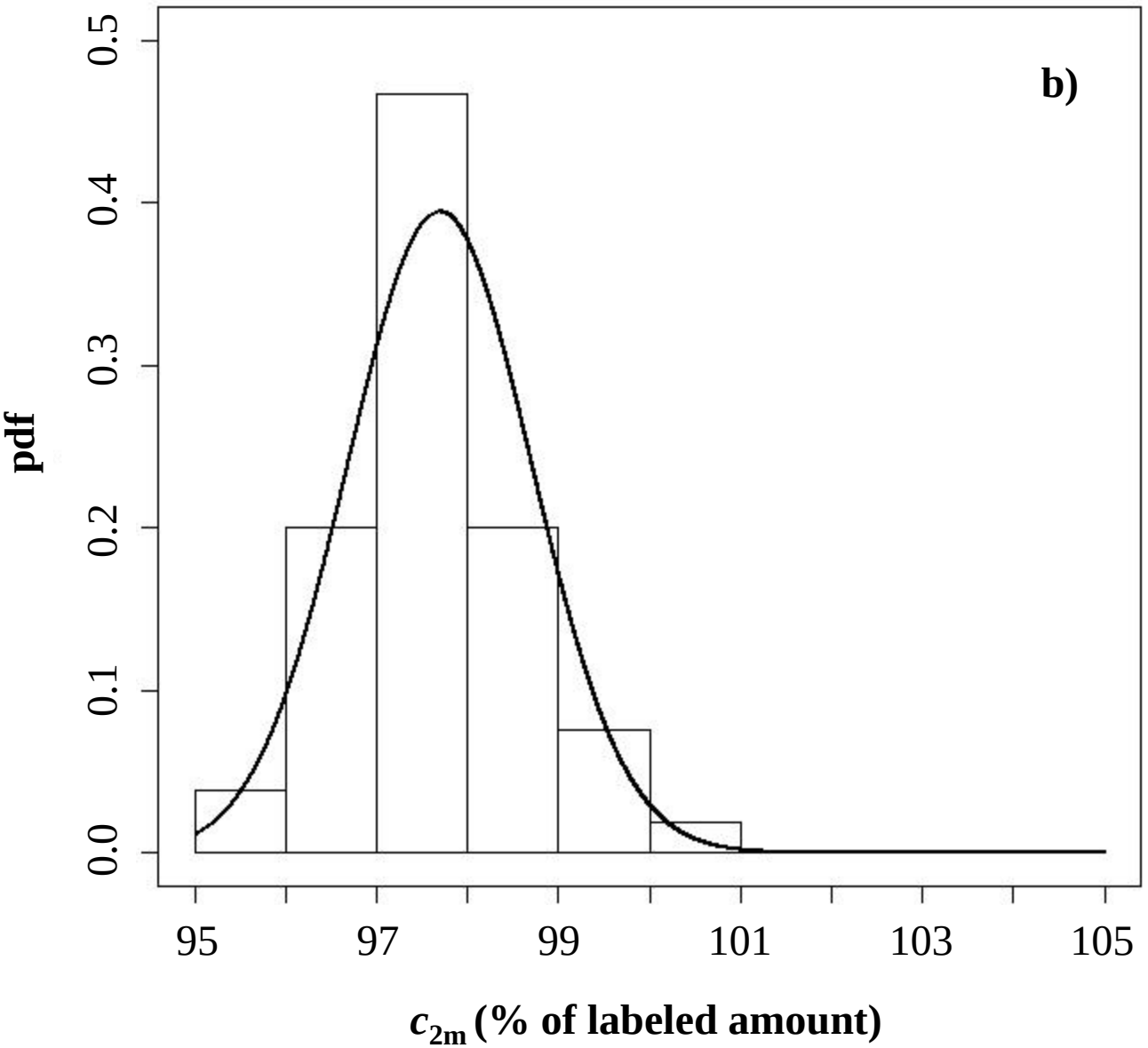
Figure


Conformity assessment risks
Producer's and/or consumer's risks relevant to each component *i*
Specific particular
Global particular
R^*_{c1} ... R^*_{ci} ... R^*_{cn}
R_{c1} ... R_{ci} ... R_{cn}
Total specific R^*_{total}
Total global R_{total}
Producer's and/or consumer's risks relevant to the material as a whole

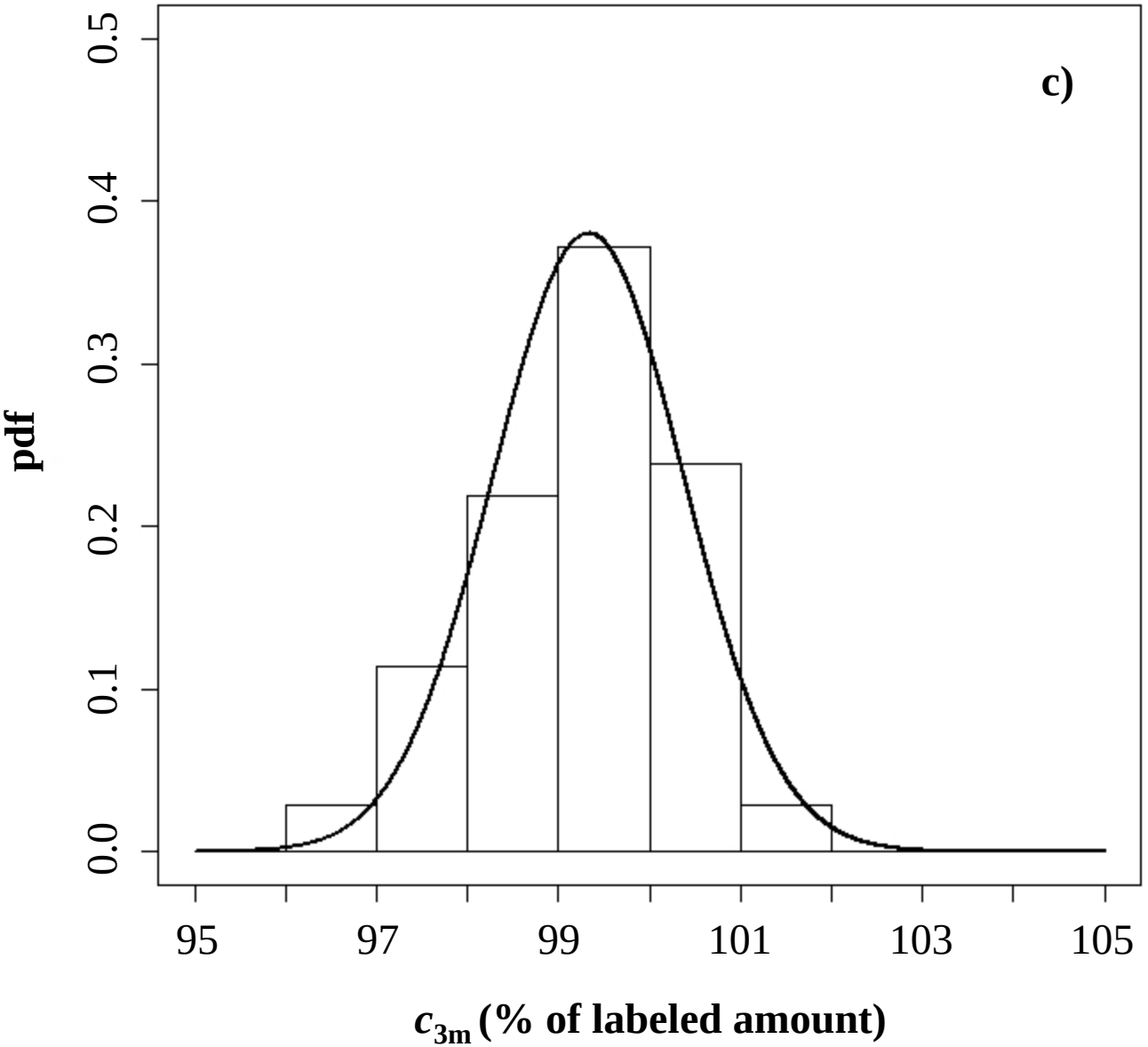
Figure



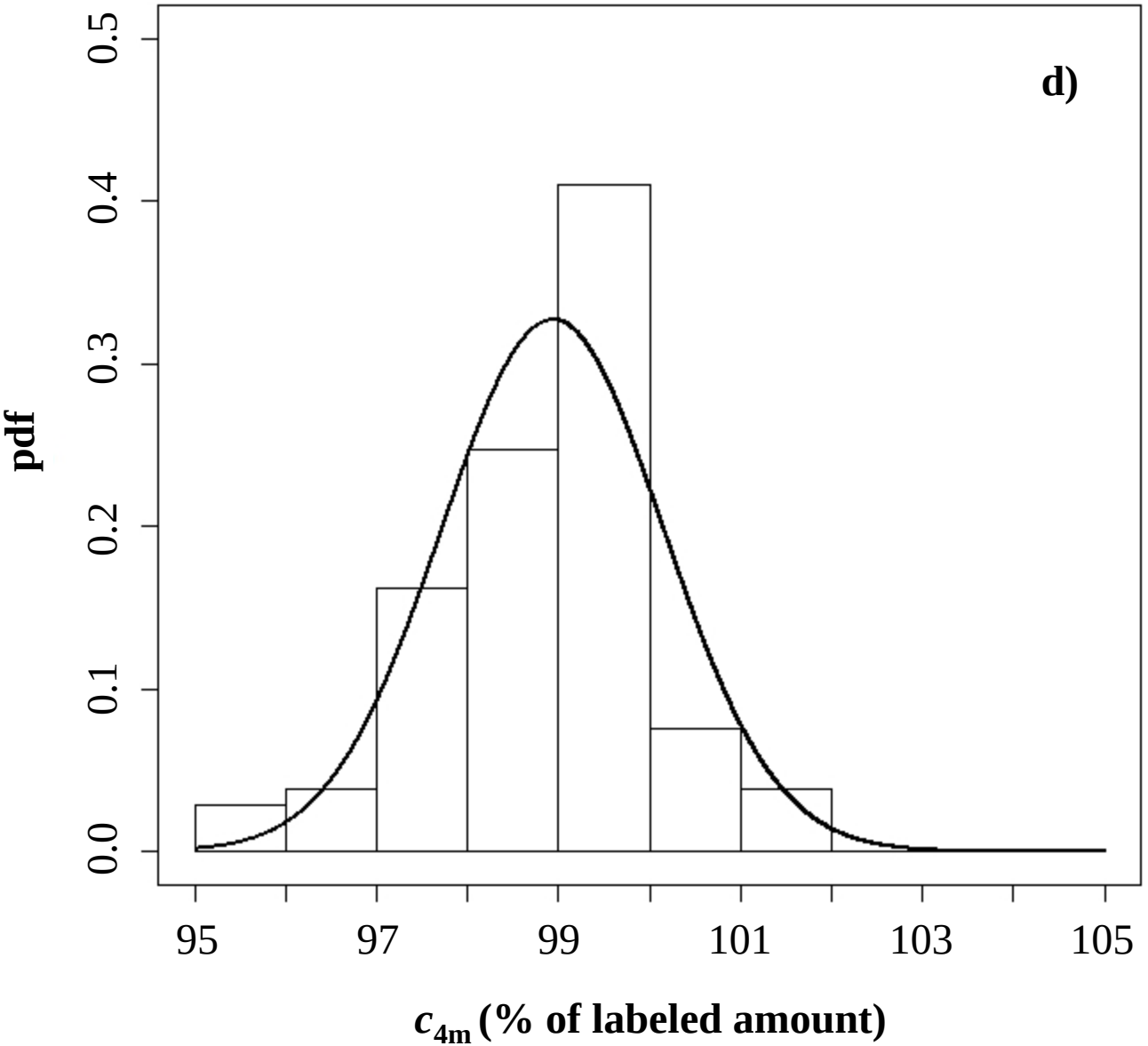
Figure



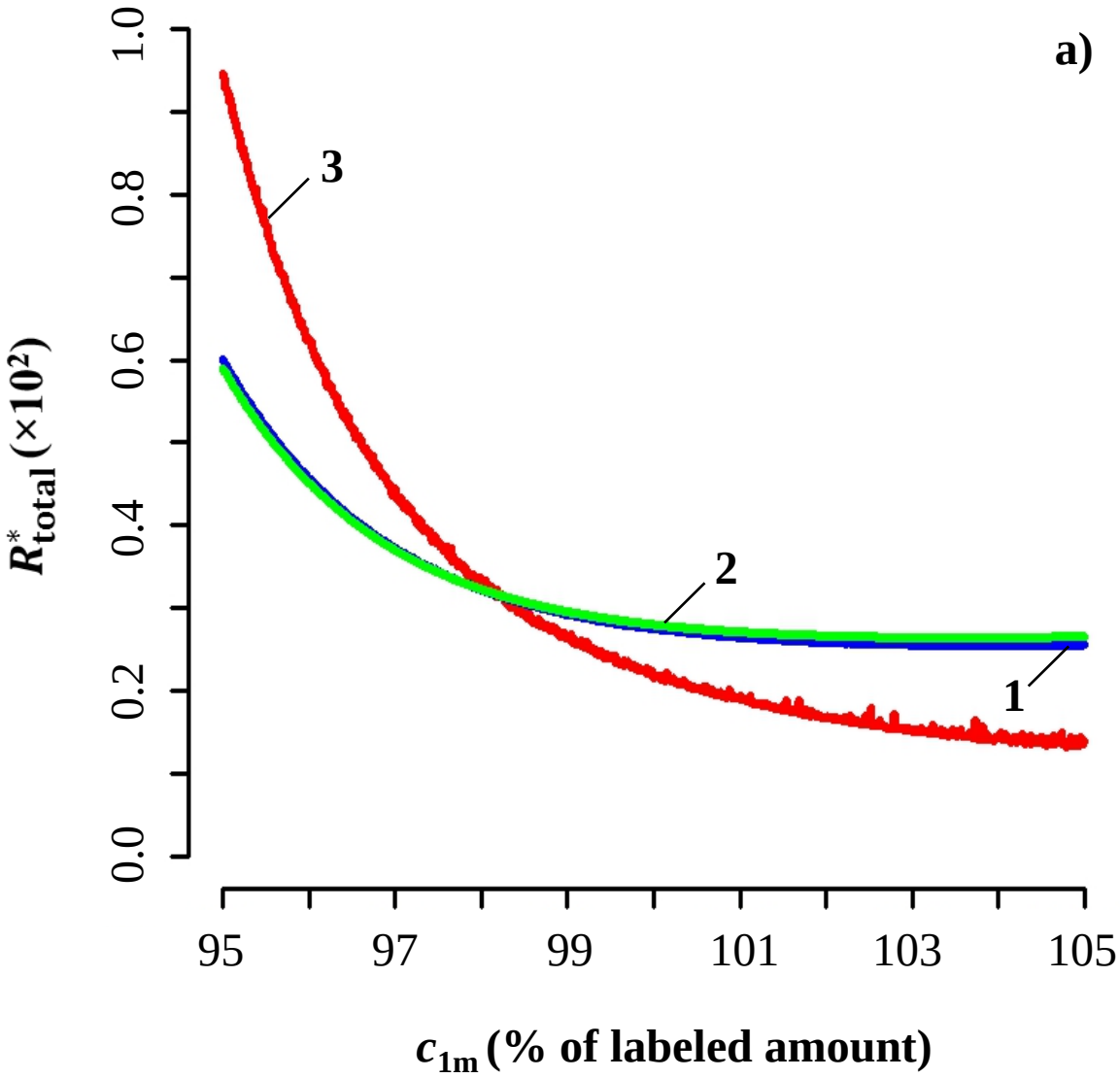
Figure



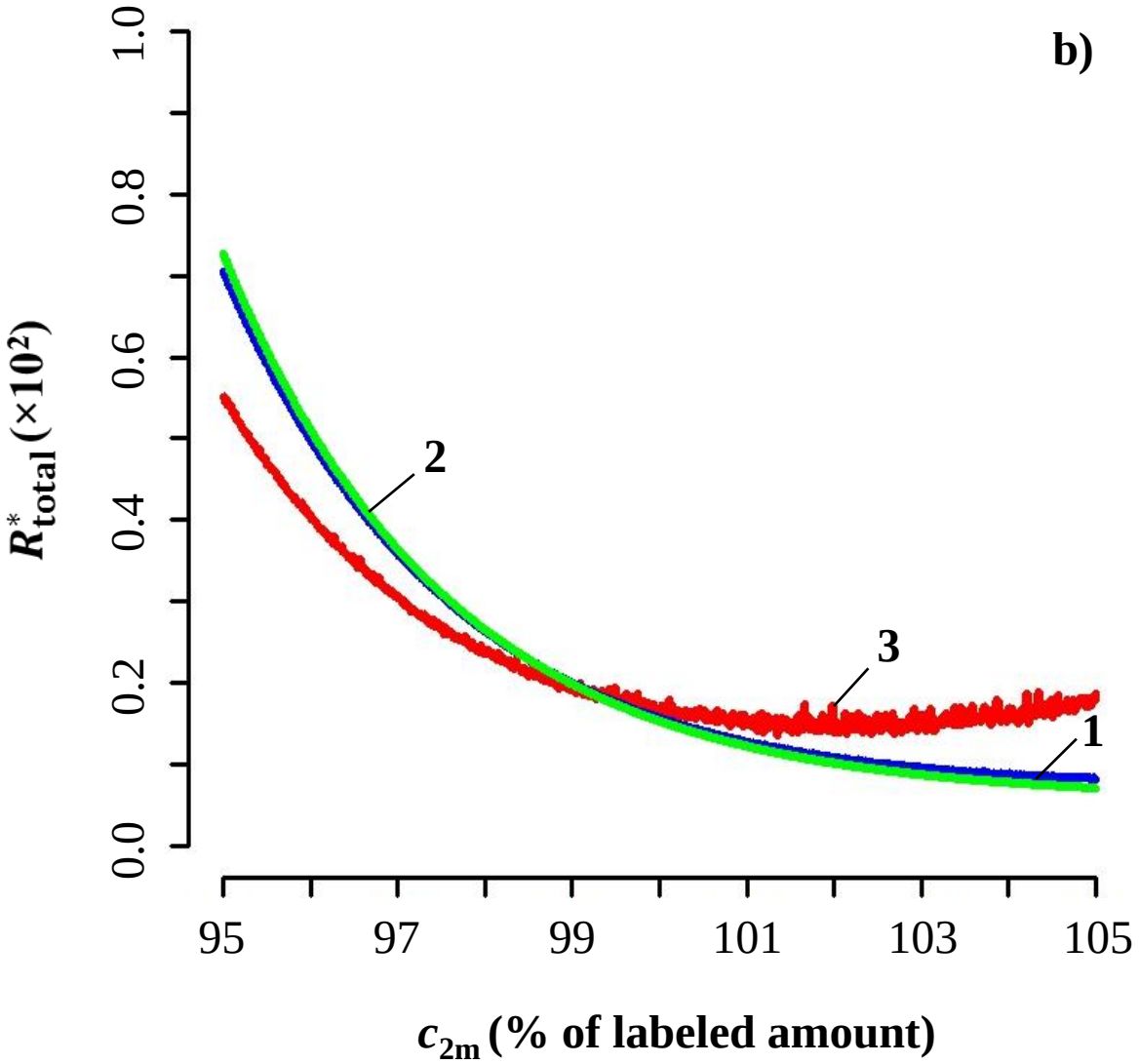
Figure



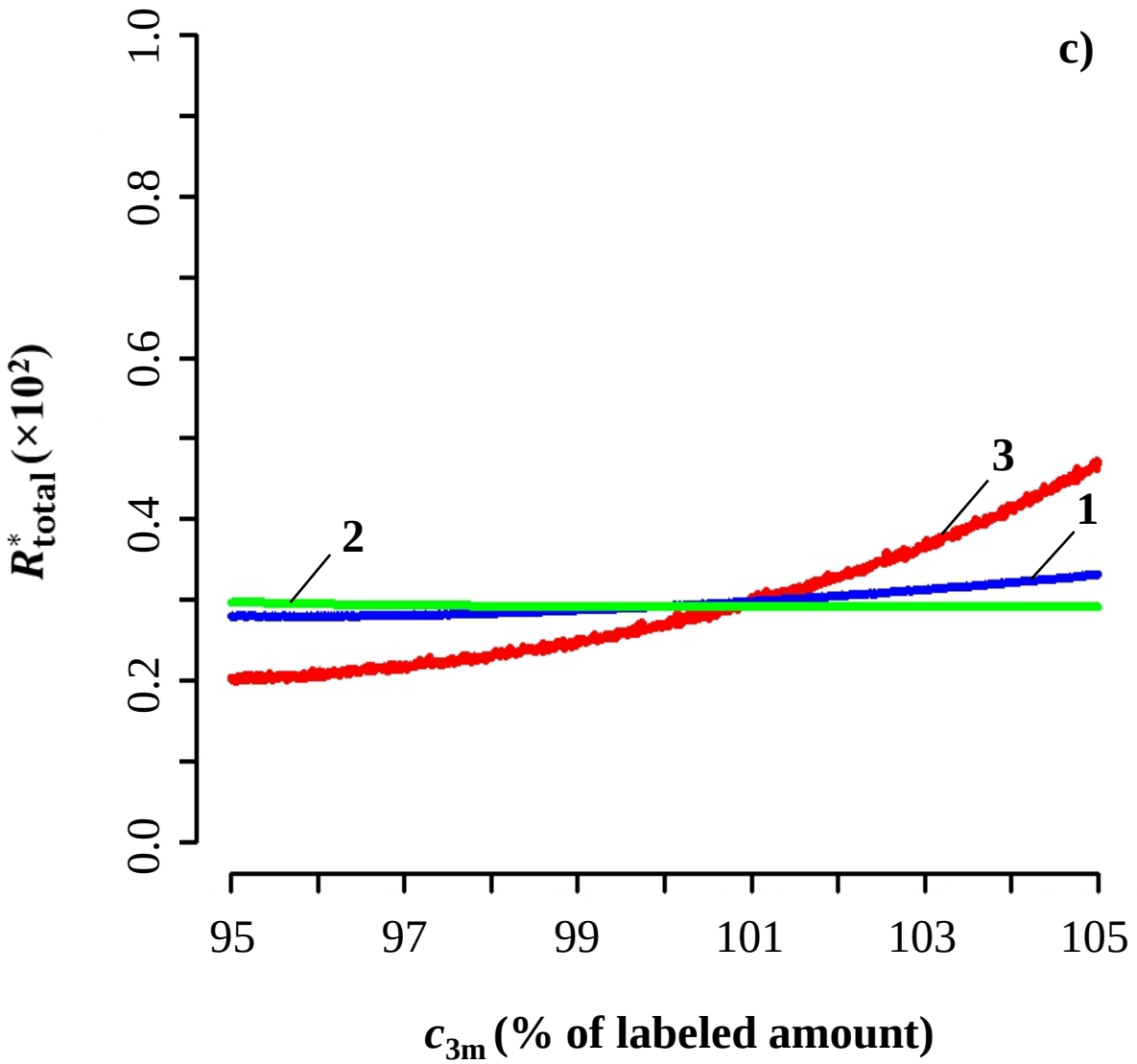
Figure


a)
3
2
1
R^*_{total} (×10²)
0.0
0.2
0.4
0.6
0.8
1.0
95
97
99
101
103
105
c_{1m} (% of labeled amount)

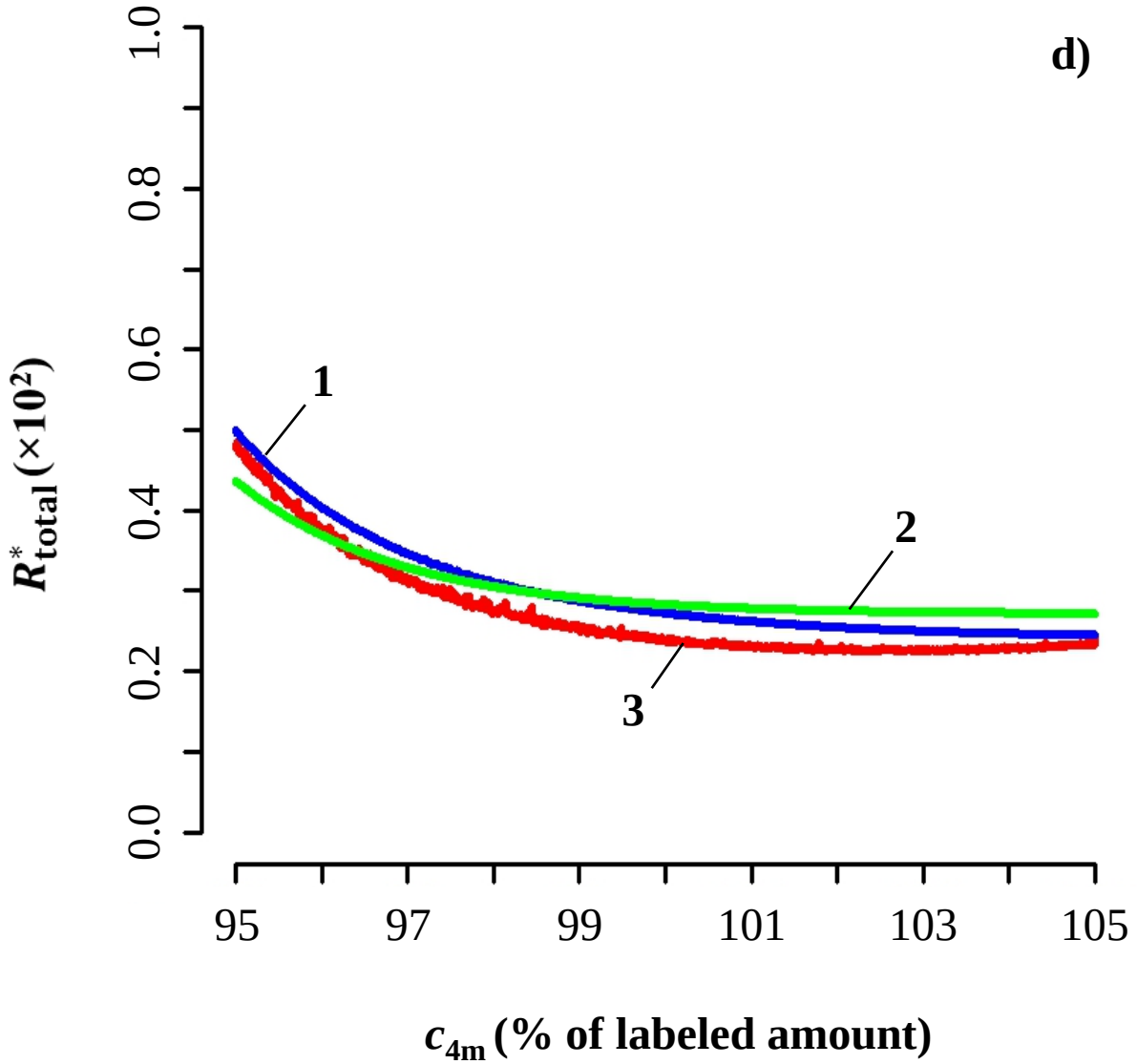
Figure


b)
R^*_{total} (×10²)
0.0
0.2
0.4
0.6
0.8
1.0
95
97
99
101
103
105
c_{2m} (% of labeled amount)
1
2
3

Figure


c)
R^*_{total} (×10²)
0.0
0.2
0.4
0.6
0.8
1.0
95
97
99
101
103
105
c_{3m} (% of labeled amount)
1
2
3

Figure


d)
1.0
0.8
0.6
0.4
0.2
0.0
R^*_{total} (×10²)
1
2
3
95
97
99
101
103
105
c_{4m} (% of labeled amount)