SCREENFOOD

CRM production based on the ISO 17034

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Analytical Chemistry

Analytical Chemistry is a discipline consists of many strong ideas and methods in a lot of areas of science

Analytical Chemistry involves separating, identifying and determining the relative amounts of the components in sample of matter

- Qualitative analysis: Reveals the chemical identity of the species in the sample

  What?

- Quantitative analysis: Establishes the relative amount of one or more of these species or analytes in numerical terms.

  How many?

Chemical Analysis (Measurement)

Quality of Measurement Results

To ensure reliable and comparable results:

- Should be close to the real value and has repeatability.

- Should be given with uncertainty value.

- Should be comparable in national and international level (traceability).

Chemical Analysis (Measurement)

Closeness to True Value

Is $C_{observed}$ measurement results close to true value?

C_{obs} → (1,18±0,05) mg/kg

C_{CRM} → (1.20 ± 0 09) mg/kg

$R\ \% = (C_{obs} x 100)/C_{CRM}$

$R\ \% = (1.18 x 100)/1.20$

$R\ \% = 98,3\ \%$

UME CRM-1209 Elements in Sea Bass

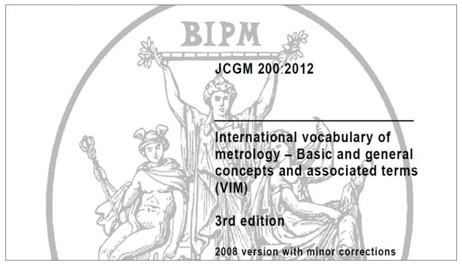
Cu (1.20±0.09) mg/g (k=2)

Measurement Uncertainty

Measurement Uncertainty

Non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used

(2.26, VIM, JCGM 200:2012).

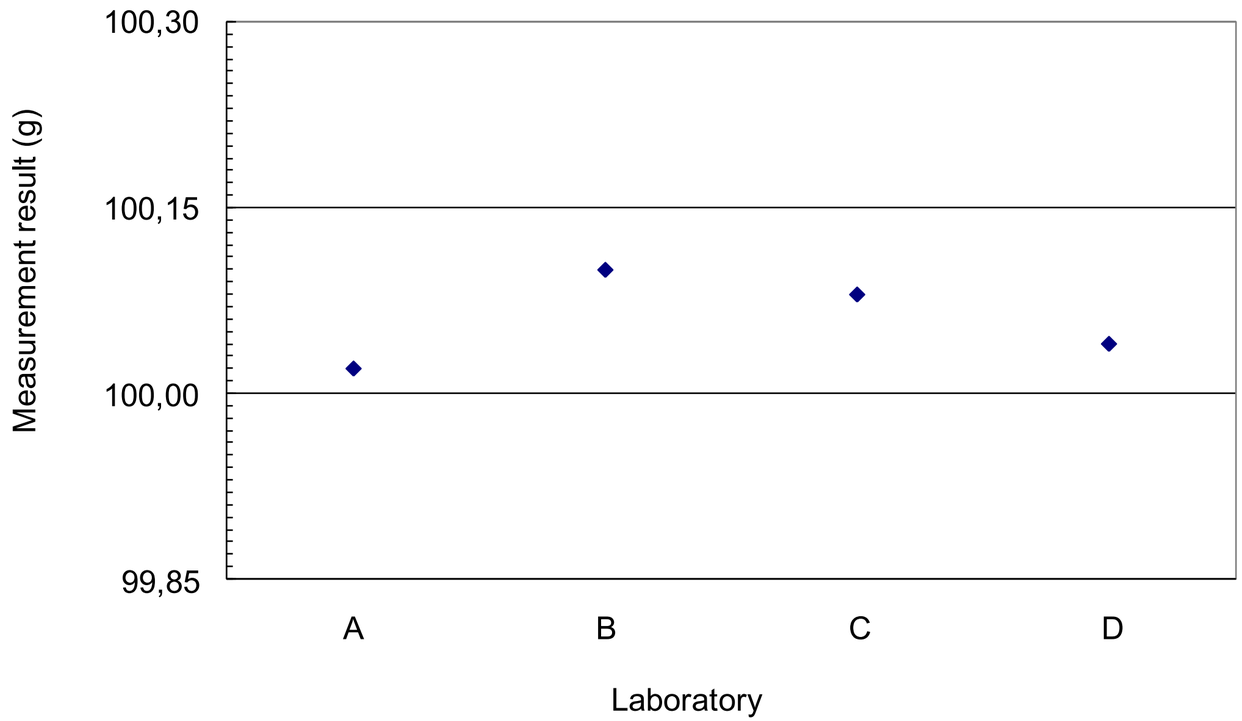


Result = value ± uncertainty

(1.18±0.01) mg/g (k=2)

Measurement Uncertainty

The Function of Measurement Uncertainty



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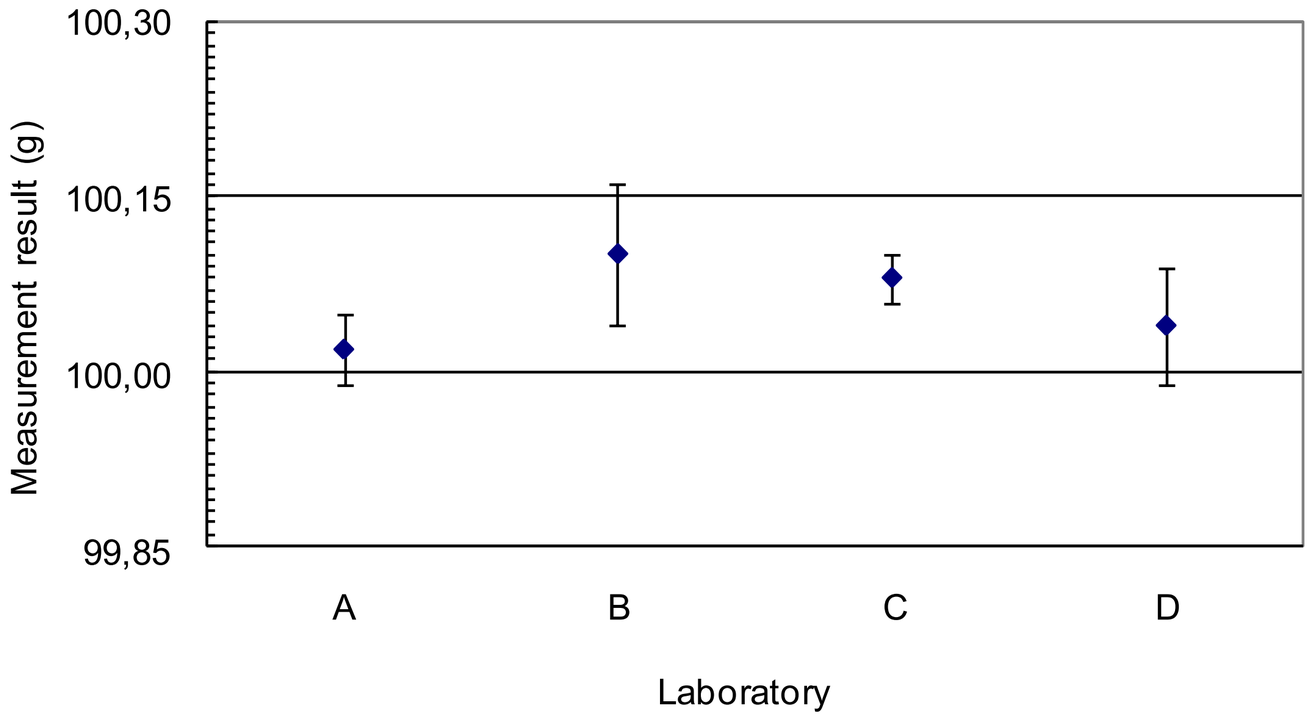

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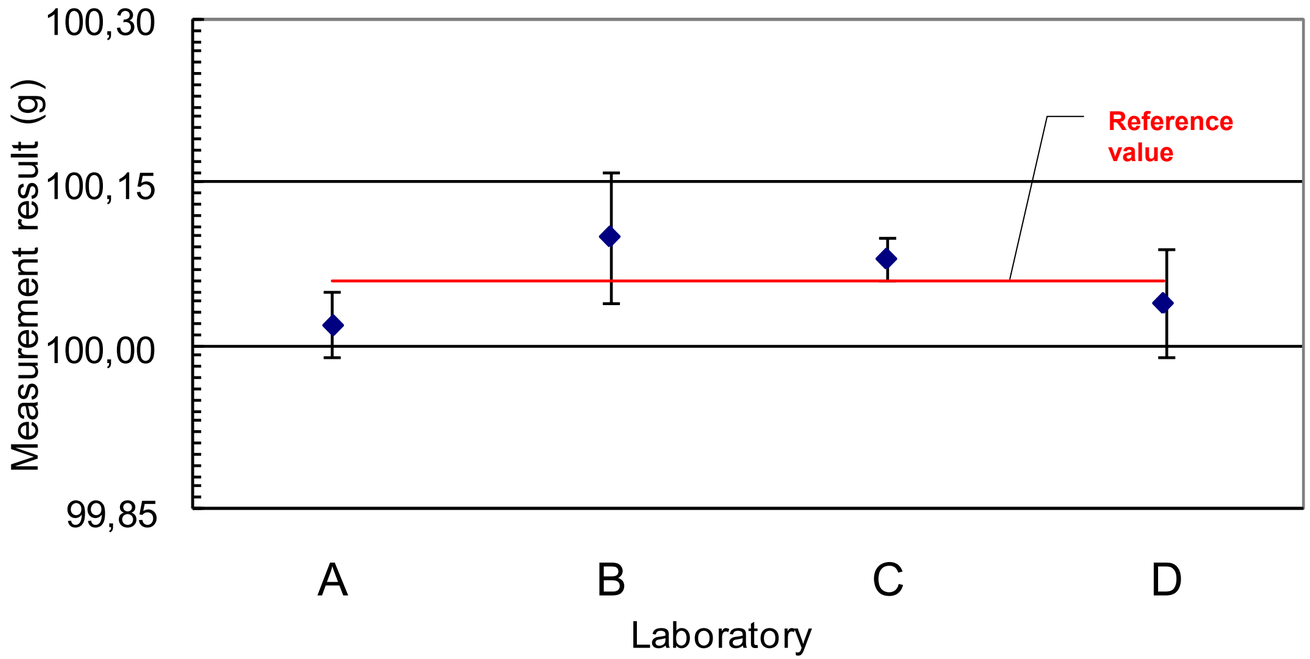

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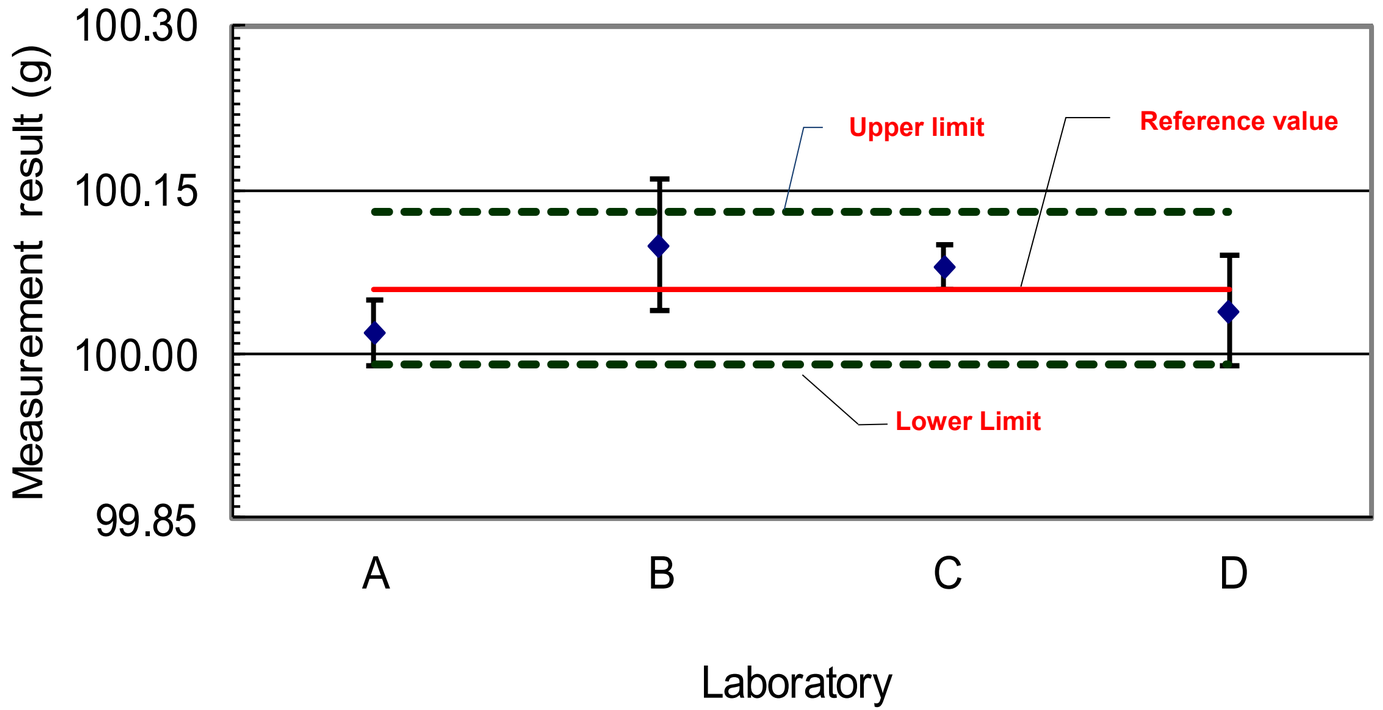
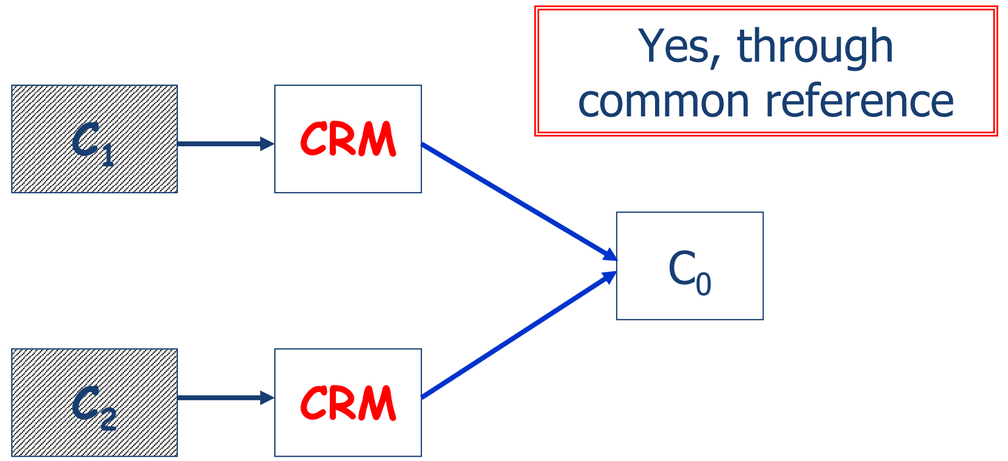


Chemical Analysis (Measurement)

Traceability

Are C1 & C2 Comparable?



UME CRM-1209 Elements in Sea Bass

Cu (1,20±0,09) mg/g (k=2)

General Information About Reference Materials

Definitions

Reference Material

Material, sufficiently homogeneous and stable with respect to one or more specified **properties**, which has been established to be fit for its intended use in a measurement process.

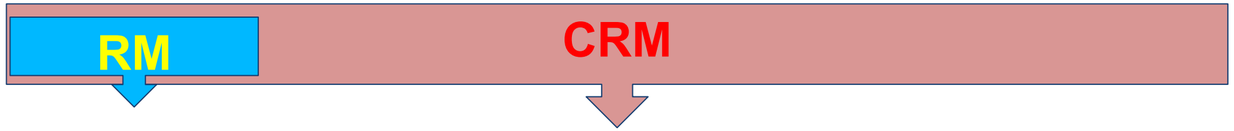
Properties can be quantitative or qualitative, e.g. identity of substances or species.

Certified Reference Material

Reference material characterized by a **metrologically valid procedure** for one or more specified properties, accompanied by an RM **certificate** (prepared acc. to ISO 33401) that provides the **value** of the **specified property**, its associated **uncertainty**, and a statement of **metrological traceability.**

ISO 17034:2016 General Requirements for the Competence of RM Producers

RM's Properties According to the Applications



	Precision Control	Accuracy (Bias) Control	Calibration	Value Assignment to Other Materials
Specification of Property of Interest	√	√	√	√
Property Value		√	√	√
Uncertainty		√	√	√
Homogeneity	√	√ ★	√ ★	√ ★
Stability	√	√ ★	√ ★	√ ★
Metrological Traceability		√	√	√
Instruction for Use	√	√	√	√
Certificate/Expiration Date		√	√	√

★ Uncertainty Contribution included in the stated uncertainty of the property value

ISO 33403:2024: Ref. Materials: Requirements and Recommendations for Use

Definitions

Property value

<of a reference material> value corresponding to a quantity representing a physical, chemical or biological property of a reference material

Certified Value

Value, assigned to a property of a reference material (RM) that is accompanied by an uncertainty statement and a statement of metrological traceability, identified as such in the RM certificate

Indicative Value

Information value
Informative value
Value of a quantity or property of a RM, which is provided for information only
❖An indicative value cannot be used as a reference in a traceability chain!

ISO GUIDE 30:2015: Ref. Materials: Selected Terms and Definitions

Classification

Calibrant

Reference material used for calibration of equipment or a measurement procedure

Quality Control Material

Reference material used for quality control of a measurement

Reference Material Types

1)Calibrator CRM's (pure materials): Characterized for chemical purity and/or trace impurity. They are used for calibration purposes.

2)Standard Solutions & Gas Mixtures: They are prepared from pure materials by gravimetrical mixing. They are used for calibration purposes.

3)Matrix (C)RM's (analyte in matrix): Characterized for major, minor and/or trace amount of chemical constituents. Prepared from a matrix having the constituent or addition of constituents to the matrix or preparation of a synthetic matrix with major matrix components. Used for method development, validation and quality control purposes.

4)Physicochemical (C)RM's: Characterized for properties like melting point, viscosity and density.

5)Reference Objects and Human made artefacts: Characterised for functional properties such as taste, smell and hardness. Microscopy samples characterized for microbiological properties or samples characterized for fiber type are also belong to this group

Application Areas of (C)RMs

- Method development
- Method validation

–Evaluation of trueness

–Estimation of uncertainty

- Calibration
- Method performance charts

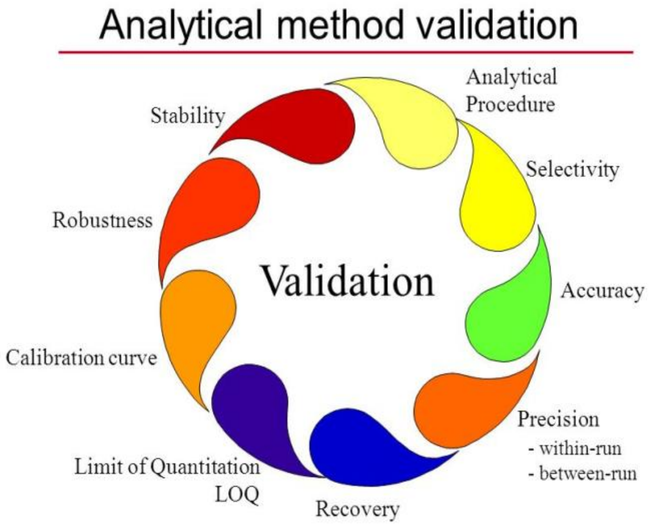
–Within Lab Quality Control (‘charts’)

–Evaluation of analyst or instrument performance

- Proficiency Tests

–Validation of Proficiency (external comparison)

- Assigning value to other materials

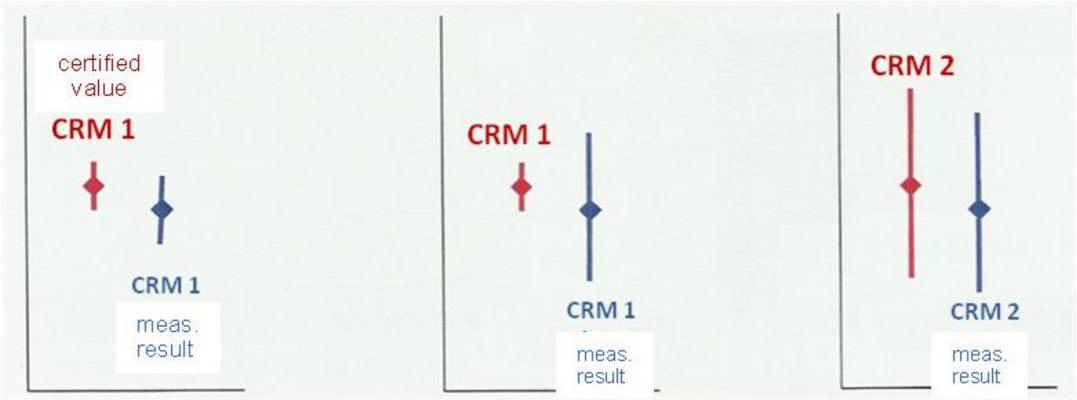


CRM’s serve for all these applications if they are properly selected and properly used!

Proper Selection of (C)RMs

➢ Defined Intended Use	➢Calibration or Quality Control Pure Materials/ Matrix Materials
➢ Measurand and Range	➢Extractable Lead, Total Lead A CRM with lower property value then lab's LOQ!
➢Matrix matching and potential interferences	➢Lead in drinking water, lead in serum, matrix differences: (eg. Fat content for food)
➢Uncertainty and Traceability	➢Is the uncertainty statement suitable acc. to GUM? (ISO/IEC Guide 98-3:2008)? Do homogeneity and stability taken into account?
➢ Certification Procedures	➢Are they in accordance with ISO 17034 & ISO Guide 35
➢ Quality Control Issues	➢Conformity of Laboratories participating in certification ISO/IEC 17025 Accreditation or CIPM MRA CMC's (Calibration and Measurement Capabilities)?
➢ Clear and Transparent Information	➢CRM certificate, Certification Report?
➢ Availability and Price	➢Can the material be reached as quickly as possible to the customer under defined conditions ? (e.g: In dry Ice: < -70 °C)

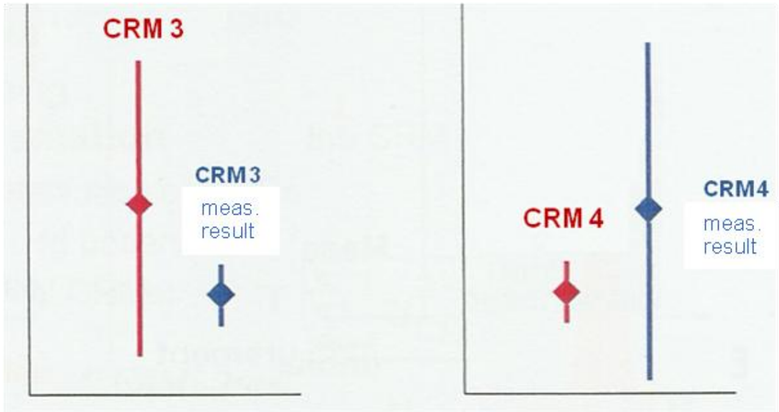
Evaluation of CRM Uncertainties



Most information about method performance

Moderate information about method performance

Little information about method performance



CRM is not suitable

Is the method suitable?

Evaluation of Method Performance by CRMs

1) Calculate the absolute difference

$$\Delta = |Mean\ value\ of\ CRM's\ measurements - CRM's\ Certificate\ Value|$$

2) Conversion of expanded uncertainty given in CRM certificate to the standard uncertainty

$$u_{\mathrm{CRM}} = \frac{U_{\mathrm{CRM}}}{k}$$

3) Estimation of the standard measurement uncertainty (u_{m})

4) Calculation of the combined uncertainty

$$u_{\Delta} = \sqrt{{u_m}^2 + {u_{\mathrm{CRM}}}^2}$$

5)Compare Δ with 2 u_{Δ}:

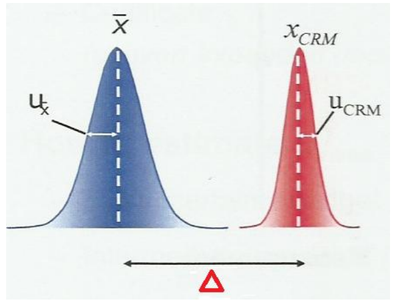
If $\Delta \leq 2\ u_{\Delta}$ Method performance is acceptable.

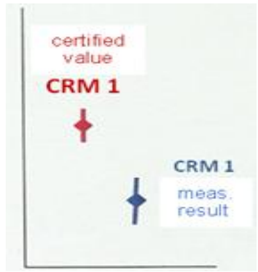
If $\Delta > 2\ u_{\Delta}$ Method performance is not acceptable.

ERM Application Note 1

https://crm.jrc.ec.europa.eu/e/132/User-support-Application-Notes

Improvement of Method Performance





Method performance is unacceptable

Reason found, Measurement repeated

Method Performance is acceptable

Detailed investigation needed to be done to find and correct the reason for unacceptable result

Despite all investigations the reason can not be found and the method performance is still unacceptable:

Further Check

1) **If the bias can be shown that it is systematic over time (eg. always 10% lower) (can much easily be seen by a control chart)**
2) **If the bias is constant or has been proven to have a mathematical relation with the concentration of the analyte in the sample**

Then,

- **The laboratory can either use a factor to correct the reported result for the bias or**
- **Without correcting the result, lab can add the influence of bias to the uncertainty**

Databases, CRM Producers, Useful Links

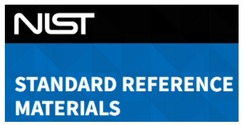
Databases:

COMAR	*www.comar.bam.de*
AOAC	http://tdrmdb.aoac.org/
TÜRKAK REMBİS	https://rembis.turkak.org.tr/
RM-App	https://www.metrofood.eu/access/e-services.html
Geological RMs	http://georem.mpch-mainz.gwdg.de/
Clinical CRMs	http://www.bipm.org/jctlm/
Key Comparisons	https://www.bipm.org/kcdb/

Some CRM Producers and Distributors:

NIST	https://www.nist.gov/srm
EC-JRC-IRMM	https://crm.jrc.ec.europa.eu/
BAM	https://www.bam.de
IAEA	https://nucleus.iaea.org/rpst
NMIJ	https://unit.aist.go.jp/nmij/english/
KRISS	www.kriss.re.kr/eng
NRC	https://nrc.canada.ca/en/certifications-evaluations-standards/certified-reference-materials
NMIA	https://shop.measurement.gov.au/collections/reference-materials
TUBITAK UME	https://rm.ume.tubitak.gov.tr
LGC	www.lgcstandards.com
Sigma-Aldrich	www.sigmaaldrich.com

Useful Information about RMs: *https://crm.jrc.ec.europa.eu/e/132/User-support-Application-Notes*



Questions

General Information About Reference Materials

Question 1

Which of the following combination of properties differ CRMs from RMs?

I) Homogeneity
II) Stability
III) Metrological Traceability
IV) A certificate prepared in accordance to ISO 33401
V) Can be used for method validation covering trueness study
VI) Can be used for method development

a) III, IV,VI
b) I, II, IV
c) III, IV, V
d) All of the above

Question 2

Which of the following groups shows the main usage areas of matrix CRMs?

I) Method development
II) Calibration
III) Validation
IV) Quality control and Quality Assurance for measurements

a) II, III, IV
b) I, III, IV
c) I, II, IV
d) All of the above

ISO 17034
Technical & Production Requirements

7. Technical and Production Requirements

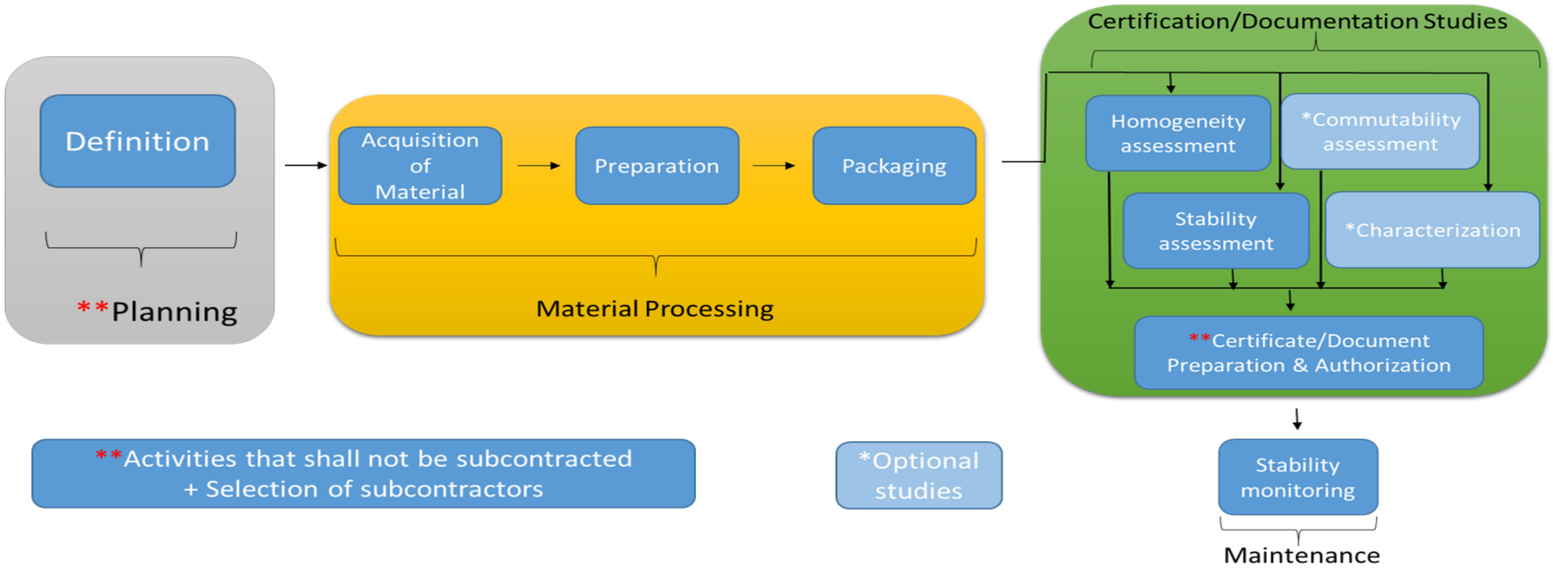
7.1 General Requirements

- The producer should address the requirements for the production of RMs.
- A CRM has at least one certified value.
- Metrological traceability applies to certified values.
- Standard contain requirements for certified values and other property values.

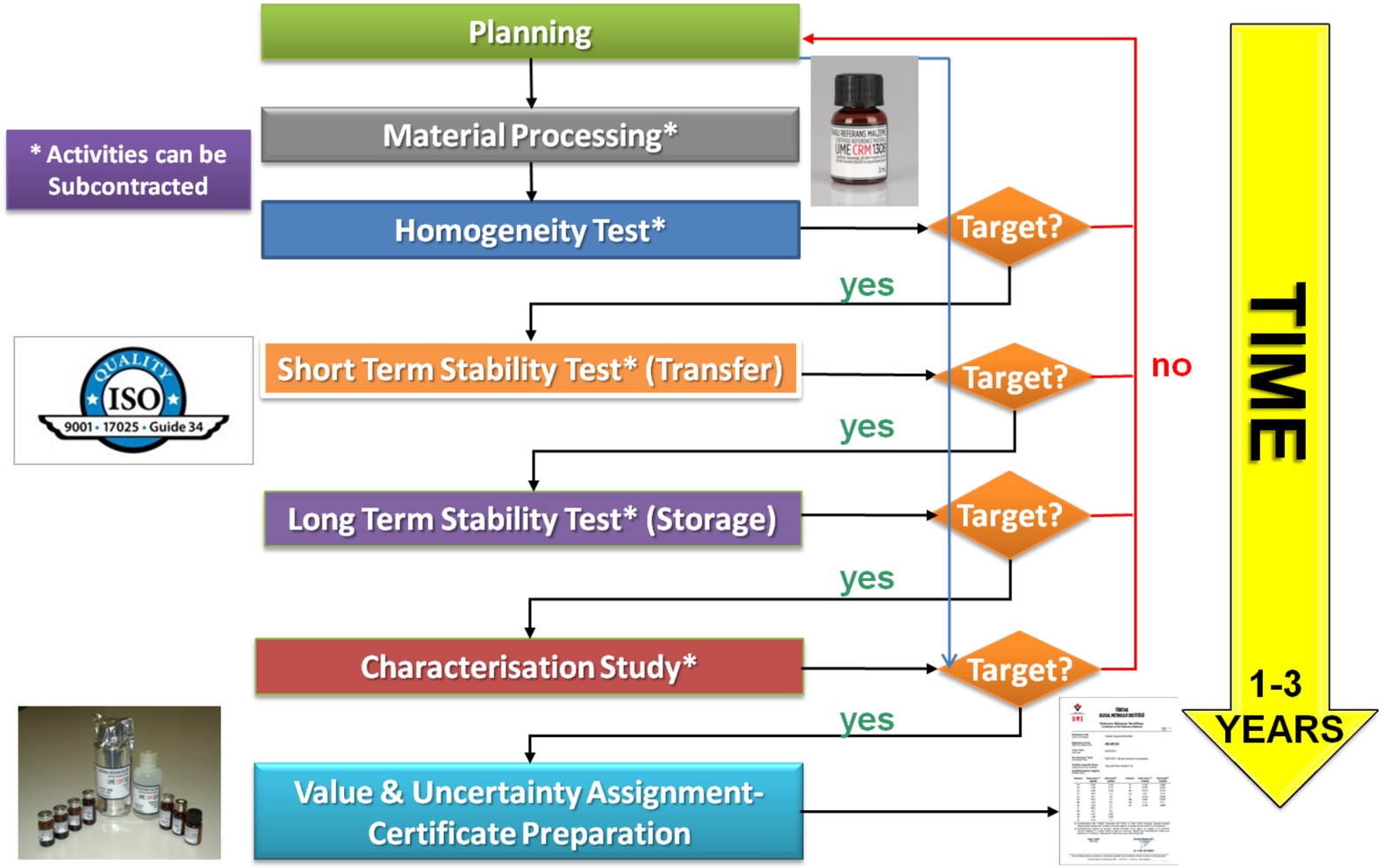
Summary of Production Requirements for RMs and CRMs

Requirement	All RMs	CRMs
Production Planning	✓	✓
Production Control	✓	✓
Material Handling-Storage	✓	✓
Material Processing	✓	✓
Measurement Procedures	✓	✓
Measuring Equipment	✓	✓
Data Integrity & Evaluation	✓	✓
Metrological Traceability of Assigned Values	✗	✓
Assessment of Homogeneity	✓	✓
Assessment and Monitoring of Stability	✓	✓
Characterization	✓ If values are to be assigned	✓
Assignment of Property Values	✓ If values are to be assigned	✓
Assignment of Uncertainties of Property Values	✗	✓ For certified values only
Documents & Labels	✓	✓
Distribution Service	✓	✓
Control of Quality and Technical Records	✓	✓
Management of non-confirming work	✓	✓
Handling of complaints	✓	✓

Main Steps in Producing and Maintaining RMs



RM Production Steps



Planning a RM Project

Planning an RM Project

Bottles?

Minimum sample Intake?

Gamma Radiation for stability?

Matrix?

Where to obtain Raw material?

Label Design?

Traceability?

When to do processing?

Which processing equipment should be used?

Storage conditions?

When to do short term stability test?

Repetability?

When to do long term stability?

Particle size distribution?

When to do homogeneity test?

Reference Temperature?

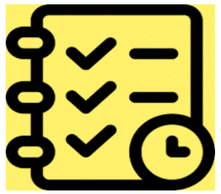
Test Temperature?

Target Concentrations?

Project Summary?

Target Analytes?

7.2 Production Planning



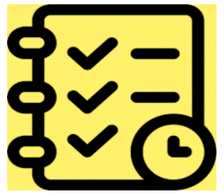
- The RMP should identify and plan processes that affect the quality of RM production, and the production plan should be documented and recorded.

  A mechanism (e.g. a management/technical advisory group) can be established to make recommendations on the production processes e.g assigning the property values of interest

- Technical input of subcontractors involved should be defined and this information should be documented and regularly reviewed.

7.2 Production Planning

•The RMP shall adress the following in planning stage:

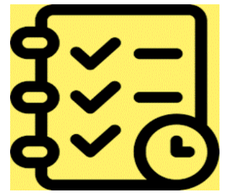


- ✓ **material selection** (including, where appropriate, sampling)
- ✓ **verification** of the **identity** of the material
- ✓ maintaining **suitable environment** for all aspects of production
- ✓ material **processing**
- ✓ selection of **measurement procedures**
- ✓ validation of **measurement methods**
- ✓ verification and calibration of **measurement equipment**
- ✓ defining **acceptance criteria** for, and assessment of, **homogeneity**
- ✓ specification of **acceptance criteria** for assessment and monitoring of **stability**
- ✓ designing and organizing **characterization study**
- ✓ assessing **commutability** (if appropriate);

Guidance on the need for commutability assessment of RMs is given in a ISO REMCO paper
http://isotc.iso.org/livelink/livelink/fetch/8854933/8854951/8854960/279217/Commutability_document_final.pdf?nodeid=16787892&vernum=-2

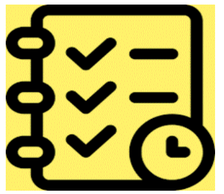
7.2 Production Planning

- The RMP shall adress the following: in planning stage:



- ✓ assigning **property values**
- ✓ establishing uncertainty budgets and estimating **uncertainties** of certified values
- ✓ defining **acceptance criteria** for **measurand levels** and their **uncertainties**
- ✓ establishing **metrological traceability** of measurement results and certified values
- ✓ issuing **RM documents**
- ✓ adequate **storage** facilities and conditions
- ✓ appropriate **labelling** and **packaging** of the RMs
- ✓ appropriate **transport** arrangements
- ✓ post-production **stability monitoring**, if applicable
- ✓ arranging **post-distribution service** for users

7.2 Production Planning



•Where multiple batches of RMs with equivalent properties are produced with similar starting materials and utilizing the same procedures, verification should ensure that information obtained from previous batches remains applicable to the new batch.

Multiple batches can be the same material produced at the same time or can be material produced at different times.

Where multiple batches are produced, some tests (homogeneity & stability) can be omited or simplified for some batches.

7.3 Production Planning & Control (Record Example)

	Planned	Realized	Explanation (If deviation from planned exists)
Measurand			
Matrix			
Parameter(s)/Analyte(s)			
Content / Range (unit)			
Uncertainty Homogeneity Short Term Stability Long Term Stability Characterization Combined Covarage Factor Expanded Uncertainty			
Traceability			
Required Amount Raw Material			
Selection Criteria for Raw Material			
Material Processing Plan			
Total Number of Units			
Amount of Material in one unit (g / mL)			
Particle Size Range			
Moisture Content (For Solids)			
Container and Cap Info.			
Storage Conditions			
Transfer Conditions			

7.4 Material Handling and Storage

- ✓ The integrity of its candidate RM shall be ensured throughout the production process (e.g. Low humidity conditions for materials that can uptake moisture).
- ✓ Candidate RMs shall be identified, preserved and separated from chemicals and other samples.
- ✓ Adequate packaging of all RMs shall be ensured (e.g. light-protecting, moisture-free or inert-gas packaging) and provide secure storage areas to prevent deterioration.
- ✓ The condition of all RMs shall be controlled at appropriate intervals throughout the storage period, in order to detect possible deterioration.
- ✓ **Packaging** and **labelling** shall be controlled to ensure conformity with **safety** and **transport** requirements.
- ✓ Measures shall be taken to protect the integrity of each RM unit is maintained to the point when it is first used


Vaccum containers


Glove box


Light protecting amber glass bottle


Vaccum sachet packaging

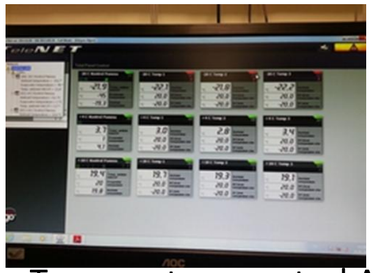

Temperature controlled storage rooms

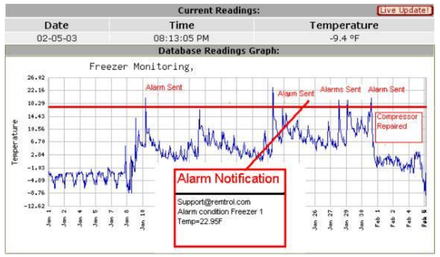
Material Handling and Storage (Examples)

Registration of produced RMs for tests or sales

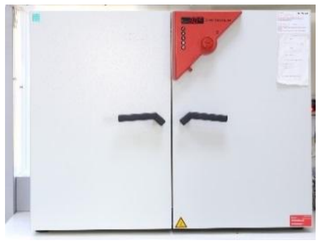
Storage of materials in temperature controlled areas

-80 °C and - 45 °C Freezers





Temperature control Alarm Systems (e-mail, SMS)



Oven for Short Term Stability Test

Climatic Cabinets Temperature & Humidity

7.5 Material Processing

Procedures for material processing shall adress the following:

- ✓ qualitative analysis for verification of material type or identity
- ✓ synthesis, purification (e.g. distillation, extraction), incubation, and transformation into the final form (e.g., grinding, blending, sieving, riffling)
- ✓ homogenization
- ✓ proper handling (e.g. protection from contamination by use of inert equipment)
- ✓ measurements for control of processing (e.g. particle size distribution, moisture content)
- ✓ pre-treatments, cleaning or sterilization of processing equipment and sample containers
- ✓ stabilization of material (e.g. drying, gamma irradiation, sterilization)
- ✓ packaging (e.g. bottling, ar
- ✓ safety precautions

Bottle Cleaning and Drying in ISO Class 6 Clean Lab

Cryogenic Titanium Mill

Homogenization

Filling and Capping

Material Processing Quality Control (Examples)

Particle Size Distribution

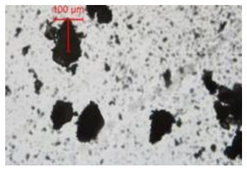
Laser Diffraction 0.2-2000 µm

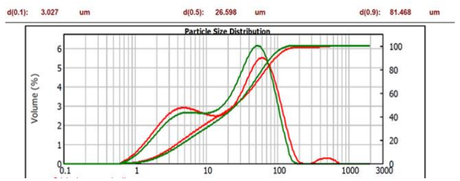
Vibrating Sieve 45-2000 µm

Airjet Sieve 45-2000 µm

Particle Size Shape, Color

Stereo Microscobe





Moisture Content

Karl Fischer with oven

Oven Drying

Multi Purpose

Balances 200 g – 60 kg

pH meter

Material Processing Planning & Report (Record Example)

Material Processing Plan & Report	Planned	Realized	Responsible, Date, Signature
Safety and Occupational Health Precautions			
Contamination and Handling Precautions			
Preparation and Cleaning of Equipment			
Material Drying Description (If applicable)			
Material Grinding Description (If applicable)			
Material Sieving Description (If applicable)			
Homogenization Description			
Filling and Labelling Description			
Cleaning Operations and Disposal of Waste			
Time and Staff Detailed Work Planning			
Work to be performed / Date / Time / Pesonnel			

Approval of the Plan			Approval of the Report		
Name Surname	Date	Signature	Name Surname	Date	Signature

Project Responsible, Project Personel, Occupational Health Responsible reviews and approves at planning and after execution.

Material Processing - Drying Equipment

Freeze Drying

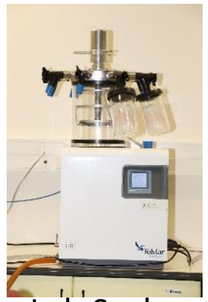
Vacuum Drying

Oven Drying

Lyophilizers

(Animal and Plant Materials)

(Roasted Hazelnut, Soil, etc.)



Lab Scale

Pilot Scale (10 kg ice, 0,5 m^2)

Production Scale (75 kg ice, 4 m^2)

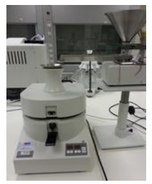
Oven with HEPA Filtered Air Flow

Material Processing - Milling Equipment

Various Mills

Food Grade Roller Mill
50 kg/hr, Hardened Steel

Cryogenic Titanium Mill
5 kg/day



High Speed Cutting Mill
1 kg/day, Steel or
Tungsten Carbide

Universal
Cutting Mill
10 kg/day,
Steel or
Tungsten Carbide

Ball Mill
10 kg/day
Steel, Agate

Mortar Mill
1 kg/day
Steel or
Tungsten Carbide

Blenders

Vacuum Blender
2 Liter capacity,
Stainless Steel

Kitchen Blender
2 Liter capacity,
Stainless Steel

Ultraturrax Chopper
Homogenizer
20-30 kg

Knives
Ceramic/ Stainless Steel

Material Processing- Sieving & Homogenisation Equipment

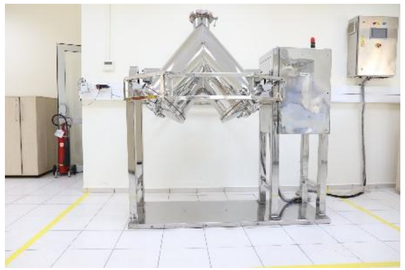
Sieving Systems

Production Scale
60 cm dia.
Stainless Steel / Nylon

Small Scale
20 cm dia.
Stainless Steel

Homogenizers

3-D Mixer (350 L)
Stainless Steel / HDPE
30, 60, 120, 240 Liter adaptors



V-Shaped Mixer
150 Liter Stainless Steel

Liquid Circulation & Filtration
200 Liter HDPE

Material Filling Equipment

Solid Powders

Semi Automatic Filling
Based on Mass
Auger Type
SS/PTFE
(10 g – 2 kg)

Semi Automatic Filling
Based on Mass
Vibration Type
SS
(100 mg – 10 g)

Manuel Filling Based on mass, Sticky powders
Laminar Flow Cabinet

Liquids

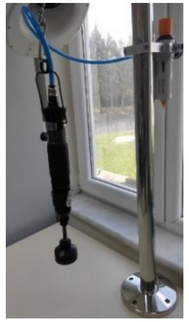
Automatic Filling
Based on Peristaltic Pumping
Inner capping, Screw & Crimp Capping
(2 mL– 120 mL)

Semi Automatic Filling
Based on Volume
for Viscous Liquids

Automatic Filling
Based on Volume
(1 mL– 20 mL)

Equipment for Cap Closure & Sealing & Labelling

Automatic
Inner Capping, Screw & Crimp Capping



Screw Cap Closure

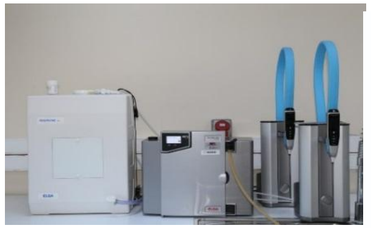
Crimp Cap Closure

Ampouling Machine
Propane-O_2 flame
(1 mL– 20 mL)

Vacuum Sachet Machine

Automatic Labelling Machine For
Preprinted Labels (Fill Order)

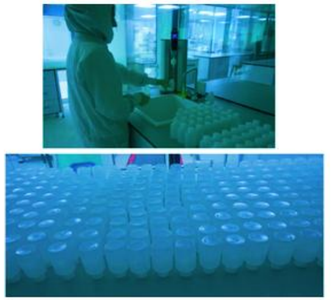
Equipment for Cleaning, Drying & Occupational Health



Water Purification Systems

Washing Machine

Ultrasound Bath



ISO 4,5,6 Clean Lab

Chemical Storage Cabinets

Point Extractors, Googles, Coats, Masks, Gloves

Fume Hoods

Glove Box

7.6 & 7.7 Measurement Procedures and Equipment

- ✓ RMP shall ensure that the relevant requirements of **ISO/IEC 17025** are met with respect to **calibration** and **testing**.
- ✓ Activities shall be consistent with the property values of RM with any standard specifications relevant to the measurement.

Lab Staff & Instrument

Competance

Training & Calibration

+

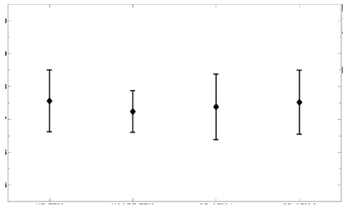
(Standard) Methods

International Organization for Standardization

Validation/Verification & Fit for Purpose

=

Measurement Results



Reliable & Traceable

7.8 Data Integrity & Evaluation

RMP shall ensure that

- ✓ all calculations & data transfers are subject to appropriate checks
- ✓ software developed inhouse or modified for specific use should be validated and fit for purpose e.g. validation can be manual calculation of spreadsheet calculation or using data sets with known solutions
- ✓ procedures are established and implemented for protecting data (entry, storage, processing)
- ✓ hardware and software's are maintained for proper functioning (environmental and operating conditions)
- ✓ unauthorized access and changes to records are prevented
- ✓ appropriate statistical procedures are used in monitoring, testing, calibration or value assignment e.g. validation of statistical procedures can be done by referencing to related literature

7.9 Metrological Traceability of Certified Values

RMP shall provide evidence of the metrological traceability of the certified value to a stated reference.

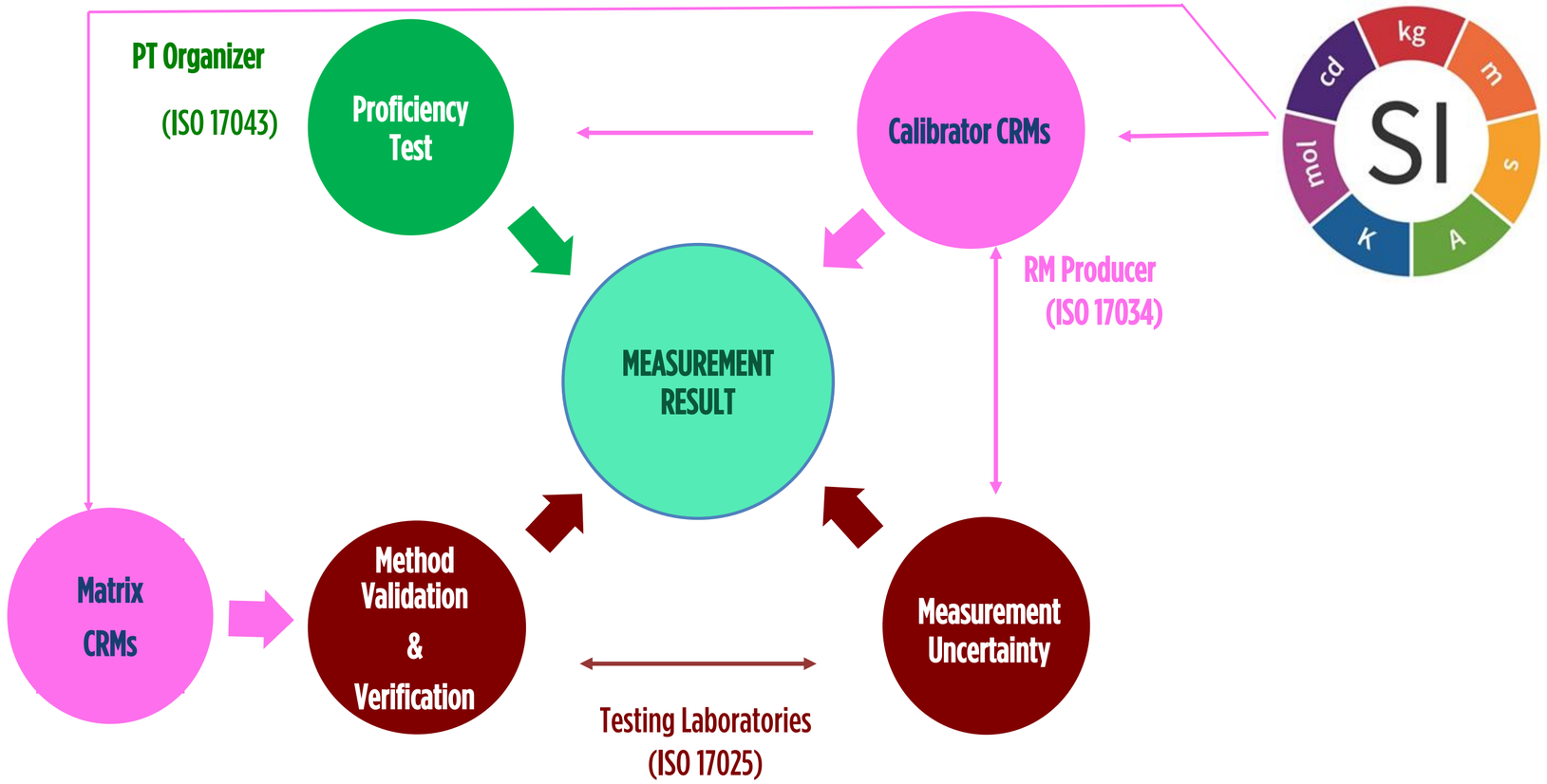
➢A combination of results obtained by different measurement procedures and/or laboratories all being traceable to the same reference is also traceable to that reference.

➢The evidence can be based on evaluation of the measurement process or on confirmation of metrological traceability by comparison of results with independent traceable values.

➢Clear identification of the property of interest, traceability of the numerical value and the stated reference contribute to the traceability of results.

- **ISO/TR 16476** contains additional information on establishment and expression of metrological traceability of certified values.

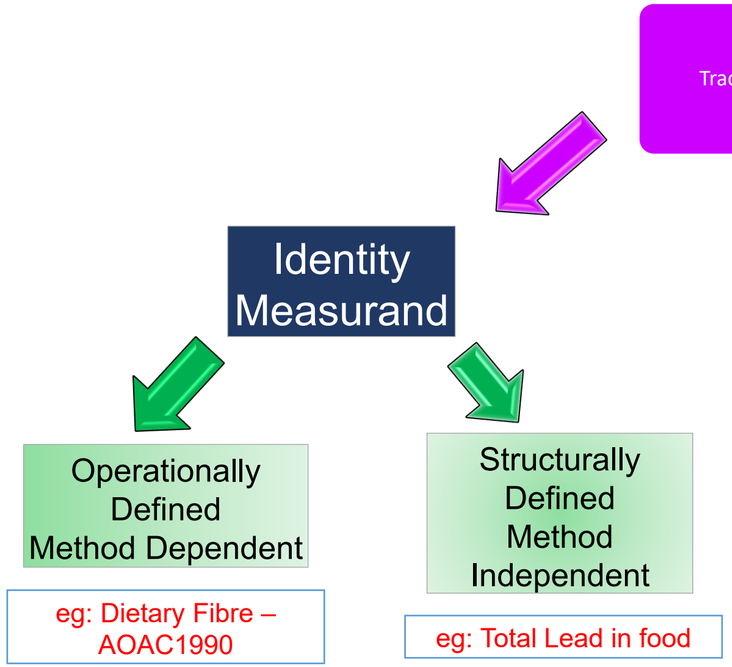
7.9 SI Traceability of Measurement Results



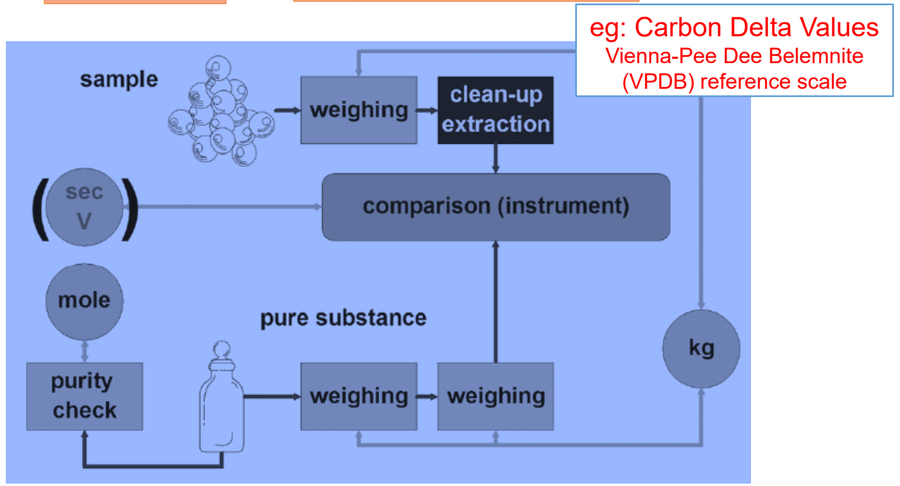
Main Components for Traceability

1. Reference Materials ; Calibrators, Matrix CRMs
2. Methot Validation / Method Verification
3. Measurement Uncertainty
4. 3rd party Accreditation and Comparisons (Proficiency Tests)

Metrological Traceability

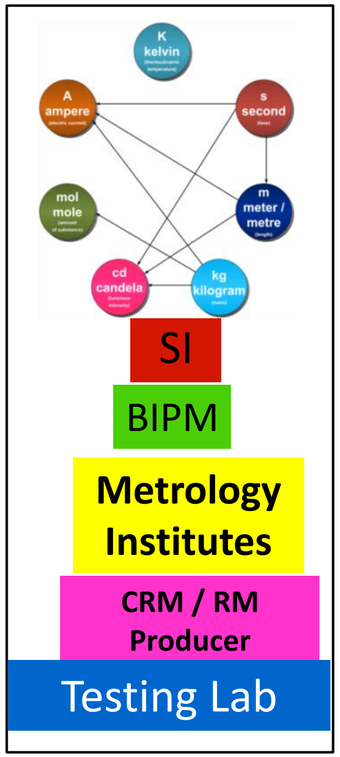


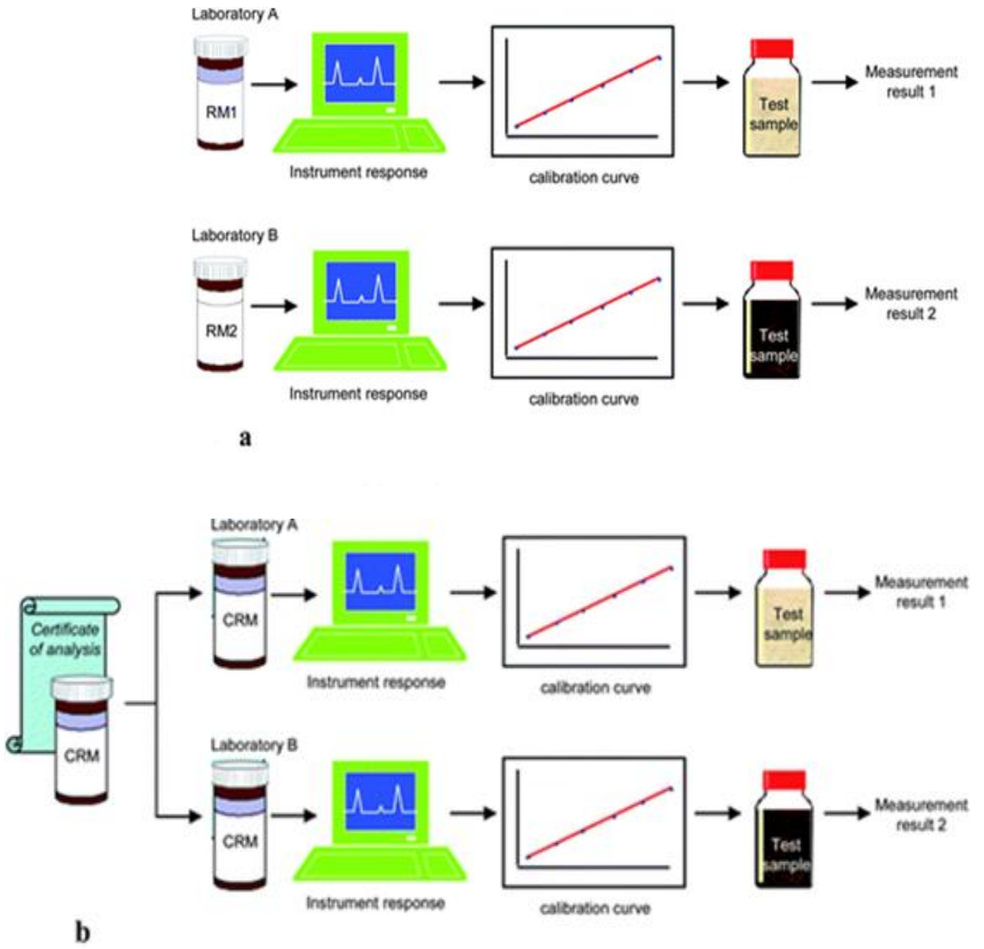
Secondary parameters that have a significant influence on the certified value or its uncertainty should also have evidence of metrological traceability. Examples of secondary parameters are temperature and humidity.



ISO/TR 16476 Establishing and expressing metrological traceability

Metrological Traceability

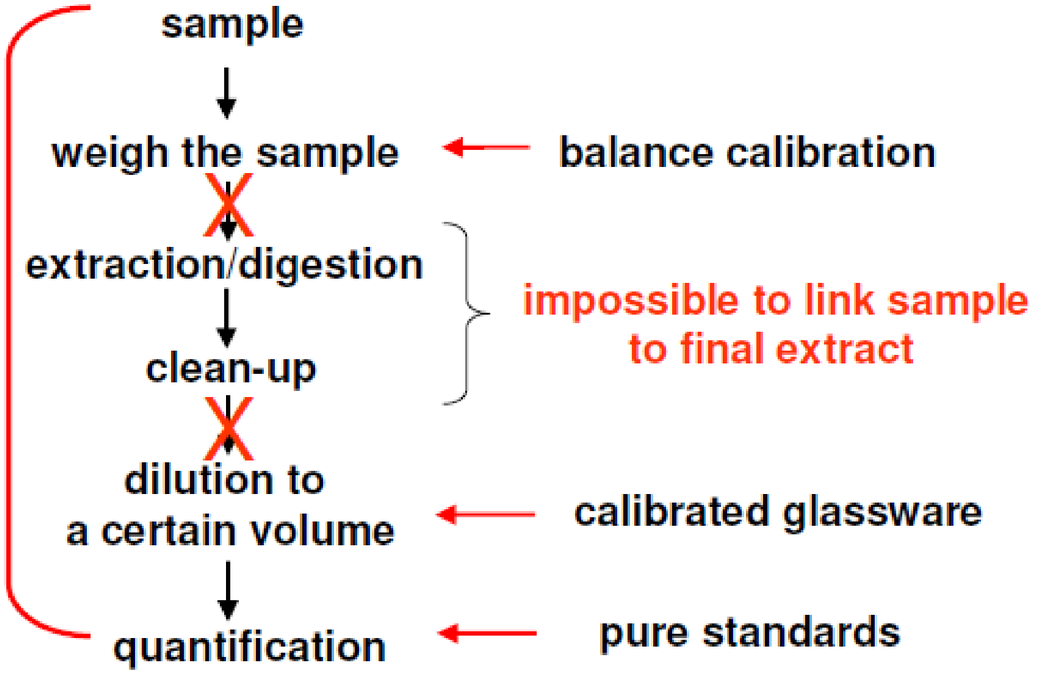


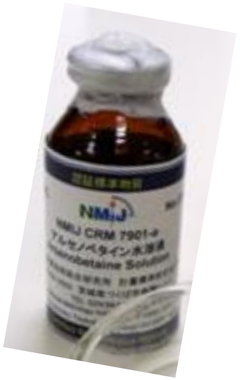


Comparable Results

Problems in Measurement Chain

Arsenobetaine in Fish





Arsenobetaine solution “Calibrator”

Verification of Traceability

Certified Value ± Uncertainty

Sample

↓

Grinding

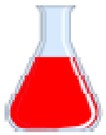
↓

Extraction

↓

Clean-up

↓



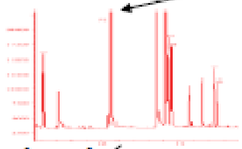
Compare

Measurement Result ± Uncertainty

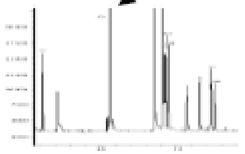
QUANTITY

? Purity?

signal



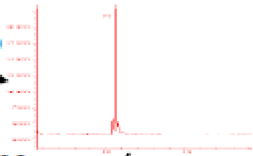
signal



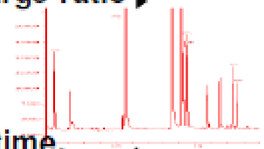
IDENTITY

Pure calibrator traceable to SI

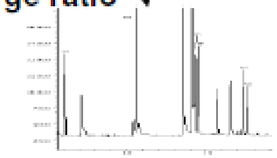
retention time, mass/charge ratio



retention time, mass/charge ratio



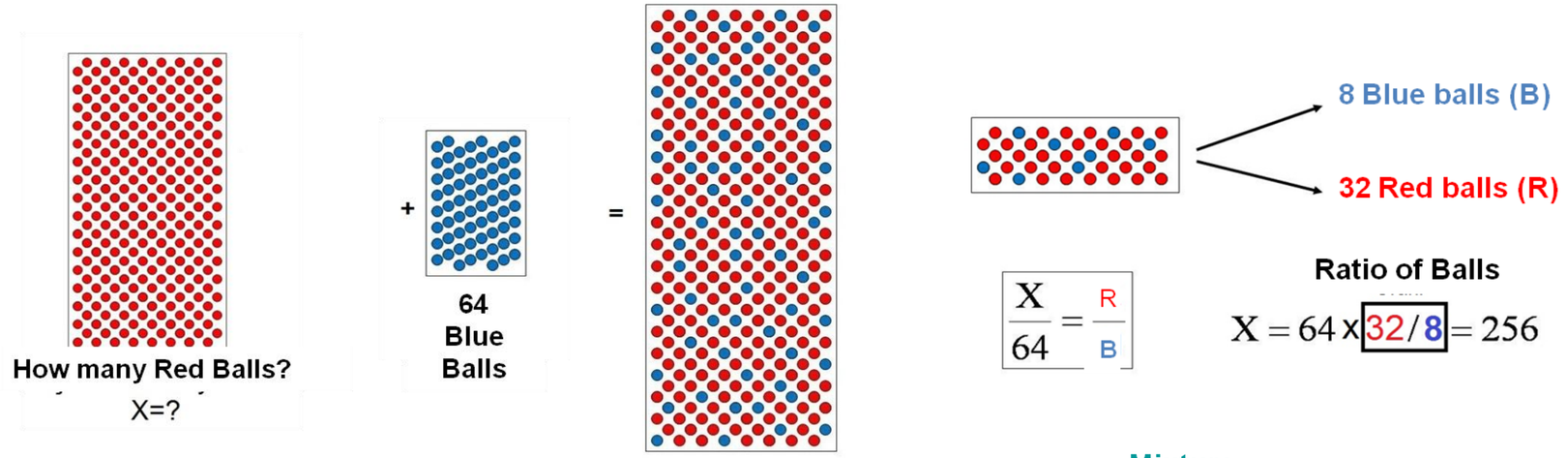
retention time, mass/charge ratio

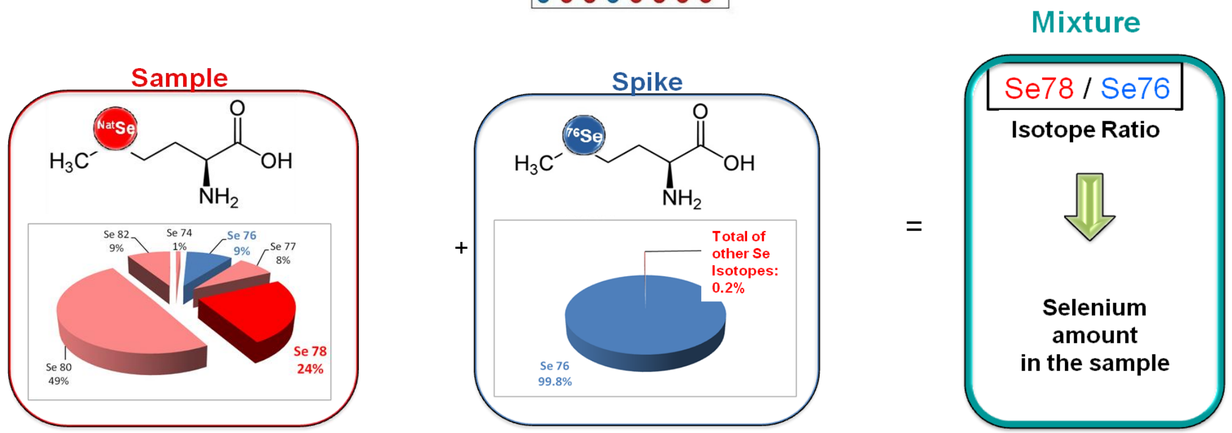


Potential Primary Methods forTraceability

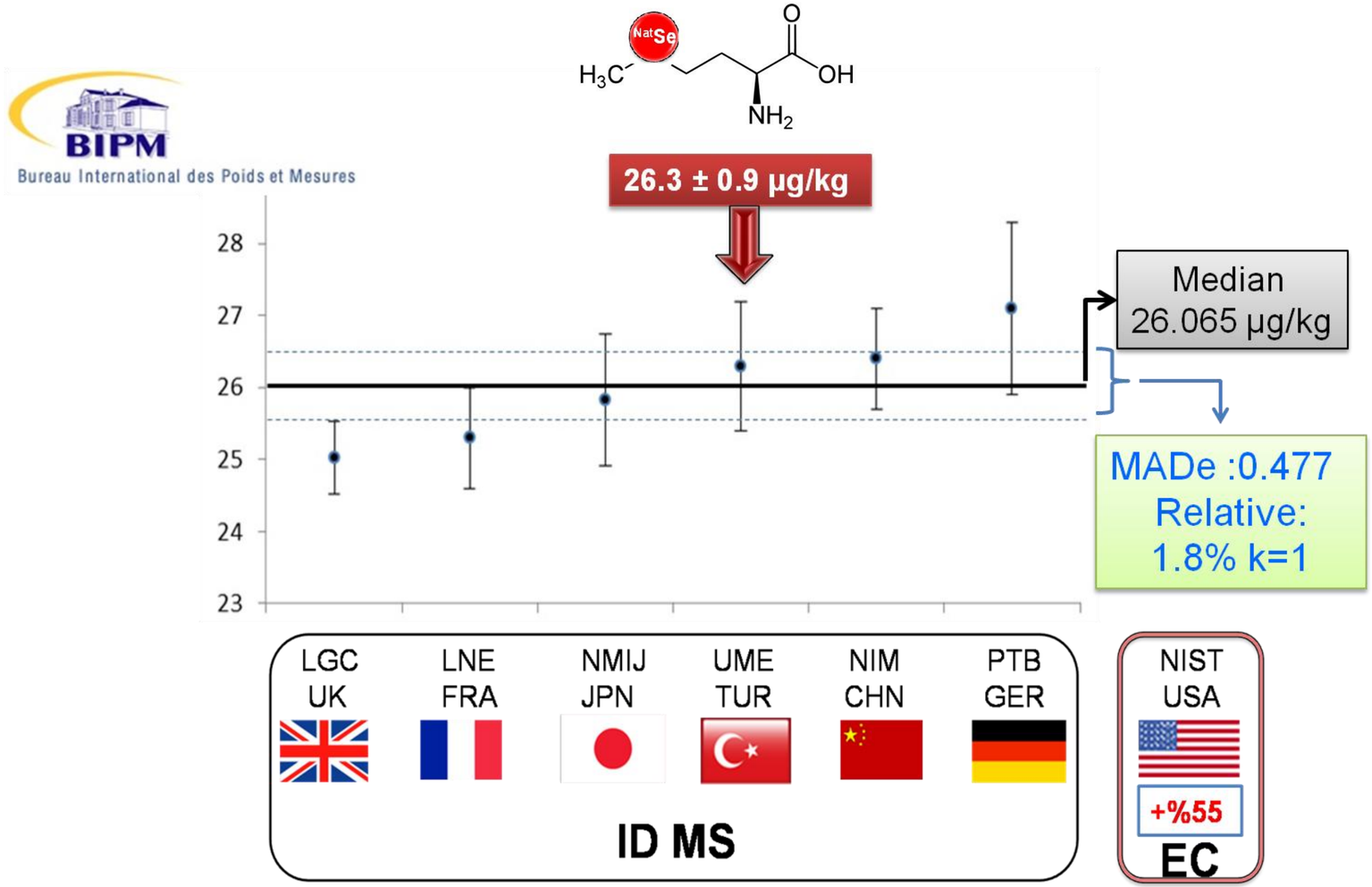
- Gravimetry
- Titrimetry
- Coulometry
- Calorimetry (differential scanning calorimetry)
- Cavity Ring Down Spectrometry
- Isotope Dilution Mass Spectrometry
- Instrumental Neutron Activation Analysis
- Quantitative Nuclear Magnetic Resonance NMR Spectroscopy

Potential Primary Method: Isotope Dilution





BIPM CCQM K-107 SeMet in Human Serum Study



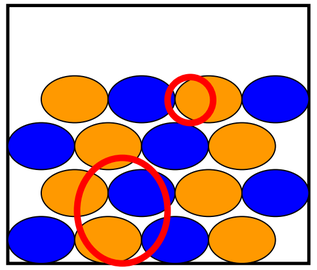
http://kcdb.bipm.org/AppendixB/appbresults/CCQM-K107/CCQM-K107.pdf

Homogeneity

- **Within Unit Homogeneity**

✓ Heterogeneity can be eliminated by increasing min. samp. intake

✓ Important to determine the min. amount for samp. intake



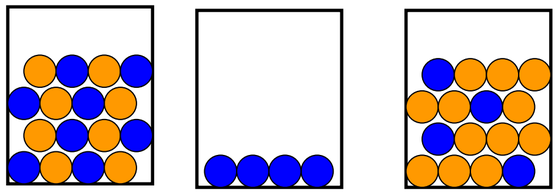
- **Between Units Homogeneity**

✓ Present Heterogeneity between units can not be eliminated.

✓ Has effect on the uncertainty of the CRM.

✓ Obtained data is used to calculate the uncertainty due to heterogeneity between the units.

✓ 10 or $\sqrt[3]{}$total number of units produced (whichever bigger) is tested.



7.10 Assessment of Homogeneity

•The producer should carry out an assessment of the homogeneity of any candidate RM in its final packaged form to ensure its fitness for purpose.

Assessment of homogeneity can include the use of prior evidence (prior experimental evidence), the conduct of an experimental homogeneity study on the candidate RM or both. In most cases, an experimental study is necessary.
Guidance on experimental homogeneity study is provided in ISO 33405.

Experimental homogeneity tests require measurements of a representative number of randomly chosen units. The units can be chosen for example by random selection, stratified random selection or systematic selection from a random start point.

•When the material is produced in multiple batches, the equivalence of the batches should be demonstrated or homogeneity of each batch should be evaluated separately

Homogeneity Test Method Selection

$$\frac{s_r}{\sqrt{n_{al}}} \leq \frac{u_{trg}}{3}$$

s_r	Reproducibility Standard Deviation
n_{al}	Number of repeated measurements
u_{trg}	Target standard uncertainty

Reproducibility: Should include all sample preparation and mesurement processes.

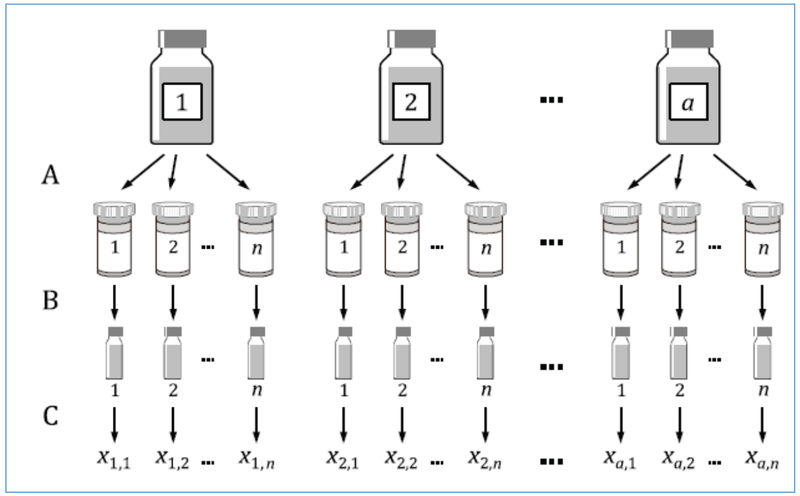
ISO 33405:2024 - Reference materials. Approaches for characterization and assessment of homogeneity and stability.

Experimental Designs for Homogeneity

sub sampling

sample preparation

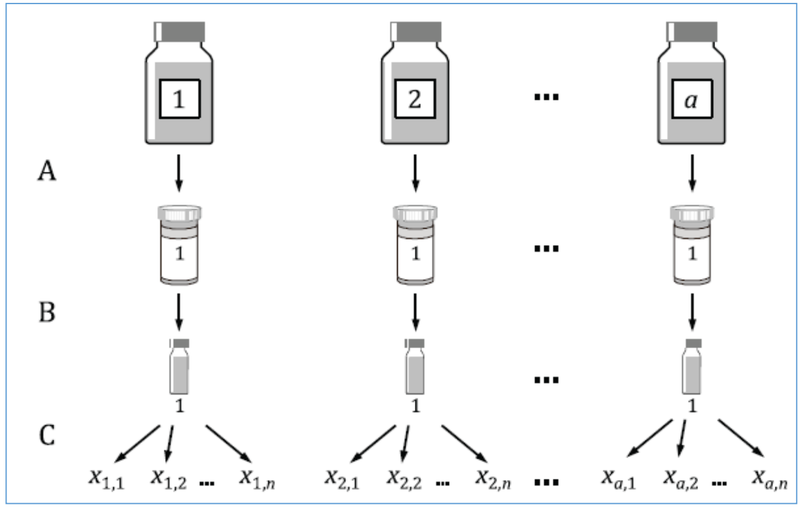
measurement



sampling

sample preparation

measurement



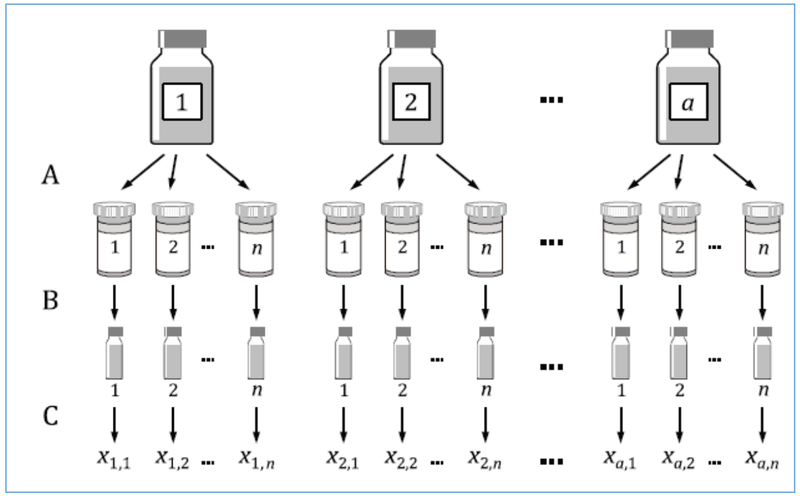
ISO 33405:2024

Experimental Designs for Homogeneity

sub sampling

sample preparation

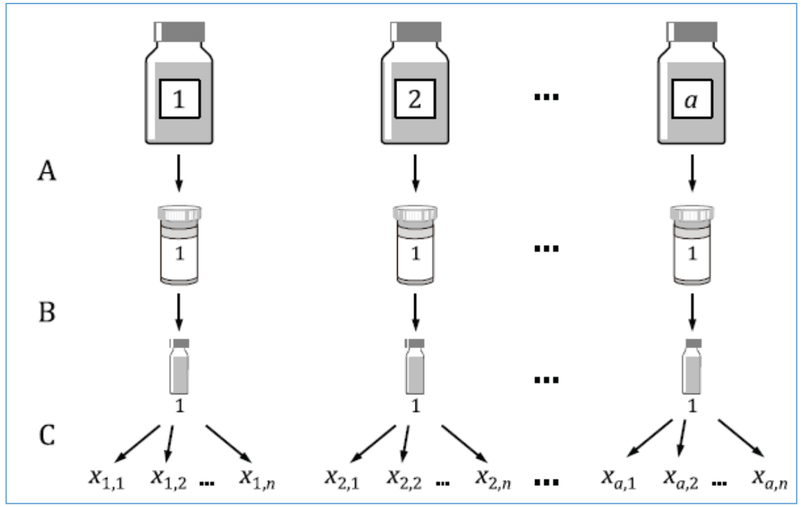
measurement



sampling

sample preparation

measurement



ISO 33405:2024

Experimental Designs for Homogeneity

Single Sequence
Simple Random order

Run 1: c a b a f e b g j d h k c h i j k f l d i l g e

2 sequence
each sequence separately random

Run 1: a e j b i d h c f l g k

Run 2: g d j f e i k l h b a c

4 units random in
3 different sequence

Run 1: c a a h b h b c

Run 2: k i i l e e l k

Run 3: g j d d f g f j

Evaluation of Homogeneity Study

- Normal distribution investigation
  (normal distribution graphics and Shapiro-Wilk Test)
- Outlier Controls (Grubbs Test)
- Unimodality (Histogram)
- Trend tests for filling order and analysis order
  (Linest Test)
- Anova

Uncertainty Calculations for Homogeneity

$$s_{wb,rel} = \frac{\sqrt{MS_{within}}}{\bar{y}} \qquad s_{bb,rel} = \frac{\sqrt{\frac{MS_{between} - MS_{within}}{n}}}{\bar{y}}$$

If method repeatability is not adequate to demonstrate present heterogeneity: $MS_{between} < MS_{within}$

$$u^{*}_{bb,rel} = \frac{\sqrt{\frac{MS_{within}}{n}}\sqrt[4]{\frac{2}{v_{MSwithin}}}}{\bar{y}} \qquad u_{rec} = \frac{|outlier - \bar{y}|}{\sqrt{3}.\bar{y}}$$

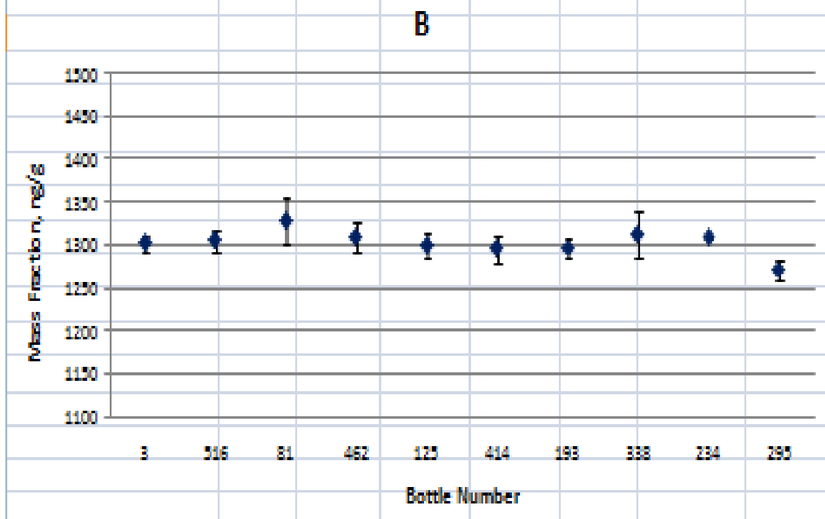
MS_{within}	mean sequare within a unit from an ANOVA
$MS_{between}$	mean sequare between-unit from an ANOVA
n	average number of replicates per unit
$v_{MSwithin}$	degrees of freedom of MS_{within}
$\bar{y}$	average of all results of the homogeneity study

Uncertainty Calculations for Homogeneity

UMECRM1204

Boron

bottle #	replicate 1	replicate 2	Average	Sdev
3	1310	1296	1303,02	10,12
516	1313	1297	1305,31	11,40
81	1349	1309	1329,01	27,71
462	1322	1299	1310,37	16,71
125	1289	1312	1300,55	15,84
414	1286	1309	1297,27	15,93
193	1291	1305	1297,95	10,36
338	1332	1293	1312,20	27,44
234	1309	1312	1310,37	2,06
295	1265	1281	1272,76	11,55



Anova: Single Factor

SUMMARY

Groups	Count	Sum	Average	Variance
Row 1	2	2606,042	1303,021	102,459612
Row 2	2	2610,6295	1305,31475	129,85467
Row 3	2	2658,0295	1329,01475	767,634153
Row 4	2	2620,74	1310,37	279,117565
Row 5	2	2601,0955	1300,54775	251,048028
Row 6	2	2594,5435	1297,27175	253,834246
Row 7	2	2595,9035	1297,95175	107,362531
Row 8	2	2624,4065	1312,20325	752,7394
Row 9	2	2620,73	1310,365	4,2632
Row 10	2	2545,514	1272,757	133,4978

ANOVA

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	3693,12394	9	410,347104	1,47510767	0,27610431	3,0204
Within Groups	2781,81121	10	278,181121			
Total	6474,93514	19				

	overall average	1303,9	
		In ng/g	In %
	swithin	16,6788	1,28%
ubb=	sbetween	8,129144587	0,62%
	u*bb	7,8869	0,60%

Evaluation of Homogeneity: Is it adequate or not?

Within Unit and Between Unit homogeneity can demonstrated to be adequate as follows:

a) Between and within unit standard deviation is smaller than characterization uncertainty (e.g: $s_{bb} < u_{char} /3$)

b) Combined CRM uncertainty can tolerate heterogeneity and material can still be useful for purpose

c) RM's for those no CRM uncertainty will be calculated, between units standard deviation s_{bb} is smaller than typical within laboratory reproducibility. In ideal : $s_{bb} < s_R / 3$

d) Statistical significance of the results between units can be evaluated with F test at %95 confidence interval.

•Not to find statistical significance does not necessarily mean that no inhomogeneity is present but it gives the necessary information to the users of the RMs that material is homogeneous enough to use.

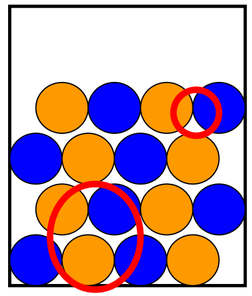
ISO 33405:2024

Within Unit Homogeneity

Two Ways to Determine Within Unit Homogeneity

1. Most sensitive method is selected and with decreased amounts of materials the method is tested in a series of measurements.

   Amount selection should be done according to the intended use of the material. If a standard method is dictating 50 grams of sample use, it is meaningless to test 5 grams for the measurements.
2. The amount used for the characterization and/or homogeneity studies is directly defined as the minimum sample intake amount without performing a dedicated minimum sample intake study.



Exercise for Homogeneity Study Planning

A CRM produced 1894 units, if the method repeatability is 5 % then for maximum 2% uncertainty for homogeneity, how many repetition in measurements should be made ? (Note that $MS_{between} < MS_{within}$)

How many units should be tested?

$$N = \sqrt[3]{1894} = 12{,}37 \approx 13$$

How many repeated measurements should be made to reach target uncertainty?

$$u^*_{bb} = \frac{RSD_{metot}}{\sqrt{n}} \sqrt[4]{\frac{2}{N(n-1)}}$$

RSD_{method} = 5%

n: number of repeated measurements

	n=3	n=4	n=5
u^*_{bb}	2.15	2.06	1.98

7.11 Assessment and Monitoring of Stability

•RMP should conduct an experimental assessment of stability before release unless the producer has evidence of stability or prior experience of stability from **closely similar** materials held for an extended period under the same planned storage conditions.
"**Closely similar**" materials are materials characterized for the same properties, which share the same matrix composition, processing conditions, similar packaging, etc.

•Where an RM is produced in multiple batches that are not individually tested for stability, the producer should **verify** the stability of a sufficient number of different batches experimentally to provide confidence in the stability of all batches.

Verification can be a simple test to confirm that different batches behave similarly or, for successive batches, do not change over their lifetime, while the experimental assessment of stability typically involves an extended study aimed at determining rates of change.

7.11 Assessment and Monitoring of Stability

RMP shall assess:

- ✓ By experiment, the **stability** of **all properties** of an RM under proposed **storage** and **transfer** conditions and choose packaging, storage and transfer conditions
- ✓ Establish any necessary advice on storage and use of the material to maintain stability at the user‘s premises;
- ✓ Monitoring of the stability of materials for long term storage which allows prompt detection of change and possible rate of change
- ✓ If the **stability** of the certified value **cannot be ensured**, reflect stated **uncertainty** for possible change in the value prior to use or, where the **change with time can be predicted**, provide info for correcting the certified value and its uncertainty for the expected change
- ✓ Where **repeated sampling** from an RM unit is allowed, assess the possible effects on the stability of the material and take action.

Stability Tests

- **Short Term Stability Test:** The changes in the material that might happen during **transfer** to customers is checked, most suitable transfer condition is determined.
- **Long Term Stability Test:** The changes in the material during **storage** is investigated for a possible degradation.

✓ Reference temperature: The temperature at which the material degradation can be accepted as negligible

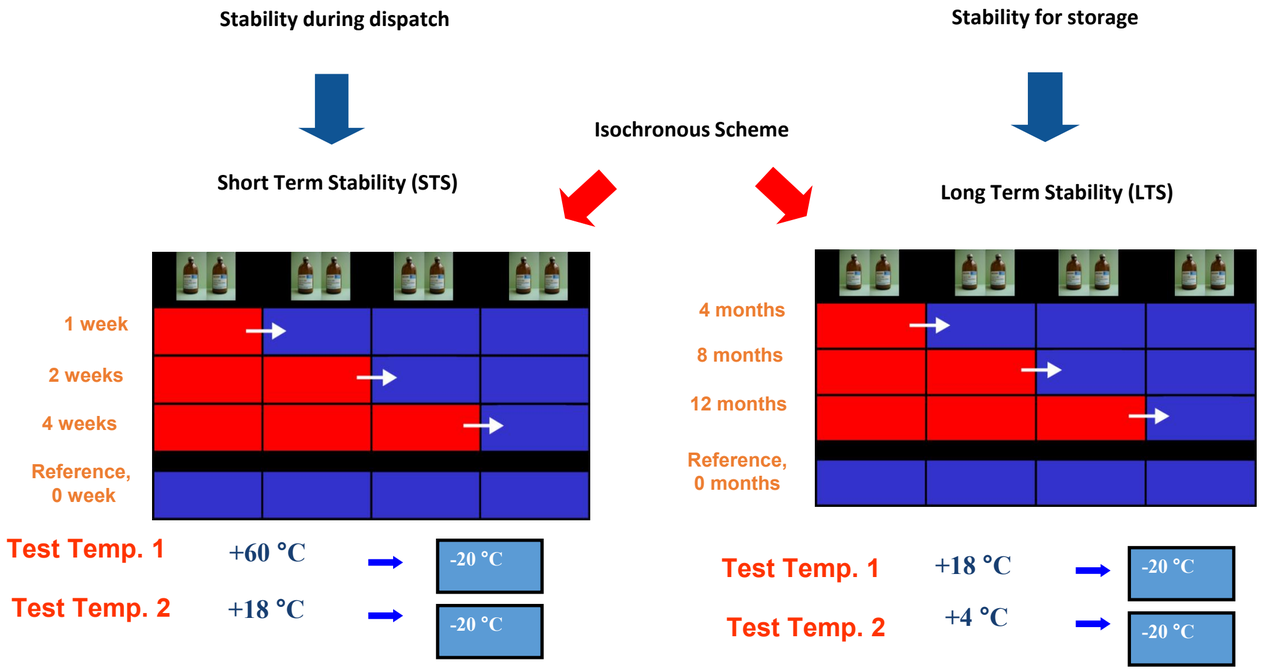
✓ Test temperatures are selected depending on transfer and storage conditions

✓ Test interval (Typically 4 weeks for STS test, 3-6-12 months for LTS test)

- Obtained data is used to estimate the uncertainty due to instability which can be seen by the STS and the LTS studies.

Stability Tests: Isochronous Design

Stability Tests: Isochronous Design



Advantage of Isochronous Study:
All samples are analysed the same day at the end of the study
⇨ precision not compromised by day-to-day variation

Calculation of Uncertainty due to Stability

Unstability: slope of the regression line
Stability Uncertainty: Uncertainty of the slope

$$u_b = \frac{s}{\sqrt{\Sigma(x_i - \bar{x})^2}}$$

$$s = \sqrt{\frac{\Sigma(y_i - \hat{y})^2}{n-2}}$$

$$\hat{y} = a + bx$$

$$b = \frac{\Sigma(x_i - \bar{x})(y_i - \bar{y})}{\Sigma(x_i - \bar{x})^2}$$

$$a = \frac{\Sigma y_i}{n} - b \cdot \frac{\Sigma x_i}{n}$$

x: Time point for measurement
$\bar{x}$: Mean of all time points
n: Total number of points
y: Measured value
$\hat{y}$: Mean of measured values

Linsinger, T.P.J., Pauwels, J., Lamberty, A., Schimmel, H., Van Der Veen, A.M.H., Siekmann, L.,"Estimating The Uncertainty of Stability for Matrix CRMs", *Fresenius J. Anal. Chem.*, ***370 (2001),*** Pp. 183-188

Stability Uncertainty

$$u_{lts,[\%]} = \frac{RSD_{results,[\%]}}{\sqrt{n\sum(x_i - \bar{x})^2}} \cdot x_{shelf} \quad \Leftrightarrow \quad n = \left(\frac{RSD_{results,[\%]} \cdot x_{shelf}}{u_{lts,[\%]}} \right)^2 \frac{1}{\sum(x_i - \bar{x})^2}$$

n: replicates per time point

How to minimize u_{LTS} ?

- shorter shelf-life (x_{shelf} smaller)
- better method repeatability (smaller $RSD_{results}$)
- longer stability study (x_i- greater)
- higher number of replicates per time point (greater n)
- more time points (greater sum)

Stability Uncertainty

u_{sts} = Transfer time * Uncertainty of Slope

u_{lts} = Storage time * Uncertainty of Slope

Assumptions:

✓t=0 There is no degradation
✓Degradation is linear with a fixed rate
✓Degradation is affecting the whole units in the same way

7.12 Characterization

•Where the producer assigns property values, characterization of the RM is required.

•The producer should clearly define whether a quantitative or a qualitative property will be characterized and, if quantitative, whether the measurand is operationally defined or is defined independently of any specific procedure.

Characterization Strategies

The producer should select a characterization strategy appropriate for the intended use of the RM.

1. Using a single reference measurement procedure (as defined in ISO/IEC Guide 99) in a single laboratory

2. Characterization of a non-operationally defined measurand using two or more methods of demonstrable accuracy in one or more competent laboratories

3. Characterization of an operationally-defined measurand using a network of **competent** laboratories;

4. Value transfer from an RM to a closely matched candidate RM performed using a single measurement procedure performed by one laboratory;

5. Characterization based on mass or volume of ingredients used in the preparation of the RM.

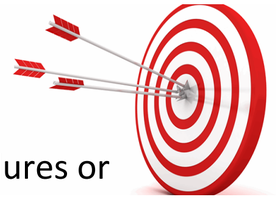
Competence of each involved lab should be demonstrated with data that was not from the material to be characterized

RMP shall document a **measurement plan** and communicate this to all personel involved in measurements.

Data shall be **technically evaluated** to confirm adherence to plan to decide inclusion or exclusion of the data.

7.13 Assignment of Property Value

- Documented procedures shall be used for the assignment of property values;



- ✓ details of the experimental designs and statistical techniques used
- ✓ how to treat and investigatigate anomalous results, including outliers
- ✓ whether weighting techniques are used to values derived from different procedures or laboratories with different measurement uncertainties
- ✓ the approach to assign uncertainties to the property values
- ✓ any other significant factors that may affect the assignment of property values

- RMP shall collect technical information on test methods and equipment with reported uncertainty information, and any evidence of laboratory performance when assigning the property values of interest.
- Outliers should not be excluded just based on statistical evidence until they have been investigated and, where possible, the reasons identified. Robust statistical methods may be applied where appropriate.

  An apparent outlier can be the only technically valid result in a data set!

- ISO Guide 35 provides guidance on valid approaches for value assignment.

7.13 Assignment of Property Value

• For certified values, the producer should identify the uncertainty contributions to be included in the assigned uncertainty.

➢Further guidance on the estimation of uncertainties is given in ISO Guide 35 and ISO/IEC Guide 98-3.

•For certified values, the producer should consider, at a minimum, uncertainty contributions of each of the following:

a) characterization, including any difference between multiple procedures used for characterization
b) between-unit and within-unit inhomogeneity
c) changes of property values during storage
d) changes of property values during transport.

- Other uncertainty contributions can be important such as changes of property values in use or on repeated sampling.
- Where values other than certified values are assigned to RMs (e.g. “indicative values” or information values) a statement of uncertainties can be appropriate to improve the use of the material

Assignment of Uncertainty to Property Value (example)

$$U_{CRM} = k \cdot \sqrt{u_{char}^2 + u_{hom}^2 + u_{sts}^2 + u_{lts}^2 + u_{oth}^2}$$

u_{char} : Uncertainty of Characterization

u_{hom} : Uncertainty of Homogeneity

u_{sts} : Uncertainty of short term (transfer) stability

u_{lts} : Uncertainty of longterm (storage) stability

u_{oth} : Other sources of uncertainty (e.g. repeated use uncertainty)

k : Coverage factor

Assignment of Uncertainty to Property Value (example)

$$U_{CRM} = k \cdot \sqrt{u_{char}^2 + u_{hom}^2 + u_{sts}^2 + u_{lts}^2 + u_{oth}^2}$$

CRM	u_{char} (%)	u_{bb} (%)	u_{lts} (%)	u_{sts} (%)
UME CRM 2203 (As)	39,7	7,3	49,7	3,2
UME CRM 2210 (Ca)	11,2	32,8	41,0	15,0
UME CRM 2211 (Cd)	36,6	7,5	48,9	7,0
UME CRM 2213 (Co)	35,1	20,2	43,4	1,3
UME CRM 2216 (Cu)	8,0	3,2	86,0	2,8
UME CRM 2229 (K)	9,2	2,3	85,1	3,4
UME CRM 2236 (Na)	19,4	8,5	62,4	9,7
UME CRM 2270 (Zn)	22,0	22,0	25,9	30,1

CRM	Certified Value (Mass Fraction)		Calculated Value (Mass Concentration)	
	C_{CRM} (mg/kg)	U_{CRM} (mg/kg) (k = 2)	C_{CRM} (mg/L)	U_{CRM} (mg/L) (k = 2)
UME CRM 2203 (As)	997,3	1,4	1009,3	1,4
UME CRM 2210 (Ca)	999,2	5,4	1006,2	5,4
UME CRM 2211 (Cd)	999,7	2,2	1010,7	2,2
UME CRM 2213 (Co)	998,6	2,1	1011,1	2,2
UME CRM 2216 (Cu)	999,3	3,7	1013,4	3,7
UME CRM 2229 (K)	1000,3	1,9	1006,0	1,9
UME CRM 2236 (Na)	997,3	3,1	1003,7	3,1
UME CRM 2270 (Zn)	998,4	3.6	1010,3	3,6

7.14 Reference Material Documents

•The producer should issue and make available an RM certificate for CRMs and product information sheet for other RMs.
•The contents of RM certificates and product information sheets should include the following:

a) title of the document;
b) unique identifier of the RM;
c) the name of the RM;
d) name and contact details of theproducer;
e) intended use;
f) minimum sample size (whenever applicable);
g) period of validity
h) storage information;
i) instructions for handling and use that are sufficient to ensure the integrity of the material;
j) page number and the total number of pages;
k) document version;
l) information on commutability of the material (where appropriate).

7.14 Reference Material Documents

RM certificates shall contain the following additional information:

a) description of the CRM;
b) property of interest, property value and associated uncertainty;
c) measurement procedure for operationally defined measurands
d) metrological traceability of the certified values;
e) name and function of RMP's approving officer.

➢Further information on the content of certificates and accompanying documentation is given in ISO Guide 31.

➢ Sector-specific requirements for RM certificates and product information sheets can exist and should be considered
(e.g. ISO 15194 for in vitro diagnostic medical devices and RMs used in these devices)

7.14 Reference Material Labels

• The RM label shall be securely attached to the product container of an individual RM unit, and shall be designed to remain intact under the defined storage and handling conditions within the lifetime of the RM, i.e. the period during which the RM is available from the producer extended by the period of validity of its certificate. The label should identify the material, the producer, its batch, and any other information necessary to enable the material to be uniquely distinguished and referenced (such as the individual sample number), where appropriate, to its product information sheet or RM certificate.

•Where the physical size of the RM unit limits the amount of information that can be contained on the label, the information shall be included elsewhere (e.g. in an RM document). A unique identifier shall be given

➢Further guidance concerning the contents of RM certificates, labels and accompanying documentation can be found in ISO 33401.

CRM Certificate (Sample)

Information on the first page of certificate

- Accreditation Logo (if available) (ISO 17034)
- CRM name, number, measurand & matrix
- Certified Value & uncertainty *(mass fraction, e.g.: mg/kg)*
- Definition of measurand & traceability claim , uncertainty
- Validity of Certificate/ CRM expiry date
- Approval date of certificate
- Sales Date
- Signature of the authorized personel
- Adress and contact information of the producer

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Certificate of the Reference Material

TÜRKAK Reference Materials Unit TS EN ISO 17034 AB-0001-RM

Page 1 / 4

Name of the Material	:	Elements in Hazelnut Certified Reference Material
Material Code	:	UME CRM 1202
Issue Date	:	31.08.2016
Revision Date	:	18.09.2019 (Revision history can be found on the last page)
Validity Period of the Certificate	:	18 months from the sales date
Certified Values	:	

Element	Certified Value[1], mg/kg	Uncertainty[1,2], mg/kg	Element	Certified Value[1], µg/kg	Uncertainty[1,2], µg/kg
B[3]	16.8	2.2	Cd[6]	6.4	0.9
Ca[4]	1550	110	Co[5]	278	28
Cu[3]	16.4	1.0			
Fe[3]	36.1	2.9			
Mg[4]	1540	150			
Mn[5]	95.3	6.3			
Ni[5]	1.60	0.17			
Sr[5]	6.68	0.46			
Zn[3]	20.4	1.8			

[1] The certified values and the uncertainties are traceable to the International System of Units (SI).
[2] The expanded uncertainty of certified value includes characterization, homogeneity, stability components and is stated as the standard uncertainty of measurement multiplied by the coverage factor $k = 2$, which for a normal distribution corresponds to a coverage probability of approximately 95 %. The standard uncertainty of measurement has been determined in accordance with GUM "Guide to the Expression of Uncertainty in Measurement".
[3] Certified value has been assigned based on the results produced by using totally independent HR-ICP-MS and ID-ICP-MS methods applied by a single laboratory.
[4] Certified value has been assigned based on the results produced by using totally independent HR-ICP-MS and FAAS methods applied by a single laboratory.
[5] Certified value has been assigned based on the results produced by using totally independent HR-ICP-MS and GF-AAS methods applied by a single laboratory.
[6] Certified value has been assigned by using ID-ICP-MS method.

TÜBİTAK UME, as a reference material producer, has been accredited by TÜRKAK according to TS EN ISO 17034 with the accreditation number AB-0001-RM.

Sales Date

Dr. Mustafa ÇETİNTAŞ
Director

The following pages are an integral part of the certificate. The use of current certificate is customers' responsibility.
Most recent certificate can be downloaded from www.ume.tubitak.gov.tr.

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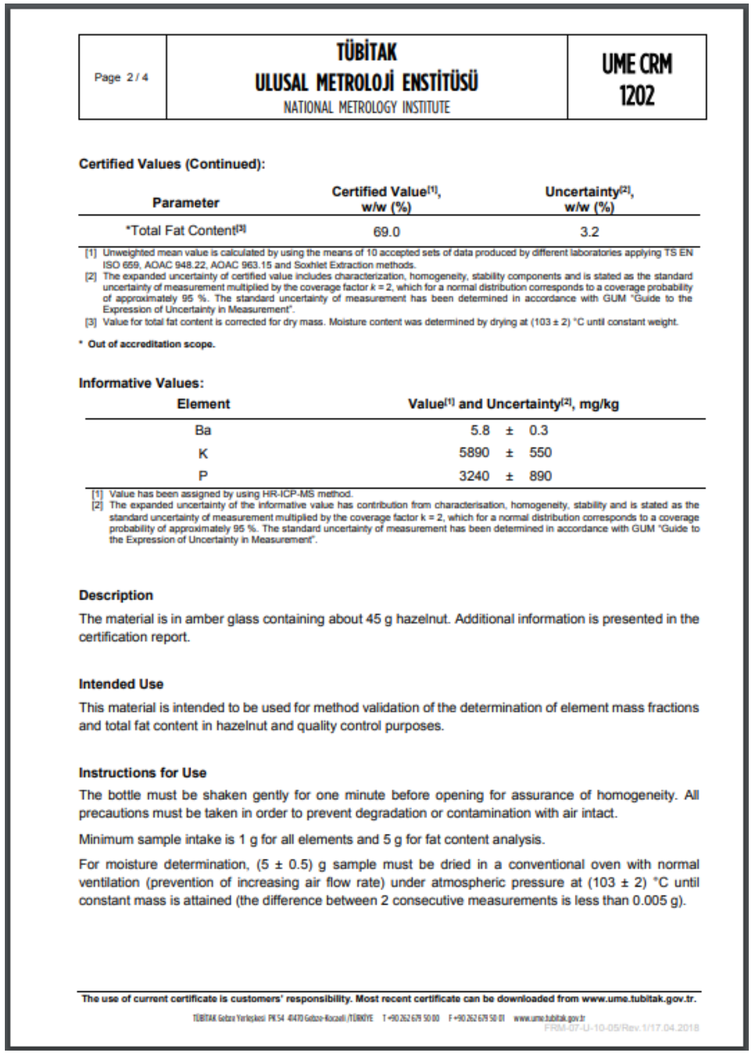
CRM Certificate (Sample)

Information on the Second Page

- **Informative Values(If applicable)**
- **Definition of the material**
- **Intended Use of the Material (*Calibration or Quality Control-QC*)**
- **Usage Instructions (Minimum sample intake, Storage, Safety Instructions)**



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UME CRM 1202

Certified Values (Continued):

Parameter	Certified Value[1], w/w (%)	Uncertainty[2], w/w (%)
*Total Fat Content[3]	69.0	3.2

[1] Unweighted mean value is calculated by using the means of 10 accepted sets of data produced by different laboratories applying TS EN ISO 659, AOAC 948.22, AOAC 963.15 and Soxhlet Extraction methods.
[2] The expanded uncertainty of certified value includes characterization, homogeneity, stability components and is stated as the standard uncertainty of measurement multiplied by the coverage factor $k = 2$, which for a normal distribution corresponds to a coverage probability of approximately 95 %. The standard uncertainty of measurement has been determined in accordance with GUM "Guide to the Expression of Uncertainty in Measurement".
[3] Value for total fat content is corrected for dry mass. Moisture content was determined by drying at (103 ± 2) °C until constant weight.

* **Out of accreditation scope.**

Informative Values:

Element	Value[1] and Uncertainty[2], mg/kg
Ba	5.8 ± 0.3
K	5890 ± 550
P	3240 ± 890

[1] Value has been assigned by using HR-ICP-MS method.
[2] The expanded uncertainty of the informative value has contribution from characterisation, homogeneity, stability and is stated as the standard uncertainty of measurement multiplied by the coverage factor k = 2, which for a normal distribution corresponds to a coverage probability of approximately 95 %. The standard uncertainty of measurement has been determined in accordance with GUM "Guide to the Expression of Uncertainty in Measurement".

Description

The material is in amber glass containing about 45 g hazelnut. Additional information is presented in the certification report.

Intended Use

This material is intended to be used for method validation of the determination of element mass fractions and total fat content in hazelnut and quality control purposes.

Instructions for Use

The bottle must be shaken gently for one minute before opening for assurance of homogeneity. All precautions must be taken in order to prevent degradation or contamination with air intact.

Minimum sample intake is 1 g for all elements and 5 g for fat content analysis.

For moisture determination, (5 ± 0.5) g sample must be dried in a conventional oven with normal ventilation (prevention of increasing air flow rate) under atmospheric pressure at (103 ± 2) °C until constant mass is attained (the difference between 2 consecutive measurements is less than 0.005 g).

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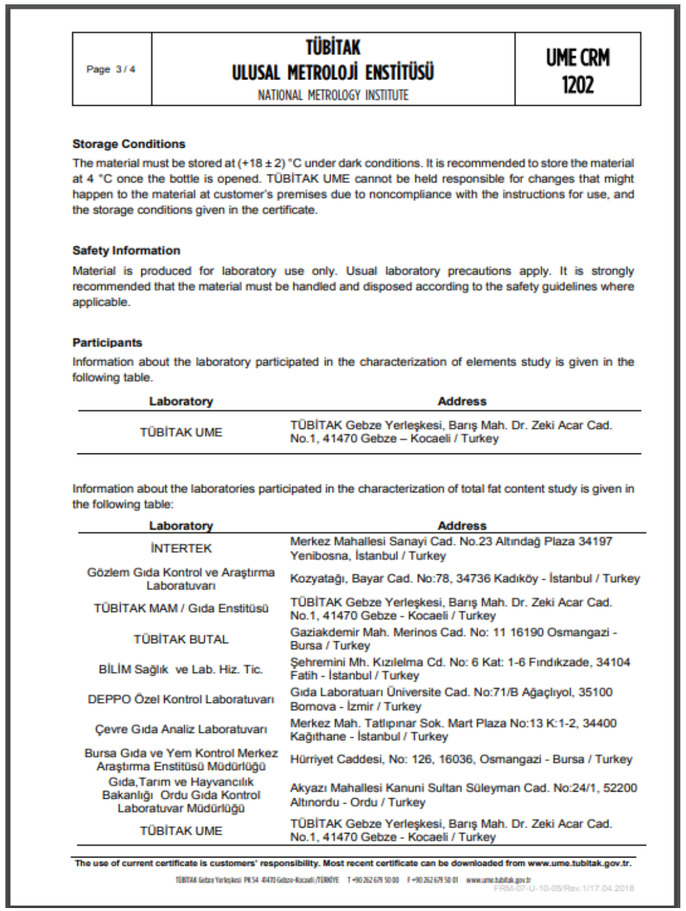
CRM Certificate (Sample)



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NATIONAL METROLOGY INSTITUTE

UME CRM 1202

Storage Conditions

The material must be stored at (+18 ± 2) °C under dark conditions. It is recommended to store the material at 4 °C once the bottle is opened. TÜBİTAK UME cannot be held responsible for changes that might happen to the material at customer's premises due to noncompliance with the instructions for use, and the storage conditions given in the certificate.

Safety Information

Material is produced for laboratory use only. Usual laboratory precautions apply. It is strongly recommended that the material must be handled and disposed according to the safety guidelines where applicable.

Participants

Information about the laboratory participated in the characterization of elements study is given in the following table.

Laboratory	Address
TÜBİTAK UME	TÜBİTAK Gebze Yerleşkesi, Barış Mah. Dr. Zeki Acar Cad. No.1, 41470 Gebze – Kocaeli / Turkey

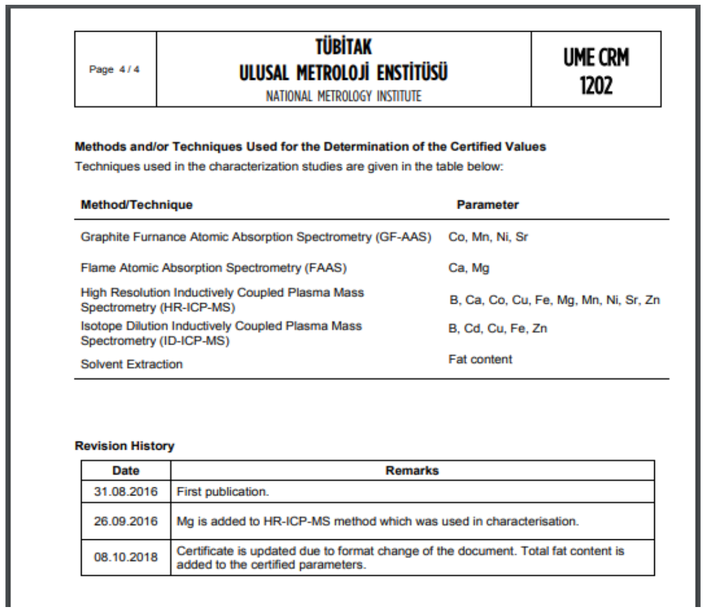
Information about the laboratories participated in the characterization of total fat content study is given in the following table:

Laboratory	Address
İNTERTEK	Merkez Mahallesi Sanayi Cad. No.23 Altındağ Plaza 34197 Yenibosna, İstanbul / Turkey
Gözlem Gıda Kontrol ve Araştırma Laboratuvarı	Kozyatağı, Bayar Cad. No:78, 34736 Kadıköy - İstanbul / Turkey
TÜBİTAK MAM / Gıda Enstitüsü	TÜBİTAK Gebze Yerleşkesi, Barış Mah. Dr. Zeki Acar Cad. No.1, 41470 Gebze - Kocaeli / Turkey
TÜBİTAK BUTAL	Gaziakdemir Mah. Merinos Cad. No: 11 16190 Osmangazi - Bursa / Turkey
BİLİM Sağlık ve Lab. Hiz. Tic.	Şehremini Mh. Kızılelma Cd. No: 6 Kat: 1-6 Fındıkzade, 34104 Fatih - İstanbul / Turkey
DEPPO Özel Kontrol Laboratuvarı	Gıda Laboratuarı Üniversite Cad. No:71/B Ağaçlıyol, 35100 Bornova - İzmir / Turkey
Çevre Gıda Analiz Laboratuvarı	Merkez Mah. Tatlıpınar Sok. Mart Plaza No:13 K:1-2, 34400 Kağıthane - İstanbul / Turkey
Bursa Gıda ve Yem Kontrol Merkez Araştırma Enstitüsü Müdürlüğü	Hürriyet Caddesi, No: 126, 16036, Osmangazi - Bursa / Turkey
Gıda,Tarım ve Hayvancılık Bakanlığı Ordu Gıda Kontrol Laboratuvar Müdürlüğü	Akyazı Mahallesi Kanuni Sultan Süleyman Cad. No:24/1, 52200 Altınordu - Ordu / Turkey
TÜBİTAK UME	TÜBİTAK Gebze Yerleşkesi, Barış Mah. Dr. Zeki Acar Cad. No.1, 41470 Gebze - Kocaeli / Turkey

The use of current certificate is customers' responsibility. Most recent certificate can be downloaded from www.ume.tubitak.gov.tr.

Information on following Pages

- **Participants of the Characterization Study**
- **Methods/Techniques used for the characterization of the materail**
- **Revision History of the Certificate**



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Methods and/or Techniques Used for the Determination of the Certified Values

Techniques used in the characterization studies are given in the table below:

Method/Technique	Parameter
Graphite Furnance Atomic Absorption Spectrometry (GF-AAS)	Co, Mn, Ni, Sr
Flame Atomic Absorption Spectrometry (FAAS)	Ca, Mg
High Resolution Inductively Coupled Plasma Mass Spectrometry (HR-ICP-MS)	B, Ca, Co, Cu, Fe, Mg, Mn, Ni, Sr, Zn
Isotope Dilution Inductively Coupled Plasma Mass Spectrometry (ID-ICP-MS)	B, Cd, Cu, Fe, Zn
Solvent Extraction	Fat content

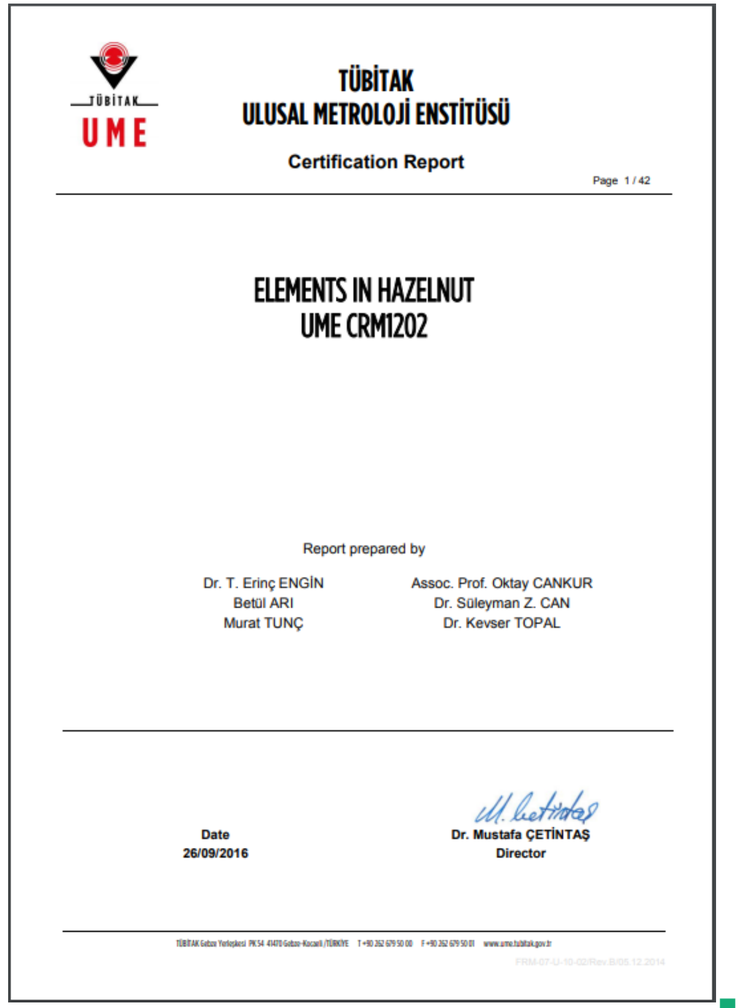
Revision History

Date	Remarks
31.08.2016	First publication.
26.09.2016	Mg is added to HR-ICP-MS method which was used in characterisation.
08.10.2018	Certificate is updated due to format change of the document. Total fat content is added to the certified parameters.

TÜBİTAK UME Reference Material Documents can be downloaded from
https://rm.ume.tubitak.gov.tr/en

CRM Certification Report-Optional (Sample)

- Detailed information about definition of the material and material processing process
- Details of the homogeneity and stability studies
- Traceability and uncertainty information
- Commutability Information (if applicable)
- Usage Instructions, references, …
- All information for the correct use of the CRM



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Certification Report

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ELEMENTS IN HAZELNUT
UME CRM1202

Report prepared by

Dr. T. Erinç ENGİN
Betül ARI
Murat TUNÇ

Assoc. Prof. Oktay CANKUR
Dr. Süleyman Z. CAN
Dr. Kevser TOPAL

Date
26/09/2016

Dr. Mustafa ÇETİNTAŞ
Director

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FRM-07-LI-10-02/Rev.8/05.12.2014

TÜBİTAK UME Reference Material Documents can be downloaded from
https://rm.ume.tubitak.gov.tr/en

CRM Certification Report-Optional (Sample)

Manipulations on the Raw Material
Material Processing Information
(Lyofilization, milling, sieving, homogenization, bottling

After all these manipulations, is the material still represent your routine samples?

CRM Certification Report-Optional (Sample)

Material Processing Details

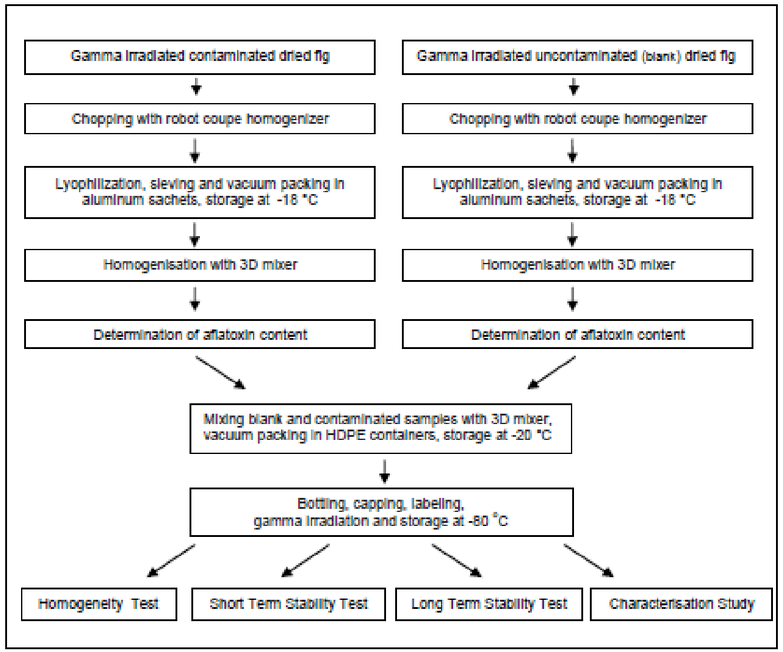

Figure 2. The flowchart of the production process of dried fig

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Certification Report

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Aflatoxin B_1, B_2, G_1, G_2 and Total Aflatoxin in Dried Fig UME CRM 1302

Report Prepared By

Assoc. Prof. Nilgün TOKMAN	Taner GÖKÇEN	Assoc. Prof. Ahmet C. GÖREN
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Dr. Burcu BİNİCİ	Mine BİLSEL	Zehra ÇAKILBAHÇE
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Date
31/08/2016

Dr. Mustafa ÇETİNTAŞ
Director

CRM Certification Report

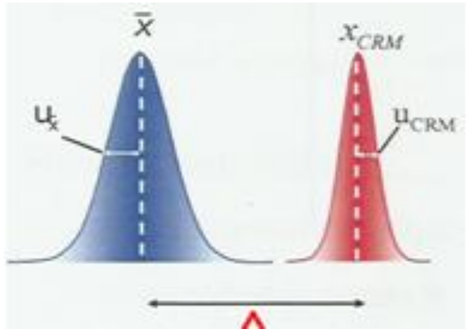
Instructions for how to evaluate CRM measurement results

- **Use of material for calibration purpose**

CRM uncertainty should be taken into account

- **Use for Method validation and Quality Control Purposes**

CRM uncertainty and measurement uncertainty should be taken into account with the difference between the CRM Certificate value and the measured CRM value



CRM RE
Certified Reference Material Result Evaluation

https://rm.ume.tubitak.gov.tr/en/crm_re/

CRM Certification Report

Evaluation of the Analytical Methods

- Suitability of the CRM for specific methods
(especially for method dependent parameters)

Method Validation Information

- Reproducibility *(between laboratory)*
- Intermediate Precision *(within laboratoory) for comparison purpose*

References

- Methods

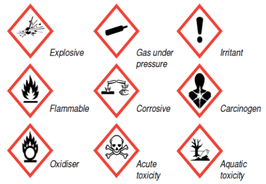
(Papers, official methods, standards)

- Related legislation information

7.15 Distribution Service

- The distribution process shall be specified including precautions needed to avoid deterioration of the RM. Appropriate documentation is provided to allow customs clearance.
- Up-to-date **records** of all RM **sales** and distribution shall be kept.
- Reasonable **guidance** and **technical support** related to the RMs shall be supplied to users.
- **Notification** of users of any **change** to the property **value** or **uncertainty** shall be done ASAP.
- Where RMs are subject to **resale** through a **distributor** (contractual relationship), all necessary information shall be shared to ensure that an effective post-distribution service is maintained.
- Where RMs are subject to **resale** by **other organizations**, there is no control over these organizations' activities. Requirements are limited to **first reseller** in this case.







7.16 Quality Control & Technical Records

•RMP shall have procedures for identification, collection, indexing, access, storage, maintenance and disposal of quality and technical records.

➢**Quality records** are objective evidences for quality or the effectiveness of the operation of the management system. eg: Internal audit reports, management reviews, and corrective action and improvement records.

➢**Technical records** are data and information from RM production and measurement procedures indicating whether specified quality or process parameters are achieved.
eg: Forms, contracts, work sheets, check sheets, control charts/graphs, calibration reports/certificates.

- ✓ RMP shall ensure that it has recorded all information that might be needed in a future dispute situation.
- ✓ All records shall be legible and stored in a suitable environment to prevent damage, deterioration or loss.
- ✓ Mistakes shall be crossed out, not erased and correct info entered alongside (signed or initialled and dated). For electronic records measures shall be taken to avoid loss or change of original info.

Records can be in the form of any type of media, such as **hard copy** or **electronic** media.




7.16 Quality Control & Technical Records

•When mistakes occur in records, each mistake shall be crossed out, not erased, made illegible or deleted, and the correct information entered alongside. All such alterations to records shall be signed or initialled, and dated by the person making the correction. In the case of records stored electronically, equivalent measures shall be taken to avoid the loss or change of original information.

• All records shall be held securely and, where appropriate, in confidence.

•The producer shall have procedures to protect electronically kept data at all times and to prevent unauthorized access to, or amendment of such data.

•The producer shall arrange for all individual measurement observations, appropriate calculations and derived data (e.g. statistical treatments and uncertainty budgets), calibration records and preparation reports to be retained for a defined period beyond which it is no longer probable that they will be referred to, the period for which the RM remains valid.

•The results of each calibration or measurement (or series of either) carried out by the producer or the subcontractor should be reported in accordance with ISO/IEC 17025




7.17 Management of non-confirming work

•The producer should have procedures that should be implemented when it establishes that any aspect of its production activities does not conform to its own specified production procedures or the agreed requirements of the customer.
•The procedures should ensure that:

a) responsibilities and authorities for the management of non-conforming work are designated;

b) the actions to be taken when any non-conforming work and/or RMs are identified including root cause analysis and a system that ensures that they are effectively implemented;

c) an evaluation of the significance of the non-conforming work is made and identification and implementation of correction and corrective action;

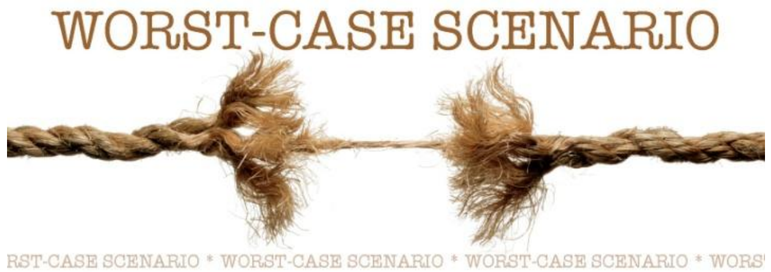
7.17 Management of non-confirming work

The procedures should ensure that:

d) where necessary, work is halted and, if appropriate, issue of the affected RM and its certificates and other appropriate documentation is withheld;
e) remedial actions such as customer notifications are taken within a defined time-frame;
f) where necessary, best efforts are employed to notify the users of the possible effects, within an appropriate period and, where necessary, non-conforming RMs and/or their certificates and other appropriate documentation already distributed, are recalled;
g) the responsibility for authorization of the resumption of work is defined;
h) where necessary, an internal audit is conducted to verify the closure and effectiveness of the corrective actions taken.

7.17 Management of non-confirming work

•The decision on recall of RMs shall be taken in a timely manner to limit the use of nonconforming RMs.



➢The identification of non-conforming RMs or problems with the management system or with production activities can occur at various places within the management system, such as complaints, quality control, checking of consumable materials, staff observations or supervision, certificate and other document checking, mangement review and internal audits.

7.18 Complaints

•The producer should be responsible for all decisions at all levels of the handling process for complaints.
•Investigation and decision on complaints shall not result in any discriminatory actions.
•The process for handling complaints shall include at least the following elements and methods:

a) a description of the process for receiving, validating, investigating the complaint, and deciding what actions are to be taken in response to it;
b) tracking and recording complaints, including actions undertaken to resolve them;
c) ensuring that any appropriate action is taken.

7.18 Complaints

•The producer receiving the complaint should be responsible for gathering and verifying all necessary information to validate the complaint.
•Whenever possible, the producer should acknowledge receipt of the complaint, and provide the complainant with progress reports and the outcome.
•The decision to be communicated to the complainant shall be made by, or reviewed and approved by, individual(s) not involved in the original RM activities in question.
• Whenever possible, the producer should give formal notice of the end of the complaint handling process to the complainant.

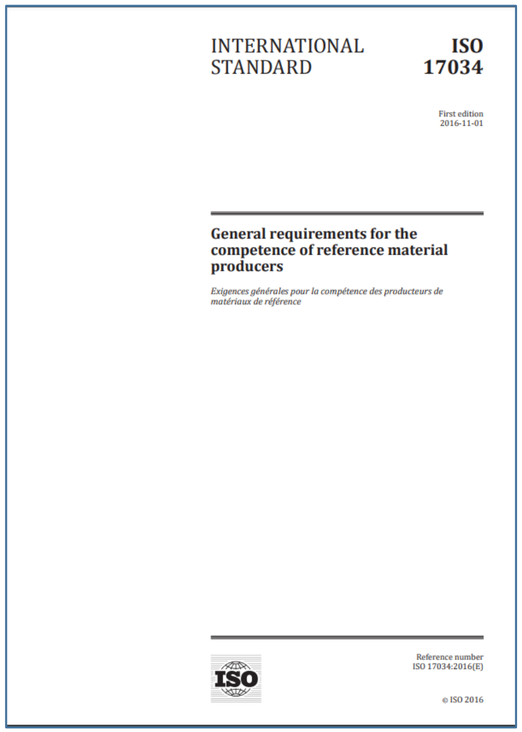
17034 Technical and Production Requirements (7.1 – 7.18)

References

ISO TC 334
Technical Committee on Reference Materials

CERTIFICATION & CONFORMITY

ISO'S COMMITTEE ON CONFORMITY ASSESSMENT (CASCO)


INTERNATIONAL STANDARD

ISO 17034

First edition 2016-11-01

General requirements for the competence of reference material producers

Exigences générales pour la compétence des producteurs de matériaux de référence

Reference number ISO 17034:2016(E)

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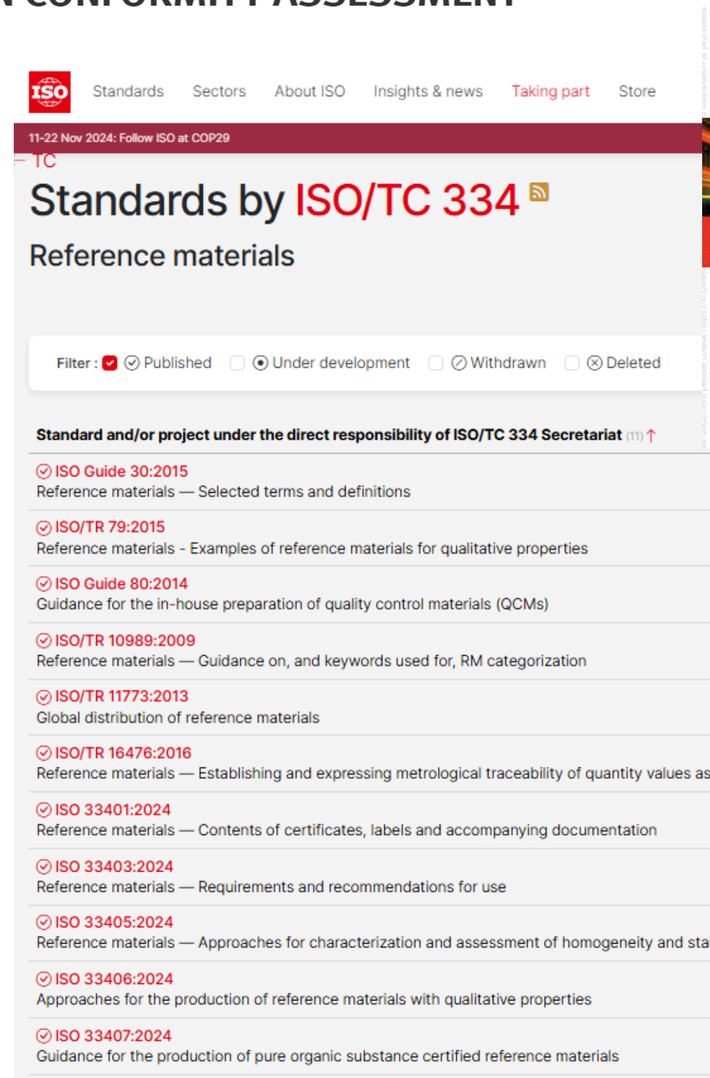
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TC

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Reference materials

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Standard and/or project under the direct responsibility of ISO/TC 334 Secretariat (11)

- ISO Guide 30:2015 — Reference materials — Selected terms and definitions
- ISO/TR 79:2015 — Reference materials - Examples of reference materials for qualitative properties
- ISO Guide 80:2014 — Guidance for the in-house preparation of quality control materials (QCMs)
- ISO/TR 10989:2009 — Reference materials — Guidance on, and keywords used for, RM categorization
- ISO/TR 11773:2013 — Global distribution of reference materials
- ISO/TR 16476:2016 — Reference materials — Establishing and expressing metrological traceability of quantity values assigned to reference r
- ISO 33401:2024 — Reference materials — Contents of certificates, labels and accompanying documentation
- ISO 33403:2024 — Reference materials — Requirements and recommendations for use
- ISO 33405:2024 — Reference materials — Approaches for characterization and assessment of homogeneity and stability
- ISO 33406:2024 — Approaches for the production of reference materials with qualitative properties
- ISO 33407:2024 — Guidance for the production of pure organic substance certified reference materials


BS ISO 33405:2024

BSI Standards Publication

Reference materials — Approaches for characterization and assessment of homogeneity and stability

BS ISO 33401:2024

BSI Standards Publication

Reference materials — Contents of certificates, labels and accompanying documentation


BS ISO 33403:2024

BSI Standards Publication

Reference materials — Requirements and recommendations for use


TECHNICAL REPORT

ISO/TR 16476

First edition 2016-06-01

Reference materials — Establishing and expressing metrological traceability of quantity values assigned to reference materials

Matériaux de référence — Etablissement et expression de la traçabilité métrologique de valeurs assignées à des matériaux de référence

https://committee.iso.org/home/tc334

https://www.iso.org/committee/8300629/x/catalogue/p/1/u/0/w/0/d/0

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23IND13
ScreenFood

Metrology for Food Safety in the Circular Economy:Targeted and Screening Methods for Contaminants in Food and Recycled Packaging

23IND13 ScreenFood

CRM Production

Matrix:

Tomato
Infant Food

Analytes:

PFOS, PFOA, PFBA, PFBS, PFDA, PFHpA, PFHxA, PFHxS, PFNA, GenX, PFPeA, PFUnDA, PFDoDA, PFTrDA, PFTeDA, PFPS, PFHpS, PFNS, PFDS, PFUnDS, PFDoDS, PTrDS, FOSA

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CRM Production

Target LOQ:

0.001-0.004 µg/kg for vegetable and infant food
(Commission Recommendation (EU) 2022/1431)

0.01-0.04 µg/kg (initial decision of the project partners)
Concentration of candidate reference material

PFOS, PFOA, PFHxS, PFNA : 0.01 µg/kg
The rest of the analytes: 0.05 µg/kg
(Decision after the first preliminary measurements of the processed materials)

RM Conditions:

1000 bottles
50 g in one bottle for original sample (infant food and fresh tomato)
2,5 g in one bottle (freeze dried tomato)

23IND13 ScreenFood

CRM Production

INFANT FOOD

The raw material of infant food was provided by JOTIS in 10 kg buckets, with a total amount of 60 kg. It is a cereal-based infant food.

Cereal Based Baby Food - Biscuit	
Nutritional values	%
Protein	16
Fat	11
Carbohydrates	64
Sugars	23
Starch	33

TOMATO

The raw material of tomato was obtained from a Turkish company named 2n14 and from the market. Following the preliminary measurements of the processed tomato matrix, a larger batch of approximately 70 kg of tomato was procured from the same Turkish company, as the matrix supplied by this company was found to be nearly free of PFAS in comparison with the market-sourced tomato

Processing of the food matrices by blending, homogenisation, bottling

CRM Production

INFANT FOOD

The spiking procedure for the infant food involved preparing a PFAS solution in methanol and adding it to a small portion of the infant food matrix.

After the solvent was evaporated, this spiked portion was blended with blank infant food to obtain a larger batch of spiked sample. Blending was performed using a 3D mixer.

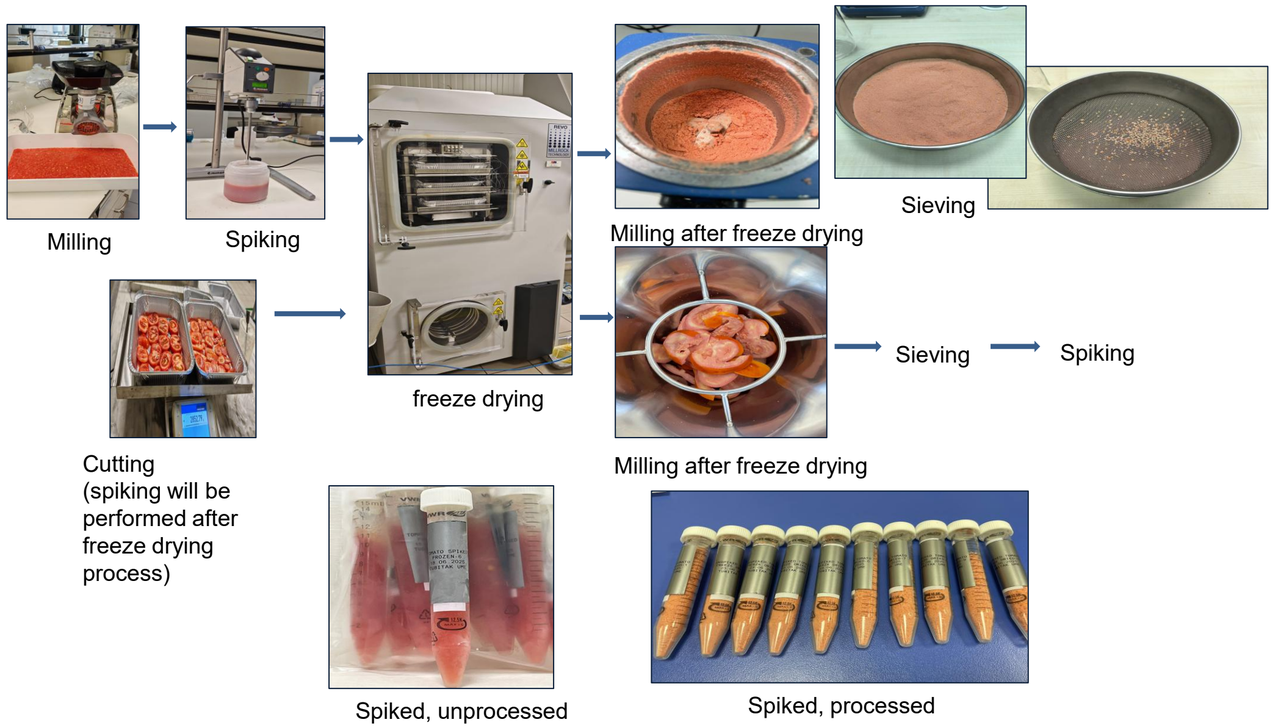
After blending, sieving and particle-size analyses were carried out. The samples will be stored in HDPE Nalgene bottles.

Processing of the food matrices by blending, homogenisation, bottling

CRM Production

TOMATO

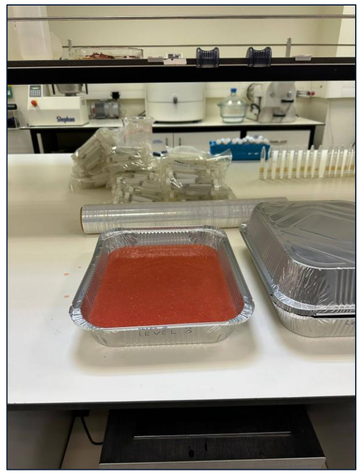
During the first feasibility study of material processing, two different processing approaches were applied to two types of tomato (those obtained from the company and from the market).



CRM Production

Processing of the food matrices by blending, homogenisation, bottling

TOMATO



Production of Certified Reference Materials

Thank You for Your Attention !

For More Information
Please do not Hesitate to Contact Us !

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