Extending conformance measures to more than one measurand – Conformity assessment of multicomponent materials or objects

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Outline

- Conformity Assessment (CA)
- Bayesian approach for CA and risks of false decisions for a single item
- Generalization to multicomponent materials or objects
- IUPAC and EMUE Projects
- Example of CA of a 4-components medicine
- Conclusions

Conformity Assessment (CA): References and concepts

JCGM 106 Guide (i.e., ISO/IEC Guide 98-4:2012): Evaluation of measurement data - The role of measurement uncertainty in conformity assessment, 2012.

Conformity (compliance) assessment:

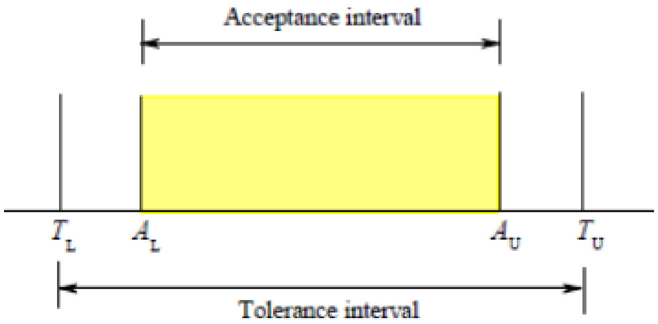
activity to determine whether specified requirements relating to a product, process, system, person or body are fulfilled.

Tolerance (specification) interval (TI):

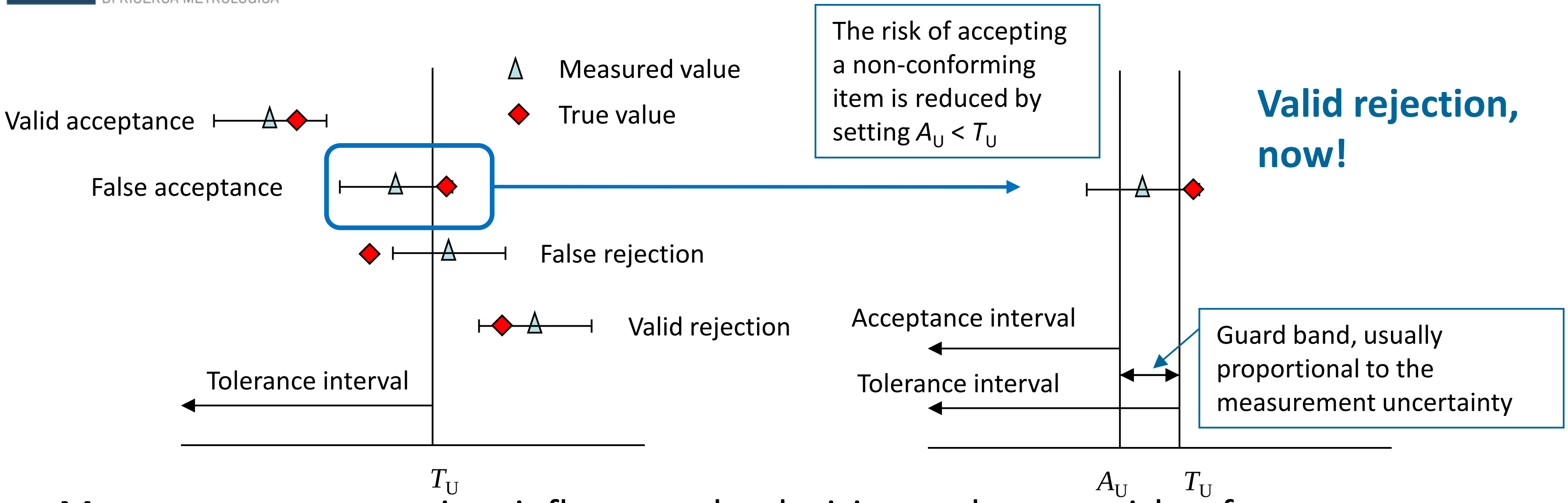
interval of permissible values of a property of a measured item (e.g., the mass concentration of a certain substance within a specific sample).

Acceptance interval (AI):

interval of measured values that results in the acceptance of the item.



CA: TI, AI and risks of false decisions



Measurement uncertainty influences the decision and causes risks of two types:

- **Consumer's** risk: probability of falsely accepting the material batch (or lot);
- **Producer's** risk: probability of falsely rejecting the batch (or lot).

✓ For a specified batch (or lot), the risks are referred to as **specific** risks.

✓ When a batch is randomly drawn from a population of such batches, the risks are referred to as **global** risks, since they characterize the material production globally.

CA: decision rules

7.1.3 When the customer requests a statement of conformity to a specification or standard for the test or calibration (e.g. pass/fail, in-tolerance/out-of-tolerance), the specification or standard and the decision rule shall be clearly defined. Unless inherent in the requested specification or standard, the decision rule selected shall be communicated to, and agreed with, the customer.

NOTE For further guidance on statements of conformity, see ISO/IEC Guide 98-4.

ISO/IEC 17025:2017

Choosing AI appropriately, the risks of incorrect decisions can be balanced in such a way to minimize the associated costs.

Decision rule is a prescription for the acceptance or rejection of a product, based on:

- the measurement result,
- the measurement uncertainty,
- the tolerance (specification) limits,
- the acceptable level of risk of an incorrect decision.

There are several types, such as

- based on guard bands → $[T_L, T_U] \neq [A_L, A_U]$
- simple acceptance (or, shared risk) → $[T_L, T_U] = [A_L, A_U]$

CA and risks of false decisions: Bayesian approach

JCGM 106 Guide provides guidance for CA of a single item with specified requirements (TI and AI).

Knowledge about an item property (the **measurand**) can be treated as a random variable and expressed in terms of a (**posterior**) **probability density function (PDF)**.

According to the **Bayes theorem**, such a pdf combines prior knowledge of the measurand and new information acquired during the measurement.

Measurement uncertainty

$$g(\eta \mid \eta_{\mathrm{m}}) = C\, g_0(\eta)\, h(\eta_{\mathrm{m}} \mid \eta)$$

The posterior PDF allows to appropriately calculate risks of false decisions in the conformity assessment of the item property.

Normalizing constant

Prior PDF

Likelihood function

True State of Product

η

To be compared with TI

Test Outcome

η_m

To be compared with AI

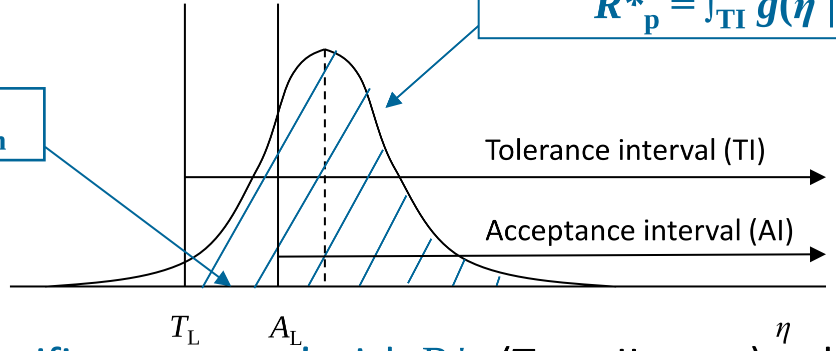
	Good	Bad
Pass		Consumer's risk
Fail	Producer's risk	

Bayesian approach: specific risks

Specific producer's risk R^*_p (Type I error): when η_m is outside AI

$$R^*_\mathrm{p} = \int_\mathrm{TI} g(\eta \mid \eta_\mathrm{m})\, \mathrm{d}\eta$$

η_m

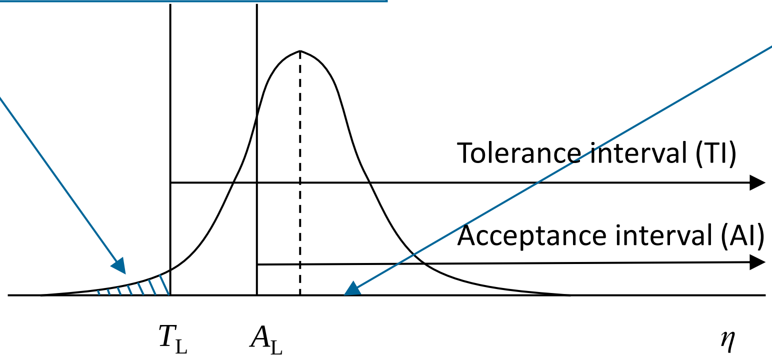


Probability that a particular rejected item is conforming.

Specific consumer's risk R^*_c (Type II error): when η_m is within AI

$$R^*_\mathrm{c} = \int_{\mathrm{TI}^\mathrm{c}} g(\eta \mid \eta_\mathrm{m})\, \mathrm{d}\eta$$

η_m



Probability that a particular accepted item is non-conforming.

Bayesian approach: global risks

Global risks are the fraction of items that are rejected/accepted, when they actually do/do not conform with specified requirement, respectively.
They characterize the item production globally.

Global producer's risk R_p: test result outside AI, but true value within TI

$$R_\mathrm{p} = \int_{\mathrm{TI}} \int_{\mathrm{AI}^\mathrm{c}} g_0(\eta)\, h(\eta_\mathrm{m} \mid \eta)\, \mathrm{d}\eta_\mathrm{m}\, \mathrm{d}\eta$$

Global consumer's risk R_c: test result within AI, but true value outside TI

$$R_\mathrm{c} = \int_{\mathrm{TI}^\mathrm{c}} \int_{\mathrm{AI}} g_0(\eta)\, h(\eta_\mathrm{m} \mid \eta)\, \mathrm{d}\eta_\mathrm{m}\, \mathrm{d}\eta$$

Generalization to multicomponent materials or objects

When **multicomponent materials** undergo CA, a component-by-component risk evaluation is not complete, since it can not give the probability of false decision on **conformity of the material as a whole**.

When CA for each *i*-th component is successful (i.e., R^*_i and R_i are small), the total probability of a false decision concerning the material as a whole (R^*_{total} and R_{total}) might still be significant: this is the **total risk**.

Correlation between test results η_{im} and between actual (‘true’) concentrations η_i often occurs and have to be taken into account:

- Several techniques are used to overcome correlations between η_{im}, but still something may happen in practice inducing correlation.
- Correlation between η_i values of concentrations of different components may be caused, for example, by stoichiometry, the law of conservation of mass and technological constraints.

IUPAC Project

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INFORMATION FOR TASK GROUP CHAIRS

THE CORE ACTIVITY OF IUPAC
is to provide critical evaluations of methods and data and to make recommendations for nomenclature, terminology, metrology, and measurement standards.

PROJECT DETAILS

IUPAC/CITAC GUIDE FOR EVALUATION OF RISKS OF CONFORMITY ASSESSMENT OF A MULTICOMPONENT MATERIAL OR OBJECT DUE TO MEASUREMENT UNCERTAINTY

Project No.:	2018-004-1-500
Start Date:	15 July 2018
End Date:	
Division Name:	Analytical Chemistry Division
Division No.:	500

✱ Objective | Description | Progress

Objective

To develop a joint IUPAC/CITAC guide for classification and quantification of risks of false decisions on conformity of a multicomponent material or object to specification or regulation limits of its chemical composition, due to measurement uncertainty.

The guide will be helpful for improvement of understanding of consequences of measurement uncertainty and correct choice of methods for testing chemical composition of multicomponent materials and objects. The opportunity to work with CITAC and prepare a joint guide (as an IUPAC TR), will give the widest possible exposure to our work and justifies, in our opinion, the requested extension.

TASK GROUP CHAIR

Ilya Kuselman

MEMBERS

D. Brynn Hibbert
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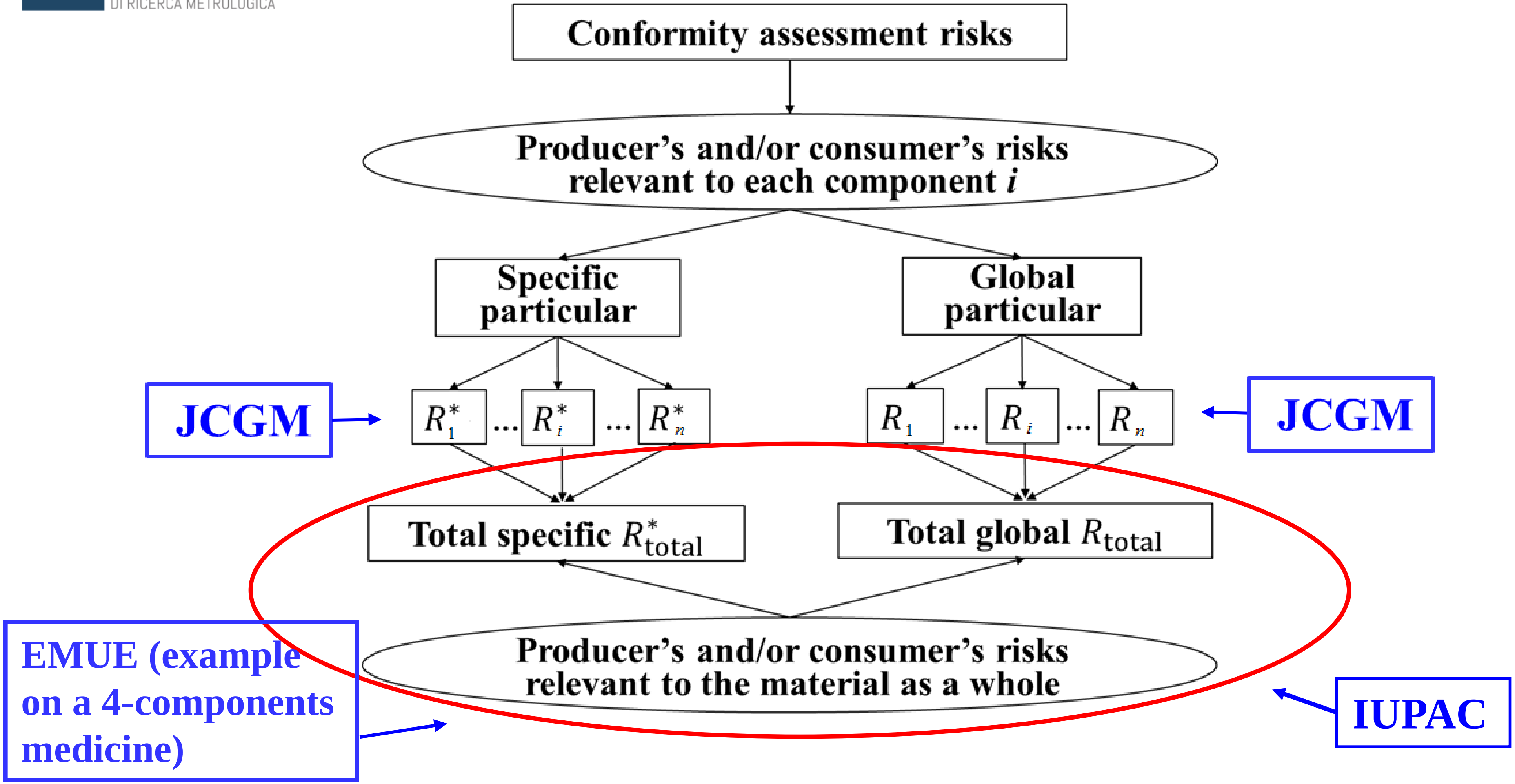
IUPAC and EMUE Projects



Correlated true and measured values

Bayes theorem for multivariated variables:

$$g(\eta \mid \eta_\mathrm{m}) = C\, g_0(\eta)\, h(\eta_\mathrm{m} \mid \eta)$$

Multivariate Posterior PDF	Multivariate Prior PDF	Multivariate Likelihood function

Total consumer's risk: All measured values within relevant AIs but at least one true value outside relevant TI

Total producer's risk: All true values within relevant TIs but at least one measured value outside relevant AI

Example: NyQuil tablets

A cold/flu medication containing four active components*:

1) acetaminophen (APAP);
2) dextromethorphan hydrobromide (DEX);
3) doxylamine succinate (DOX);
4) phenylephrine hydro-chloride (PE).

Tolerance (and acceptance) limits: 95.0 % - 105.0 % of the labelled amount (325 mg, 10 mg, 6.25 mg and 5 mg, respectively).

Relative uncertainty: 0.028.

Population of 105 lots.

Distributional assumptions:

- $\boldsymbol{\eta} \sim \mathrm{MVN}(\boldsymbol{m}, \boldsymbol{S})$ – prior PDF, with $\boldsymbol{m} = [m_1, m_2, m_3, m_4]$ and $S_{ij} = r_{ij}\, s_i\, s_j$
- $\boldsymbol{\eta}_{\mathrm{m}} \sim \mathrm{MVN}(\boldsymbol{\eta}, \boldsymbol{U})$ – likelihood, with $U_{ij} = r_{ij}\, u_i\, u_j$

Component	Index i	Mean m_i, % of labelled amount	Standard deviation s_i, % of labelled amount
APAP	1	99.18	1.37
DEX	2	97.70	1.02
DOX	3	99.33	1.05
PE	4	98.94	1.22

Component r_{ij}	Index i/j	APAP 1	DEX 2	DOX 3	PE 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

* *Talanta* **174** (2017), pp. 789-796

Example: Total (specific) consumer's risk

Case: $\eta_{mi} = m_i$ for i = 1, …, 4 (each η_{mi} within its AI) → the tested tablet is accepted. The risk for the consumer is the probability that at least one η_i is outside its TI, that is 1 – P(η_1 in T_1, η_2 in T_2, η_3 in T_3, η_4 in T_4):

$$1 - \int_{TI1} \int_{TI2} \int_{TI3} \int_{TI4} g(\eta_1, \eta_2, \eta_3, \eta_4 \mid \eta_{m1}, \eta_{m2}, \eta_{m3}, \eta_{m4})\, d\eta_1\, d\eta_2\, d\eta_3\, d\eta_4$$

where $g(\eta_1, \eta_2, \eta_3, \eta_4 \mid \eta_{m1}, \eta_{m2}, \eta_{m3}, \eta_{m4})$ is a multivariate normal PDF whose parameters depend on η_m, S and U.

$\boxed{R^*_{total} = 0.0029 \text{ (specific)}}$

$$\left.\begin{aligned} R^*_1 &= 0.0003 \\ R^*_2 &= 0.0023 \\ R^*_3 &= 0.0000 \\ R^*_4 &= 0.0002 \end{aligned}\right\}$$

Specific risks, for each component separately (JCGM 106)

Example: Total (global) consumer's risk

Drawing a tablet at random from the whole production, the probability that all its $\eta_{\mathrm{m}i}$ are inside their AIs but at least one η_i is outside its TI is calculated from the joint PDF of true and measured results $g_0(\eta)\,h(\eta_\mathrm{m}\,|\,\eta)$, by means of M MC simulations:

$$\#\{[\eta_1, \eta_2, \eta_3, \eta_4, \eta_{\mathrm{m}1}, \eta_{\mathrm{m}2}, \eta_{\mathrm{m}3}, \eta_{\mathrm{m}4}] \mid \eta_{\mathrm{m}1} \text{ in } \mathrm{A}_1, \eta_{\mathrm{m}2} \text{ in } \mathrm{A}_2, \eta_{\mathrm{m}3} \text{ in } \mathrm{A}_3, \eta_{\mathrm{m}4} \text{ in } \mathrm{A}_4, (\eta_1 \text{ out } \mathrm{T}_1) \text{ OR } (\eta_2 \text{ out } \mathrm{T}_2) \text{ OR } (\eta_3 \text{ out } \mathrm{T}_3) \text{ OR } (\eta_4 \text{ out } \mathrm{T}_4)\} / M$$

$$\boxed{R_\mathrm{total} = 0.0018 \text{ (global)}}$$

$$\left.\begin{array}{l} R_1 = 0.0005 \\ R_2 = 0.0019 \\ R_3 = 0.0000 \\ R_4 = 0.0002 \end{array}\right\}$$

Global risks, for each component separately (JCGM 106)

Conclusions

- Generalization of JCGM 106 approach to multicomponent materials or objects.
- Multivariate Bayesian modelling, taking into account uncertainties in the test results of each component and possible covariances between them.
- Calculation of total risks of false decisions, both specific and global risks and both for the producer and the consumer.
- Codes developed in R and Excel ambient are available.

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THANK YOU FOR YOUR ATTENTION!

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