CCQM-K148.a
Purity of Bisphenol A

Key Comparison Track A

Final Report
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SUMMARY

The CCQM-K148.a comparison, undertaken with a parallel pilot study CCQM-P187.a, was coordinated by the BIPM on behalf of the Consultative Committee for Amount of Substance: Metrology in Chemistry and Biology (CCQM) Working Group on Organic Analysis (OAWG). It was undertaken for National Measurement Institutes (NMIs) and Designated Institutes (DIs) which provide measurement services in organic analysis under the CIPM Mutual Recognition Arrangement (MRA) and was designated a Track A comparison within the OAWG implementation of the CCQM Strategy for Programme Development 2017-2026.[1]

The ability to assign the mass fraction content of the primary component in a solid organic material that an NMI makes available as a pure substance Reference Material or that is used by an NMI in-house as a Primary Reference Material[2] is a critical technical competency for the provision of SI-traceable quantitative measurement results in organic analysis. The purity property value assigned to the Primary Reference Material in a measurement hierarchy anchors the calibration chain for all results linked to that material.

Participation in the series of Track A purity comparisons organized by the OAWG allows an NMI/DI to demonstrate that their procedure for the assignment of a purity property value and its associated uncertainty are fit for purpose for their intended application. Evidence of successful participation in formal, relevant international comparisons is required under the CIPM Mutual Recognition Arrangement (MRA) to support calibration and measurement capability (CMC) claims made by NMIs and DIs.[3]

Sixteen NMIs in addition to the coordinating laboratory, BIPM, submitted results in CCQM-K148.a.[a] Participants were required to assign the mass fraction content of Bisphenol A (BPA) present in a solid material containing BPA as the principal component.

Nine participants assigned their final value for the comparison through the combination of values obtained by independent mass balance and qNMR methods. One participant reported a combined value from combination of results obtained by mass balance, qNMR and freezing point depression methods. Five participants reported a result from a mass balance method only and two reported a result by qNMR only. The Key Comparison Reference Value (KCRV) for the BPA content in the comparison material was assigned using a Hierarchical Bayesian Random Effects Model (HB REM) estimator from the values reported by twelve of the participants. Five participants requested to remove their results from consideration for the calculation. The KCRV was 995.7 ± 0.6 mg/g. The KCRV assignment is consistent with the procedure recommended in Table 1 of document OAWG-19/064: *Decision guide for selecting CCQM Model 1 key comparison reference value estimation procedures*.[4]

The comparison protocol indicated that participation in CCQM-K148.a supports capabilities for assigning the mass fraction content of the primary component, having molar mass in the range (75 – 500) g/mol and classified as non-polar (pK_{ow} < -2), in a neat organic solid where the mass fraction content of the primary component in the material is in excess of 950 mg/g.

[a] NIST registered to participate in the comparison but were unable to submit a result due to the impact on their activities of the US Federal Government shutdown during the period December 2018 - January 2019.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

ACRONYMS

BPA	Bisphenol A
BPE	Bisphenol E
BPF	Bisphenol F
CCQM	Consultative Committee for Amount of Substance: Metrology in Chemistry and Biology
CMC	Calibration and Measurement Capability
CRM	Certified Reference Material
DI	Designated Institute
DoE	Degrees of Equivalence
DSC	Differential Scanning Calorimetry
DSL	der Simonian-Laird
FPD	Freezing-point depression
GC-FID	gas chromatography with flame ionization detection
GC-HRMS	gas chromatography with high-resolution mass spectrometry detection
GC-MS	gas chromatography with mass spectrometry detection

HB REM	Hierarchical Bayes Random Effects Model estimator
HPLC	high performance liquid chromatography
HS GC-MS	head space gas chromatography with mass spectrometry detection
ICP-MS	Inductively coupled plasma with mass spectrometry detection
ICP-OES	Inductively coupled plasma with optical emission spectroscopy detection
IDMS	isotope dilution mass spectrometry
LC	liquid chromatography
LC-CAD	liquid chromatography with charge aerosol detection
LC-DAD	liquid chromatography with diode array (UV) detection
LC-FLD	liquid chromatography with fluoresence detection
LC-HRMS	liquid chromatography with high-resolution mass spectrometry detection
LC-MS	liquid chromatography with mass spectrometry detection
KC	Key Comparison
KCRV	Key Comparison Reference Value
KCRU	Key Comparison Reference Uncertainty
MRM	(MS) Multiple Reaction Monitoring
NMI	National Metrology Institute
NMR	Nuclear Magnetic Resonance spectroscopy
OAWG	Organic Analysis Working Group
pK_{ow}	negative log (base 10) of the octanol-water partition coefficient
qNMR	quantitative nuclear magnetic resonance spectroscopy
RH	relative humidity
SIM	(MS) selected ion monitoring
SPE	solid phase extraction
TIC	total ion chromatogram

SYMBOLS

d_i	degree of equivalence of a result x_i with the KCRV: x_i - KCRV
% d_i	percent relative degree of equivalence: $100 \cdot d_i$/KCRV
k	coverage factor for expanded uncertainty $U(x) = k \cdot u(x)$
s	standard deviation of a series of quantity values: $s = \sqrt{\sum_{i=1}^{n}(x_i - \bar{x})^2/(n-1)}$
t_s	Student's t-distribution expansion factor
w_i	mass fraction content of organic analyte reported in kg/kg or subunits thereof
x	a quantity value
$u(x)$	standard uncertainty of quantity value x
$U_{95}(x)$	expanded uncertainty defined such that the range $x \pm U_{95}(x)$ is asserted to include the true value of the quantity with a 95 % level of confidence
x_i	the i^{th} member of a series of quantity values
$\bar{x}$	mean of a series of quantity values: $\bar{x} = \sum_{i=1}^{n} x_i/n$

INTRODUCTION

The ability to undertake suitable purity value assessment on materials intended for use, either internally or externally, as pure substance reference materials is considered a core competency for the provision of SI-traceable measurement services in organic analysis. Evidence of successful participation in relevant international comparisons is required under the CIPM MRA to support measurement capability claims (CMCs) in organic analysis made by NMIs and DIs.

At the April 2018 meeting of the CCQM the OAWG Chair presented for approval the proposal from the OAWG for Key Comparison CCQM-K148.a "Purity of Bisphenol A".[5] CCQM-K148.a was primarily undertaken in order to benchmark participants' capabilities for the purity assignment of a non-polar organic compound (pK_{OW} < -2) having a molar mass in the range (75 – 500) g/mol. It is a component of the OAWG strategy of Track A key comparisons that serve to underpin and benchmark NMI capabilities for the provision of primary calibration services for organic analysis.[1] The properties of Bisphenol A (BPA) meet these target requirements. It was also selected for its ready availability, stability, relative ease of transport and the significant contemporary interest in BPA as an analyte. It is found widely in the general environment and food supply from degradation of common industrial plastics. Concerns regarding adverse health effects due to its potential activity as an endocrine system disruptor have resulted in widespread implementation of environmental and food safety programs monitoring exposure to BPA.[6]

TIMELINE

Date	Action
April 2016	Comparison proposal accepted by the OAWG for investigation
October 2016	Draft protocol presented to OAWG as potential Track A Key Comparison
April 2017	CCQM Plenary approves the OAWG proposal to undertake the comparison
April 2018	OAWG approve the CCQM-K148.a comparison protocol and advise CCQM
September 2018	Call for participation distributed to OAWG members
October 2018	Registration deadline for participation
November 2018	Study samples shipped to participants.
February 2019	Results provided to the coordinating laboratory
April 2019	First discussion of results at OAWG meeting
December 2019	First Draft A report with KCRV proposal distributed to OAWG
April 2020	Second Draft A report distributed to OAWG
November 2020	Draft B report distributed to OAWG
TBD	Final report published in KCDB

Table 1: Timeline for CCQM-K148.a

MEASURAND

Participants were required to report the mass fraction of BPA, the major component, in one unit of the comparison material. The structure, nomenclature and basic properties of BPA are shown in Figure 1. The units recommended for reporting the mass fraction of BPA present in the CCQM-K148.a comparison material were mg/g.

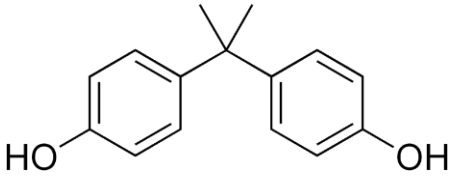


Figure 1: Structure of Bisphenol A (BPA)

IUPAC Name: 4-[2-(4-Hydroxyphenyl)propan-2-yl]phenol
Formula: $C_{15}H_{16}O_2$; Molecular Weight = 228.3 ; pK_{OW} = -3.3 [7]

Figure 1: Structure, nomenclature and properties of Bisphenol A

Participants using a mass balance (summation of impurities) procedure to assign the BPA content were required to report the mass fraction assignment and associated combined standard uncertainty of each sub-class of impurity contributing to their overall result assignment. The sub-classes of impurities to be quantified for a mass balance assignment of BPA included some or all of:

i. total related structure organics;
ii. water;
iii. volatile organic compounds (VOCs);
iv. total non-volatiles/inorganics.

COMPARISON MATERIAL

The BPA source material used by the BIPM to prepare the comparison material was purchased from a commercial supplier. Its qualitative identity was confirmed and its purity was estimated by the BIPM. The bulk material was not subject to further physical treatment prior to its subdivision into units during production of the comparison material batch. The analysis report accompanying the material indicated compliance of the production batch with manufacturer's specifications for the following properties: colour, form, IR spectrum, HPLC purity and solubility in methanol. The structure, molecular weight and estimated pK_{ow} of BPA are shown in Figure 1.

A batch of 264 individually numbered units having the BIPM identifier code OGP.027 were prepared. Each unit contained in excess of 500 mg of the BPA powder in an amber glass vial closed using a rubber insert cap and crimped with an aluminium seal.

The impurity profile of the batch was determined at the BIPM and an assessment of the homogeneity and stability of the units of BPA, the related structure impurity components present in the material and its water content was undertaken.

The recommended minimum sample amounts (mg) for analysis by method were as follows:

LC-UV	20
KFT	50
TGA	10
EA	10
qNMR	5

In the case of the LC-UV method, participants were advised that the recommended minimum sample size reflected the procedure employed by the BIPM and was not regarded as a critical value. From the observed results for stability and homogeneity of the material, the BIPM advised participants that sample sizes of 5 mg could be used for chromatographic analysis of the comparison sample for the determination of related structure impurity content without the introduction of significant effects due to potential sample inhomogeneity.

Characterization of Study Material

The methods used to investigate, assign and confirm the quantitative composition of the CCQM-K148.a candidate material by the BIPM are summarised below.

Related structure impurity content was investigated by:

a. LC-UV
b. LC-hrMS/MS
c. ^{1}H NMR

Water content was evaluated by:

a. coulometric Karl Fischer titration using heated oven transfer from the sample
b. thermogravimetric analysis (TGA)
c. microanalysis (% C, H content) as a consistency check
d. sorption balance (mass variation as a function of RH)

Residual solvent content was evaluated by:

a. ^{1}H NMR
b. TGA as a consistency check

Non-volatile/ inorganics content :

a. TGA under high-temperature oxidative conditions
b. microanalysis (% C, H content) as a consistency check

Main component content: direct assay by qNMR

The mass fraction content of BPA present in the comparison material was assessed by the BIPM to be in excess of 990 mg/g.

Homogeneity Assessment of Study Material

The homogeneity of the main component and related structure impurities in the candidate material was investigated using high-performance liquid-chromatography coupled in sequence with a diode array detector (DAD) to detect and quantify the resolved components through detection at fixed wavelengths corresponding to local maxima for BPA (UV @ 220, 280 and 360 nm). A Phenomenex ODS Hypersil (250 x 4.6 mm; 5 µm particle) HPLC column with a gradient elution method over 35 minutes from an initial mixture of 40% mobile phase A (water) / 60% mobile phase B (methanol) containing 0.05% formic acid to a final mixture of 5% A / 95% B containing 0.05% formic acid, followed by washing and re-equilibration, based on a literature method, was used.[8] Subsequent to the discussion of participant results it was found that acidification of the elution solvents with formic acid was required to avoid the formation of artefacts arising from *in situ* oxidative coupling of BPA, presumably through suppression in solution of the formation of phenolate ion from BPA which was susceptible to oxidation. The method was developed using a test mixture containing BPA and commercially-available standards of four impurities reported in

the literature[9] as commonly present in BPA: Bisphenol E (BPE), Bisphenol F (BPF), 4-isopropylphenol and 4-tertbutylphenol. It was optimized to achieve baseline separation of these compounds from the primary BPA peak and was applied for homogeneity testing of the comparison material. The BPA and related structure impurity content of samples taken from ten vials selected at a regular interval from the filling sequence was determined. Three significant impurities, none of which corresponded in retention time to the test mixture components, and a number of minor peaks were observed in the chromatogram obtained with detection at 280 nm.

Plots of the normalised relative response results over the vial filling sequence for BPA in Figure 15.a and for the two major impurities are presented in Figures 15.b and 15.c in Appendix A.

The uncertainty contributions due to inhomogeneity of the main component and of the related structure impurity content were evaluated by simple ANOVA of the combined homogeneity test results. This allowed for the estimation of the contributions due to both method variability (s_{wb}) and that due to (potential) variation in content between sample units (s_{bb}) to the overall uncertainty associated with the repeat analysis of one sample unit ($u_{c,bb}$), as shown in equation 1.

$$u_{c,bb}^2 = s_{bb}^2 + \frac{s_{wb}^2}{n} \quad (1)$$

The standard deviation of the results obtained between the sample units was used as the estimator for the between-unit variance. The method repeatability set the lower limit (u^*_{bb}) to this estimator as given by equation 2.

$$u^*_{bb} = \sqrt{\frac{MS_{within}}{n}}\sqrt[4]{\frac{2}{\nu_{MSwithin}}} \quad (2)$$

where MS_{within}, n and $\nu_{MSwithin}$ are respectively the mean sum of squares for within unit result variation, the number of measurements per unit (2 for duplicate analyses) and the degrees of freedom of MS_{within}. The uncertainty contribution due to inhomogeneity of the sample (u_{bb}) was estimated as s_{bb} or u^*_{bb}, depending on which of these was larger.

In cases where the mean sum of squares for between unit results ($MS_{between}$) was smaller than MS_{within}, s_{bb} could not be calculated and u^*_{bb} was used as the estimate of the uncertainty contribution due to sample inhomogeneity.

Linear regression plots were calculated for the homogeneity study results as a function of both sequential filling and analysis order. The slopes of the lines were tested for significance on a 95 % confidence level as a check for trends in relative content over either the homogeneity analysis sequence or the filling sequence, but no evidence for significant trends was found.

Acceptable uncertainty contribution estimates due to inhomogeneity were found for the two major impurities observed in the sample. Table 2 shows the estimated content, $u_{bb(rel)}$ and $u_{bb(abs)}$ for each of the major related structure impurities, and a combined value for the maximum overall uncertainty contribution from between unit inhomogeneity (u_{bb}) of the related structure impurities content of the material. Quadratic combination of the absolute inhomogeneity uncertainty estimates for each impurity gave the combined estimate for the BPA material used in CCQM-K148.a as 0.12 mg/g.

ANOVA Estimate	BPA	Impurity 1	Impurity 2
% peak area (280 nm)	99.2*	0.17	0.12
Within-unit, s_{wb}:	0.59 %	0.62 %	3.5%
Between-unit, s_{bb}:	($MS_{bb} < MS_{wb}$)	0.20%	($MS_{bb} < MS_{wb}$)
u^*_{bb}	0.22%	0.23%	1.3%
Assigned homogeneity uncertainty, u_{bb}	**0.22 %**	**0.23%**	**1.3%**
F	0.112	1.310	0.537
Fcrit	3.106	3.106	3.106

Table 2. Homogeneity assessment for BPA and related structure impurity content

* It was confirmed after review of the combined participant results that the relative response value reported for BPA in Table 2 was biased low due to the use of a neutral rather than acidified elution solvent. This resulted in the formation of artefact impurities. The relative BPA peak area at 280 nm was closer to 99.6% when the analysis was repeated using an elution solvent mixture acidified with formic acid. The two reported major impurities were still present at levels consistent with their original estimates when the acidified solvent system was used.

Stability Assessment of Study Material

An isochronous stability study of BPA and its related structure impurity content was performed using a reference storage temperature of -20 °C and test temperatures of 4 °C, 22 °C and 40 °C. Twenty-eight units from the candidate batch were selected by stratified random sampling from each quartile of the candidate material batch. Assigned units were stored at each test temperature and two units from each test temperature set were transferred to reference temperature storage at two-week intervals up to eight weeks in total. Using the same LC-UV method implemented for the homogeneity study, baseline results established from four units stored throughout at the reference temperature were compared with the results for the sets of units subject to each of the storage test temperatures.

Solutions corresponding to approximately 20 mg of the comparison material made up in 10 ml of acetonitrile were gravimetrically prepared for each sample. The UV-response data for each component was normalised with respect to the average response of the reference samples. The results were plotted against storage time at elevated temperature for each condition and the slopes of each plotline were tested for significance at a 95 % confidence level for evidence of instability of the mass fraction of each component under each storage condition.

No significant trends were observed in the stability of the content of either the BPA component or the main related structure impurities under the test conditions. It was concluded that provided the material was not exposed to temperatures in excess of 40 °C no additional precautions regarding temperature control during the shipment and storage of the material was required. Uncertainty contributions arising from the instability of BPA under the recommended storage conditions was assessed to be negligible.

Normalised plots of the results obtained for the stability of the BPA component under storage for up to eight weeks at 40 °C is shown in Figure 16.a in Appendix B. The corresponding plots for the BPA Impurities 1 and 2 are shown in Figures 16.b and 16.c. Similar plots but with smaller observed variation were obtained for the sets of units stored at both 4 °C and at 22 °C.

PARTICIPANTS, INSTRUCTIONS AND SAMPLE DISTRIBUTION

The call for participation was circulated in September 2018 within the OAWG membership with the distribution of samples commencing in November 2018. The initial deadline for submission of results in February 2019 was extended to the beginning of March 2019. A preliminary result summary was distributed to the comparison participants in late March 2019 and the first discussion of results occurred at the April 2019 OAWG meeting. Appendix C reproduces the Call for Participation and Comparison Protocol circulated to the membership of the OAWG and Appendix D the comparison registration form. Eighteen institutes registered to participate in the key comparison. Four institutes (three NMIs and one DI) registered to participate in the parallel pilot study CCQM-P187.a. The institutes that reported a result for CCQM-K148.a are listed in Table 3. The institutes participating in CCQM-P187.a and results obtained are not discussed in this report.[10]

NMI or DI	Acronym	Country	Contact
National Measurement Institute, Australia	NMIA	Australia	Stephen Davies Stephen.Davies@measurement.gov.au
Instituto Nacional de Metrologia, Qualidade e Tecnologia	INMETRO	Brazil	Eliane Pires do Rego ecrego@inmetro.gov.br
National Research Council of Canada	NRC	Canada	Jeremy Melanson jeremy.melanson@nrc-cnrc.gc.ca
National Institute of Metrology, China	NIM	China	Can Quan quancan@nim.ac.cn
Government Laboratory of Hong Kong	GLHK	China	W. H. Lam wfwong@govtlab.gov.hk
Physikalisch-Technische Bundesanstalt	BAM	Germany	Rosemarie Philipp rosemarie.philipp@bam.de
National Chemical Metrology Laboratory	EXHM	Greece	Elias Kakoulides metrology@gcsl.gr
National Metrology Institute of Japan	NMIJ	Japan	Yuko Kitamaki y-kitamaki@aist.go.jp
Centro Nacional de Metrología	CENAM	Mexico	Alejandro Castorena aperez@cenam.mx
D.I. Mendeleev Institute for Metrology	VNIIM	Russia	Anatoly Krylov a.krylov@b10.vniim.ru
Health Sciences Authority	HSA	Singapore	Tang Lin Teo TEO_Tang_Lin@hsa.gov.sg
National Metrology Institute of South Africa	NMISA	South Africa	Maria Fernandes-Whaley mfwhaley@nmisa.org
Korea Research Institute of Standards and Science	KRISS	South Korea	Seonghee Ahn sahn@kriss.re.kr
National Institute of Metrology (Thailand)	NIMT	Thailand	Sornkrit Marbumrung sornkrit@nimt.or.th
National Metrology Institute of Turkey	UME	Turkey	Mine Bilsel mine.bilsel@tubitak.gov.tr
LGC Limited	LGC	United Kingdom	Cailean Clarkson Cailean.clarkson@lgcgroup.com
Bureau International des Poids et Mesures	BIPM	France	Steven Westwood Steven.Westwood@bipm.org

Table 3: Institutions reporting results for CCQM-K148.a

Either two or three units of the comparison material were shipped by the coordinating laboratory to each participant. The number of vials provided depended on whether the participants intended to use a single assignment method or the combination of the results from multiple approaches. Each participant completed and returned a receipt form advising the comparison coordinator if any obvious damage had occurred to the vials during shipping and indicating whether a monitoring strip inside the container indicated exposure to a temperature in excess of 37 °C during the shipping process. No problems were reported in shipment of the comparison materials due to significant customs clearance delay, damage in transit or exposure to excessive temperature.

One unit of the comparison material was provided for use in method development purposes. Participants were requested to report a value derived solely from data obtained using the remaining vial(s). A single estimate for the mass fraction of the BPA content in units of mg/g was required. In addition participants using a mass balance procedure were required to report the combined mass fraction assignment and associated uncertainty for each contributing sub-class of impurity: total related structure organics, water, VOCs and total non-volatiles/inorganics content.

The general operations at NIST were interrupted as a result of the shutdown of the United States Federal government which occurred from 22 December 2018 to 25 January 2019. As this corresponded to the majority of the time scheduled for analysis of the CCQM-K148.a material, although NIST had registered to participate and received the sample materials they were unable due to factors outside their control to complete the characterization of their material to the requirements of their quality system and as a result withdrew from submission of a result for the comparison.

A copy of the spreadsheet provided for submission of results is reproduced in Appendix E.

A copy of the Core Competency template as circulated to the participants is reproduced in Appendix F. This template erroneously ascribed the comparison scope as being for the assignment of compounds in the molecular weight range 100 – 500, whereas the HFTLS in the comparison protocol specified the molecular weight range as 75 – 500. For the individual Core Competency claims received from the participants compiled in Appendix N this error has been corrected.

RESULTS

Participants were required to assign the mass fraction content of BPA in the comparison material.

In addition to the quantitative result for the main component, participants were required to provide summaries of their analytical methods, their approach to value assignment and their budget for uncertainty estimation and to specify their Core Competencies demonstrated in this study

Participants using a mass balance procedure were required to report the combined mass fraction assignment and associated uncertainty for the assigned sub-classes of impurity; total related structure organic impurities, water, residual solvent and total non-volatiles/inorganics content.

In addition participants were encouraged but not required to identify and provide mass fraction estimates for all significant individual impurity components quantified in the comparison sample.

Apart from NIST, for the reason noted previously, results were submitted by all the registered participants and in addition by the coordinating laboratory.

Five participants submitted a result for BPA content obtained by use of a mass balance method only and two by a qNMR method only. The remaining ten key comparison participants reported a value obtained by combining results from mass balance and qNMR data. In addition NMIJ also used a DSC method to directly assess the main component purity and their reported value was derived from the results of all three methods. A summary of the approach used by each participant to assign the BPA content of the comparison material is provided in Appendix G (a) and to verify the assigned value in Appendix G (b). The individual participant approaches for the value assignment and estimation of the associated measurement uncertainty are outlined in Appendix H.

Two participants in the key comparison (NIM and UME) reported values for BPA content using a mass balance approach to assign their key comparison value and by stand-alone qNMR methods in the parallel CCQM-P187.a pilot study.

Participant Results for BPA content in CCQM-K148.a

The reported results for the BPA content of the CCQM-K148.a key comparison are listed in Table 4 and are plotted in Figure 2. The reported results are plotted with bars associated with each data point corresponding to the standard uncertainty of the individual result ($\pm\ u_c$, $k = 1$).

NMI	x (mg/g)	$u(x)$ (mg/g)	$u_{rel}(x)$ (%)	k	$U_{95}(x)$ (mg/g)	$U_{rel}(x)$ (%)
BAM	995.4	0.46	0.046	2	0.91	0.091
BIPM	993.3	1.7	0.171	2	3.4	0.34
CENAM	977.02	0.26	0.027	2	0.52	0.052
EXHM	994.23	0.64	0.64	2	1.28	0.13
GLHK	996.3	2.5	0.251	2	4.9	0.49
HSA	995.2	1.5	0.151	2	3.0	0.30
INMETRO	995.7	0.6	0.060	2	1.2	0.12
KRISS	995.87	0.82	0.082	2.45	2.02	0.202
LGC	995.8	1.2	0.121	2	2.5	0.25
NIM	996.41	1.08	0.108	2	2.17	0.217
NIMT	987.8	2.76	0.279	2	5.60	0.56
NMIA	997	0.9	0.090	2.3	2.0	0.20
NMIJ	996.1	0.50	0.050	2	1.00	0.10
NMISA	989.6	4.0	0.404	2	8.0	0.80
NRC	993.7	2.4	0.242	2	4.8	0.48
UME	996.64	3.03	0.304	2	6.06	0.606
VNIIM*	997.75	0.146	0.015	2	0.29	0.029

Table 4: Reported results for BPA content in CCQM-K148.a (mg/g)

* VNIIM reported a revised value for BPA content of 996.42 ± 0.50 mg/g after studies undertaken subsequent to the initial circulation of results and discussion

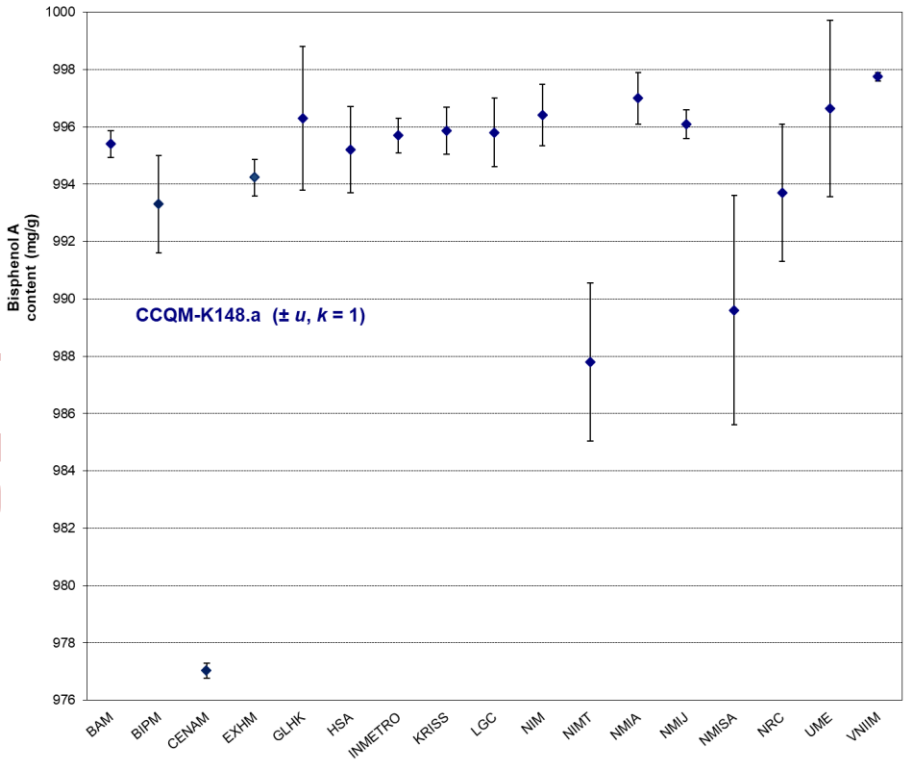


Figure 2: Participant Results for BPA content in CCQM-K148.a

Reported results for BPA content in the CCQM-K148.a material by participant sorted by alphabetical order of the NMI. Dots represent the reported value, x; bars the standard uncertainty, $u(x)$, in units of mg/g.

BPA content by Mass Balance

All of the participants reporting results in the comparison incorporated a mass balance study in their assessment of the material to some extent. The mass balance approach was used as:

- the sole method (CENAM, NIM, NIMT, NMIA, VNIIM)
- combined with a separate qNMR result (BIPM, EXHM, GLHK, HSA, INMETRO, KRISS, LGC, NMISA, UME)
- combined with separate qNMR and DSC results (NMIJ)
- supporting data when a qNMR method was used for the result assignment (BAM, NRC).

A compilation of the BPA assignments reported by participants using a full mass balance method is given in Table 5. After review of their results BIPM, NMISA and VNIIM requested that their mass balance data should not be included in subsequent KCRV assignments. The reported results of CENAM and NIMT were assigned as significant outliers also. A set of statistical estimators derived from the remaining ten results are given in Table 6.

NMI	x (mg/g)	$u(x)$ (mg/g)	k	$U_{95}(x)$ (mg/g)
BIPM*	992.3	2.2	2	4.4
CENAM*	977.02	0.26	2	0.52
EXHM	994.33	0.55	2	1.1
GLHK	996.8	1.58	2	3.16
HSA	995.8	1.83	2	3.70
INMETRO	995.92	0.28	2	0.56
KRISS	996.35	0.62	2.2	1.37
LGC	995.3	2.2	2	4.4
NIM	996.4	1.08	2	2.17
NIMT*	987.8	2.76	2	5.6
NMIA	997	0.9	2.3	2.0
NMIJ	995.9	0.55	2	1.1
NMISA*	992.9	1.4	2.4	3.4
UME	996.65	3.03	2	6
VNIIM*,#	997.75	0.146	2	0.29

Table 5: Results for BPA content by Mass Balance (mg/g)

* results not used in the calculation of a combined estimator for BPA content by mass balance.

\# VNIIM reported a revised value of 996.42 ± 0.50 mg/g after studies undertaken subsequent to the circulation of results and initial discussion.

Estimator	u? [i]	X (mg/g)	$u(X)$ (mg/g)	$U_{95}(X)$ [ii] (mg/g)
Mean	No	996.05	0.25	0.57
Median	No	996.14	0.25	0.57
DSL-Mean	Yes	995.84	0.29	0.66

Table 6: Statistical Estimators for BPA content by Mass Balance (mg/g)

i. Utilizes information in the reported uncertainties?

ii. $U_{95}(X) = t_s \cdot u(X)$, where t_s is the two-tailed Student's t critical value (2.26 where $n = 10$) for 95 % coverage

The participant content assignments are plotted in alphabetical order in Figure 3.

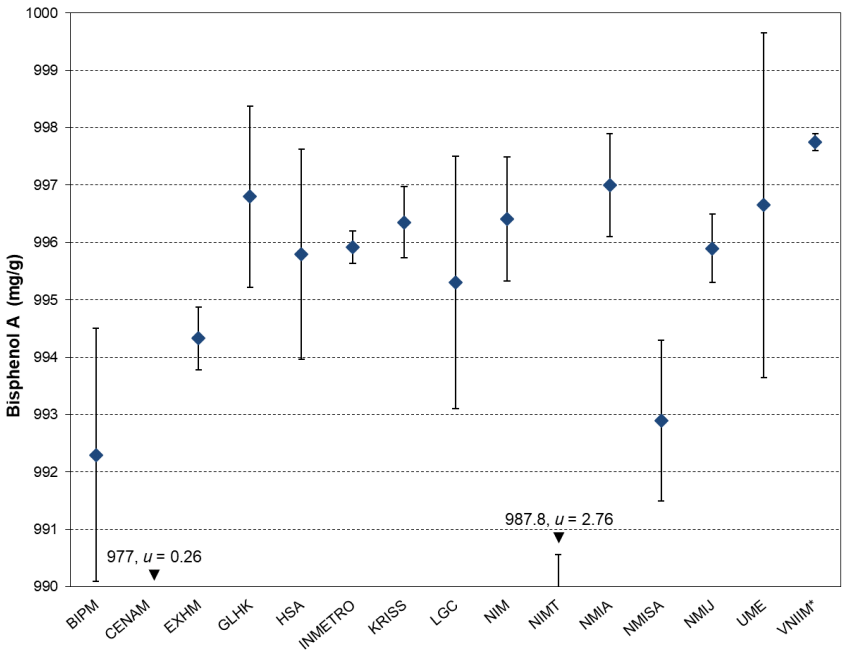


Figure 3: Mass Balance Results for BPA in CCQM-K148.a

Results for BPA content in CCQM-K148.a obtained by a mass balance method.
Dots represent a reported value, *x*; bars the associated standard uncertainty, *u*(*x*), in units of mg/g.
* The value initially reported by VNIIM is shown. They reported a revised value of 996.42, u = 0.25 mg/g as a result of further studies undertaken subsequent to the initial circulation of results.

Related Structure Impurity content

The presence of two major impurities related to BPA in structure was reported in the comparison material by most participants, along with a number of impurities present at significantly lower levels. Figure 4 shows the structures proposed initially for the two major impurities. The presence of the 2,4´-isomer of BPA (**1**) as one of these impurities was independently established by several participants through comparison with chromatographic, mass spectral and NMR properties of authentic standards of (**1**). The other significant impurity was identified as a polycyclic BPA-related compound of molecular formula $C_{27}H_{30}O_3$. Its structure was proposed by several participants, based on literature precedent, as 4-(4´-hydroxyphenyl)-7-[4´-hydroxy phenyl(propan-2-yl)]-2,2,4-trimethyl chromane [**(2)**, Fig. 4]. Subsequent to the initial result discussion, GLHK undertook an NMR study of a purified sample of the impurity isolated directly from the comparison material by semi-preparative HPLC. They reported that the ^{1}H NMR data obtained did not correspond with the reported data for **(2).**[11] Based on 2D-NMR experiments GLHK proposed the structure of the second impurity instead as 4-(4´-hydroxyphenyl)-6-[4´-hydroxyphenyl(propan-2-yl)]-2,2,4-trimethylchromane [(**3**), Fig. 4]. The correspondence received from Dr Annie Wong from GLHK reporting this assignment, with comparison of the reported NMR spectral data for (**2**) with the spectrum obtained by GLHK, are provided in Appendix I.

As noted earlier, numerous trace level BPA-related impurities were also visibly present in LC-UV chromatograms of the material. Individual participants made tentative identifications of some of these components, generally based on mass spectral data, but no consensus was reported for their identity. As collectively they make a minor contribution to the final content assignment of BPA

and there was some variability in the observed impurity profile it was not deemed necessary for the intended purpose of the comparison to fully identify each or distinguish between those inherently present in the material and those which were potentially artefacts formed in solution.

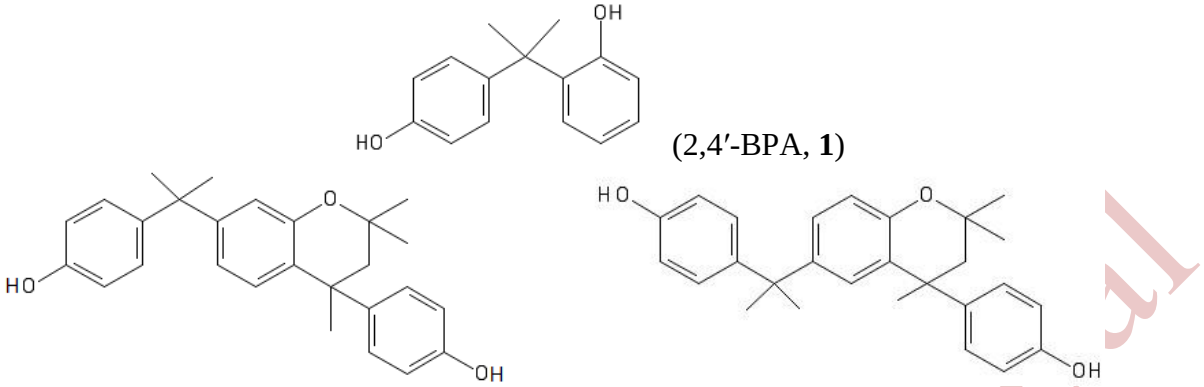


Figure 4: BPA-related impurities, (**1**) and (**3**) in the CCQM-K148.a material.

(**2**) is an alternative structure proposed by some participants for the structure of the impurity corresponding to (**3**) based primarily on a literature structure assignment for this impurity.

The assignments for total related structure impurity content reported by participant are listed in Table 7 and plotted in Figure 5.

NMI	x (mg/g)	$u(x)$ (mg/g)	k	$U_{95}(x)$ (mg/g)
BAM	5.67	0.79	2	1.58
BIPM	6.1	1.8	2	3.6
CENAM	21.63	0.257	2	0.51
EXHM	4.681	0.501	2	1.00
GLHK	2.81	0.71	2	1.41
HSA	3.74	0.93	2	1.85
INMETRO	3.26	0.27	2	0.54
KRISS	2.21	0.023	2.26	0.051
LGC	2.8	0.5	2	1.0
NIM	3.21	1.08	2	2.16
NIMT	8.31	1.76	2	3.52
NMIA	3	0.14	2.3	0.3
NMIJ	3.522	0.541	2	1.082
NMISA	7.1	1.4	2	2.8
NRC	4.06	0.4	2	0.8
UME	2.89	0.27	2	0.54
VNIIM*	1.89	0.14	2	0.28

Table 7: Estimates for total related structure impurity content in CCQM-K148.a (mg/g)
* VNIIM reported a revised value for related structure impurity content of 3.22, u = 0.245 mg/g after further studies undertaken subsequent to the initial circulation of the results and discussion.

Methods based on LC-UV were the predominant approach used to analyze the material for related structure impurity content. Other methods used included LC-CAD, LC-FLD, LC-MS/MS, GC-MS and GC-FID. A summary of the chromatographic methods and conditions used per participant are given in Appendix J. The HPLC separations reported shared common features, notably the elution times of the two major impurity components relative to each other and to the BPA primary component. However the absolute retention times, extent of resolution and the observed minor related structure impurity profiles varied between participants. Some representative example chromatograms are provided in Appendix K to illustrate these similarities and differences.

It was noted by several participants that formation of artefact peaks occurred if neutral or basic LC-eluant was used and that this phenomenon was suppressed when the eluant was acidified.

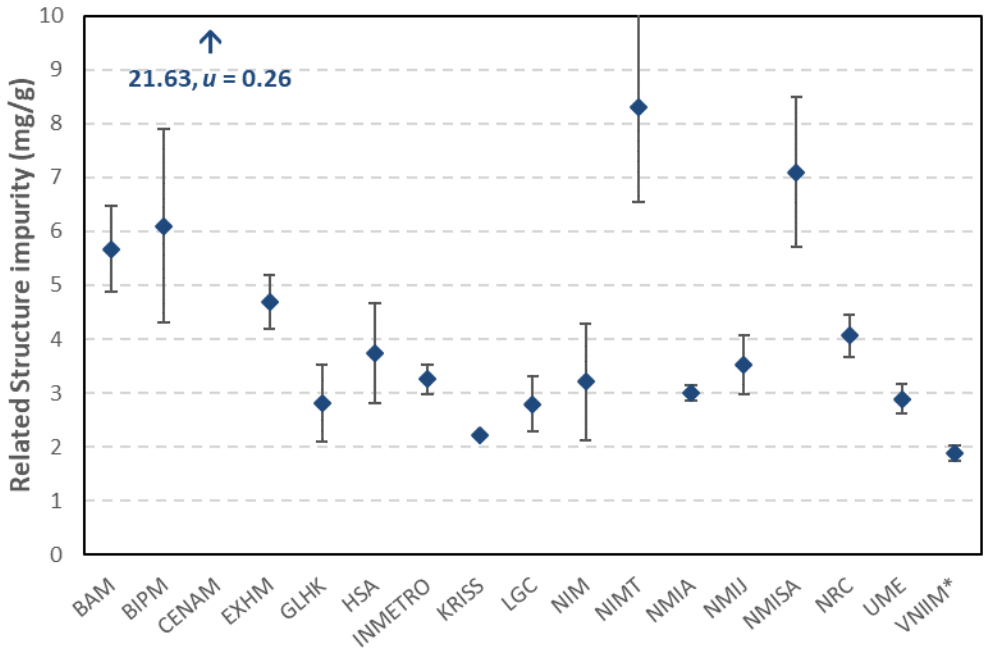


Figure 5: Total related structure impurity content in CCQM-K148.a

Dots represent the reported value, x; bars the associated standard uncertainty, $u(x)$, in units of mg/g. * The value originally reported by VNIIM is shown. They provided a revised estimate of 3.22 mg/g (see note to Table 7) after studies undertaken subsequent to the initial circulation of results.

A summary of the content estimates reported for the two major related structure impurities present in the material is given in Table 8. Several participants independently established 2,4´-BPA as one of these impurities. Most participants also noted the presence of another significant related structure impurity, subsequently assigned structure (3), however only a few proposed a structure assignment. In some cases it was identified as an organic impurity of molecular formula $C_{27}H_{30}O_3$.

Compound	n	Mean (mg/g)	Std. dev (mg/g)
2,4´-Bisphenol A (**1**)	14	1.49	0.24
4-(4´-Hydroxyphenyl)-6-[4´-hydroxyphenyl (propan-2-yl)]-2,2,4-trimethylchromane (**3**)	12*	1.25	0.27

Table 8 – Estimates of specific related structure impurity content in CCQM-K148.a
* Number of participants reporting an estimate for the impurity, even where its structure was not identified. Several participants proposed the alternative structure (**2**) based on a literature identification.[11]

Water content

The values reported for water content in CCQM-K148.a are listed in Table 9 and plotted in Figure 6. All participants used coulometric Karl Fischer titration, either after introduction of the sample directly into the titration cell or through transfer of the water content into the titration cell from an oven-heated aliquot of the comparison material using a flow of dry gas.

NMI	x (mg/g)	$u(x^-)$ (mg/g)	$u(x^+)$ (mg/g)	k	$U_{95}(x^-)$ (mg/g)	$U_{95}(x^+)$ (mg/g)
BAM	0.4	0.01	0.01	2	0.02	0.02
BIPM	0.25	0.06	0.12	2	0.12	0.24
CENAM	1.36	0.0314	0.0314	2	0.063	0.063
EXHM	0.993	0.05	0.05	2	0.10	0.10
GLHK	0.393	0.021	0.021	2	0.041	0.041
HSA	0.445	0.056	0.056	3.18	0.177	0.177
INMETRO	0.815	0.076	0.076	2	0.15	0.15
KRISS	0.793	0.068	0.068	4.3	0.291	0.291
LGC	0.87	0.53	0.53	2	1.06	1.06
NIM	0.342	0.064	0.064	2	0.127	0.127
NIMT	3.85	2.117	2.117	2	4.23	4.23
NMIA	0	0	0.6	2.3	0	1.4
NMIJ	0.46	0.049	0.049	2	0.098	0.098
NMISA	0	0	0.026	2.4	0	0.062
UME	0.05	$7.33E^{-7}$	$7.33E^{-7}$	2	$1.47E^{-6}$	$1.47E^{-6}$
VNIIM	0.36	0.04	0.04	2	0.08	0.08

Table 9: Results for water content in CCQM-K148.a (mg/g)

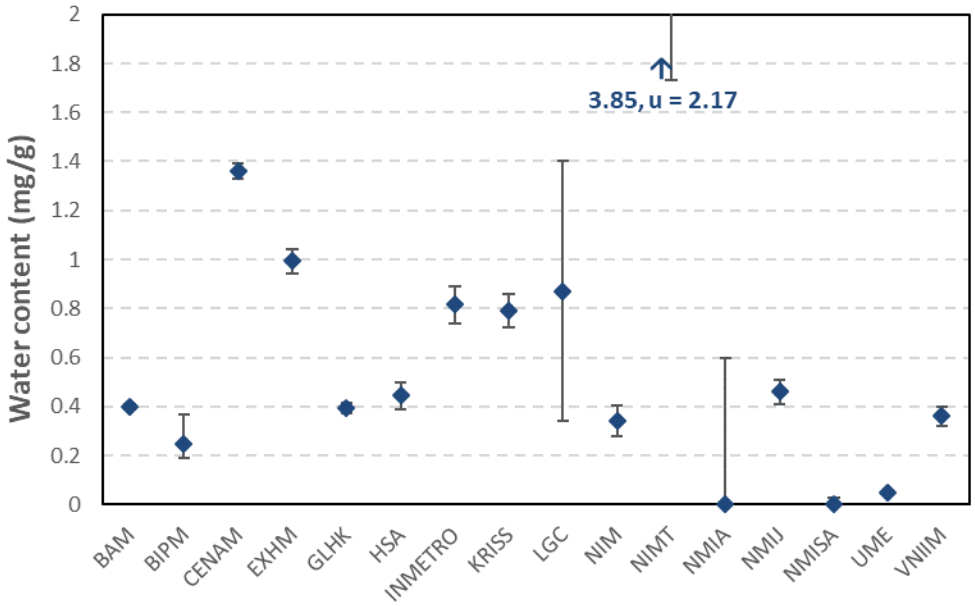


Figure 6: Water content in CCQM-K148.a

Reported results by participant for water content in CCQM-K148.a.
Data points represent the reported value; bars the associated standard uncertainty, *u*, both in units of mg/g.

An overview of the individual KFT method used to determine water content is given in Table 10.

Participant	KFT Method summary	Laboratory Environment	Checked by TGA?
BAM	Addition as solution in MeOH, 4 x 30 mg	23 °C, 20-30 % RH	
BIPM	Oven transfer @ 150 °C, 5 x 50 mg	22 °C, 45-50 % RH	Y
CENAM	Addition as powder, 2 x 30 mg	19-20 °C, 45 % RH	
EXHM	Addition as powder, 2 x 50 mg	22 °C, 40 % RH	
GLHK	Oven transfer @ 170 °C, 4 x 60 mg	23 °C, 43 % RH	
HSA	Addition as powder, 4 x 50 mg	22-27 °C, 36-46 % RH	Y
INMETRO	Addition as powder, 2 x 50, 1 x 100 mg	18-22 °C, 48-66 % RH	Y
KRISS	Oven transfer @ 140 °C, 3 x 60 mg	24 °C, 37 % RH	
LGC	Oven transfer @ 130 °C ; 4 x 50 mg	18 °C, 34 % RH	
NIM	Addition as powder, 7 x 60 mg	18-23 °C, 15 % RH	
NIMT	Addition as powder, 10 x 10 mg	20-22 °C, 52-55 % RH	
NMIA	Addition as powder, 2 x 80 mg	20-21 °C, 59-66 % RH	
NMIJ	Addition as powder, 4 x 50 mg	23-24 °C, 22-24 % RH	
NMISA	Oven transfer @ 155 °C, 1 x 50, 1 x 100 mg	21-23 °C, 40-48 % RH	Y
UME	Oven transfer @ 150 °C, 3 x 25 mg	21 °C, 42 % RH	Y
VNIIM	Oven transfer @ 110 °C, 3 x 100 mg	25 °C, 33 % RH	

Table 10: Method outline and environmental conditions for water content measurements of the CCQM-K148.a comparison material

Figure 7 is a comparison plot of water content obtained by KFT using direct addition of sample into the titration cell (red) or oven heating of an aliquot (blue) for transfer of water vapour.

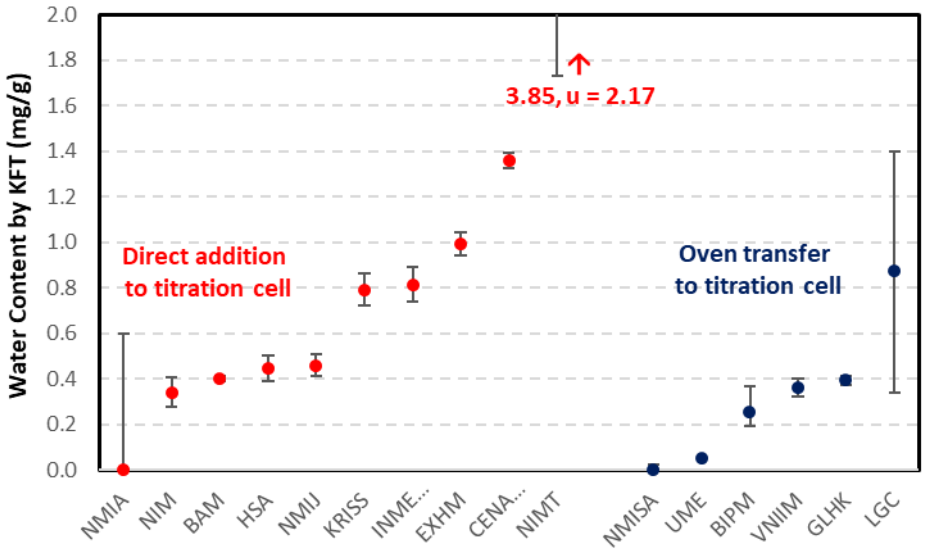


Figure 7: Water content in CCQM-K148.a by sample introduction method

Water content in CCQM-K148.a material by KFT measured using either direct addition (red) or heated oven transfer (blue) to deliver the sample water content into the titration cell. Dots represent the reported water content; bars the associated standard uncertainty, *u*, both in units of mg/g.

Volatile organics content

Fifteen participants provided information on the volatile organics content of CCQM-K148.a. Ten participants reported no evidence for the presence of residual solvent above their method detection limits. The results reported by participants with their associated standard uncertainties (k = 1) are listed in Table 11 and are plotted in Figure 8.

Only one participant reported a significant level (> 0.1 mg/g) of this class. An overview of methods used by each participant to assign and verify total VOC content is provided in Appendix G.

NMI	x (mg/g)	$u(x^-)$ (mg/g)	$u(x^+)$ (mg/g)	k	$U_{95}(x^-)$ (mg/g)	$U_{95}(x^+)$ (mg/g)
BAM	0.00011	0.00002	0.00002	2	0.00004	0.00004
BIPM	0	0	0.15	2	0	0.3
CENAM	0					
EXHM	< 0.02	0.01	0	2	0.02	0
GLHK	0	0	1	2	0	2
HSA	0	0	0.66	3.18	0	2.11
INMETRO	0	0	0.0043	2	0	0.0086
KRISS	0.6	0.62	0.62	2.2	1.36	1.36
LGC	0	0	0.58	2	0	1.16
NIM	0.035	0.006	0.006	2	0.012	0.012
NIMT	0	0	0.415	2	0	0.83
NMIA	0					
NMIJ	0.05	0.03	0.03	1.65	0.05	0.05
NMISA	0.00065	0.00013	0.00013	3.2	0.0004	0.0004
UME	0					

Table 11: Volatile organics content in CCQM-K148.a (mg/g)

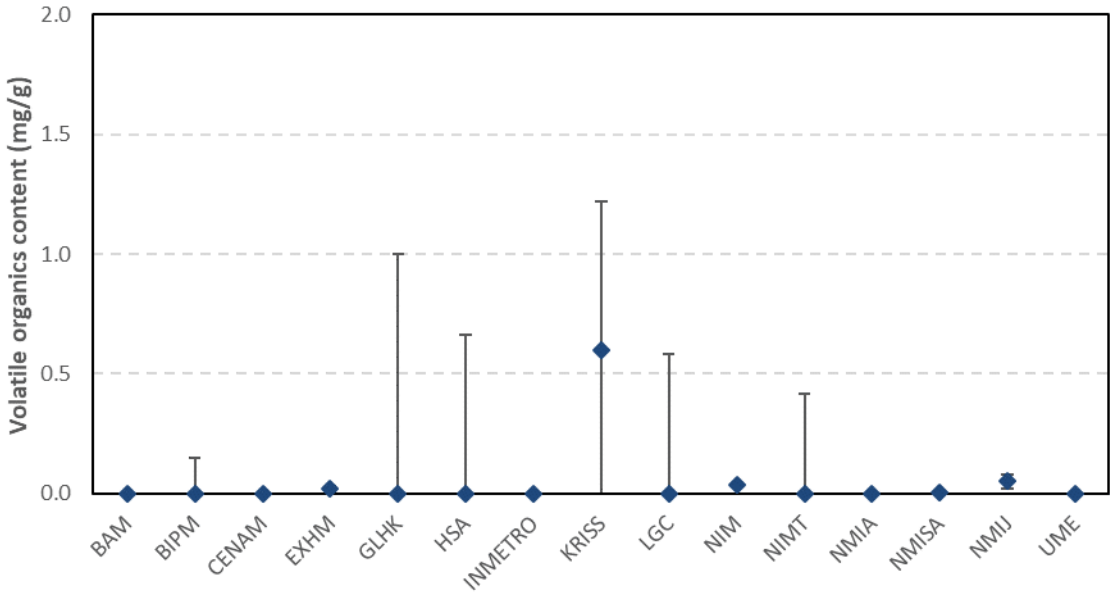


Figure 8: Volatile organics content in CCQM-K148.a
Reported results by participant for total residual organic solvent in CCQM-K148.a
Dots represent the reported value; bars the associated standard uncertainty, u, both in mg/g.

Non-volatiles/inorganics content

Fifteen participants investigated the content of non-volatile material in the sample. The reported values were small in all but one case and are listed in Table 12 and plotted in Figure 9. The methods used by participant are outlined in Appendix G. LGC were the sole participant to report a significant level of this impurity, based on results obtained by ICP-OES. Five other participants investigated the material by ICP techniques without reporting significant levels of impurity.

NMI	x (mg/g)	$u(x^-)$ (mg/g)	$u(x^+)$ (mg/g)	k	$U_{95}^-(x)$ (mg/g)	$U_{95}^+(x)$ (mg/g)
BIPM	0	0	0.21	2	0	0.42
CENAM	0.0258	0.0074	0.0074	2	0.015	0.015
EXHM	< 0.02	0.01	0.01	2	0.02	0
GLHK	0	0	1	2	0	2
HSA	0	0	1.44	2.26	0	3.27
INMETRO	0	0	0.014	2	0	0.028
KRISS	0.05	0.026	0.026	4.3	0.11	0.11
LGC	1.02	0.26	0.26	2	0.51	0.51
NIM	0.0046	0.0014	0.0014	2	0.0028	0.0028
NIMT	0	0	0.415	2	0	0.83
NMIA	0	0	0.3	2.3	0	0.7
NMIJ	0.056	0.033	0.033	1.65	0.054	0.054
NMISA	< 1	0.32	0	2.4	0.79	0
UME	0					
VNIIM	< 0.001	0.00025	0	2	0.0005	0

Table 12: Non-volatile content in CCQM-K148.a (mg/g)

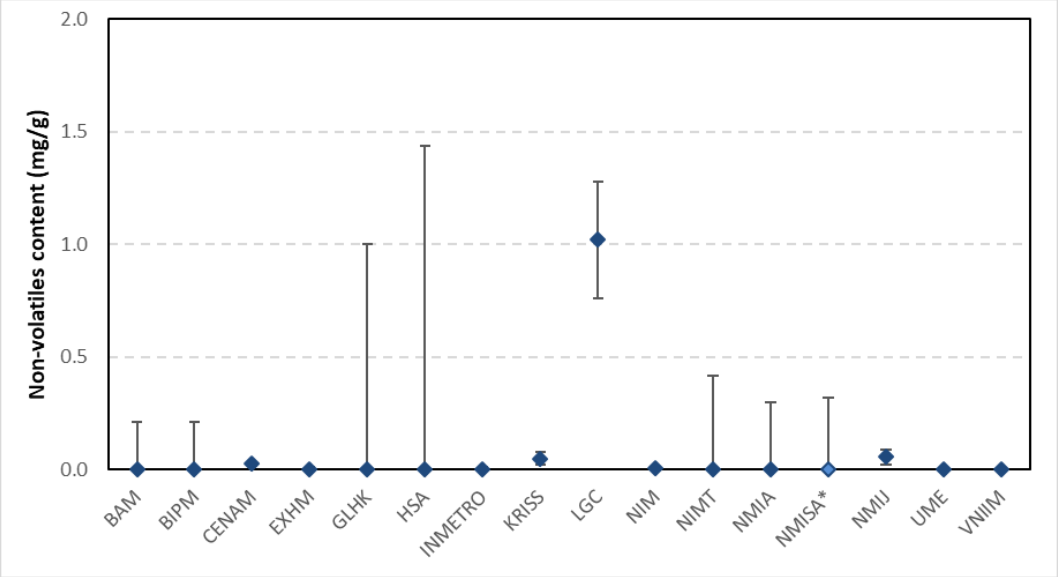


Figure 9: Non-volatile content in CCQM-K148.a

Reported results by participant for total non-volatile content in CCQM-K148.a
Dots represent the reported value; bars the associated standard uncertainty, *u*, in mg/g.
*NMISA value reported as "< 1 mg/g" For clarity this is shown as 0 mg/g with an asymmetric uncertainty, where the confidence range for the true value does not exceed 1 mg/g.

BPA content by qNMR

As noted in the introductory discussion fourteen of the seventeen participants reporting results in the CCQM-K148.a comparison incorporated a qNMR study to some degree in their assignment of the material. qNMR assignments were:

- the sole method (BAM, NRC)
- combined with a mass balance result
  (BIPM, EXHM, GLHK, HSA, INMETRO, KRISS, LGC, NMIJ,[a] NMISA, UME)
- not used for the key comparison value assignment but obtained as additional information when a mass balance assignment was reported as the comparison result (NIM, NMIA).

NIM and UME reported stand-alone qNMR results for BPA content in the CCQM-P187.a parallel pilot study. The reported qNMR data used for the assignment or confirmation of the key comparison result by participants is listed in Table 13 and plotted in Figure 10.

NMI	x (mg/g)	$u(x)$ (mg/g)	k	$U_{95}(x)$ (mg/g)
BAM	995.4	0.46	2	0.91
BIPM	994.4	2.2	2	4.4
EXHM	994.14	0.714	2	1.43
GLHK	995.8	1.89	2	3.78
HSA	994.2	2.24	2	4.48
INMETRO	995.4	1.03	2	2.06
KRISS	995.4	0.9	2.45	2.2
LGC	996	1.5	2.03	3
NMIJ	996.3	0.6	2	1.2
NMISA*	986.2	3.97	2	7.9
NRC	993.7	2.4	2	4.8
UME	996.49	3.03	2	6.06

Table 13: Results for BPA content in CCQM-K148.a by qNMR.

* Result not included in calculation of estimator for BPA content by qNMR

A set of statistical estimators for the BPA content estimate derived from the eleven retained qNMR values reported by participants in CCQM-K148.a are listed in Table 14.

Estimator	u? [i]	X (mg/g)	$u(X)$ (mg/g)	$U_{95}(X)$ [ii] (mg/g)
Mean	No	995.31	0.27	0.61
Median	No	995.40	0.34	0.75
DSL-Mean	Yes	995.40	0.30	0.67

Table 14: Statistical Estimators for BPA content in CCQM-K148.a by qNMR (mg/g)

i. Utilizes information in the reported uncertainties?

ii. $U_{95}(X) = t_s \cdot u(X)$, where t_s is the two-tailed Student's t critical value (t = 2.23 for n = 11 for 95 % coverage)

[a] The NMIJ value also includes data obtained by FPD as well as by mass balance and qNMR methods

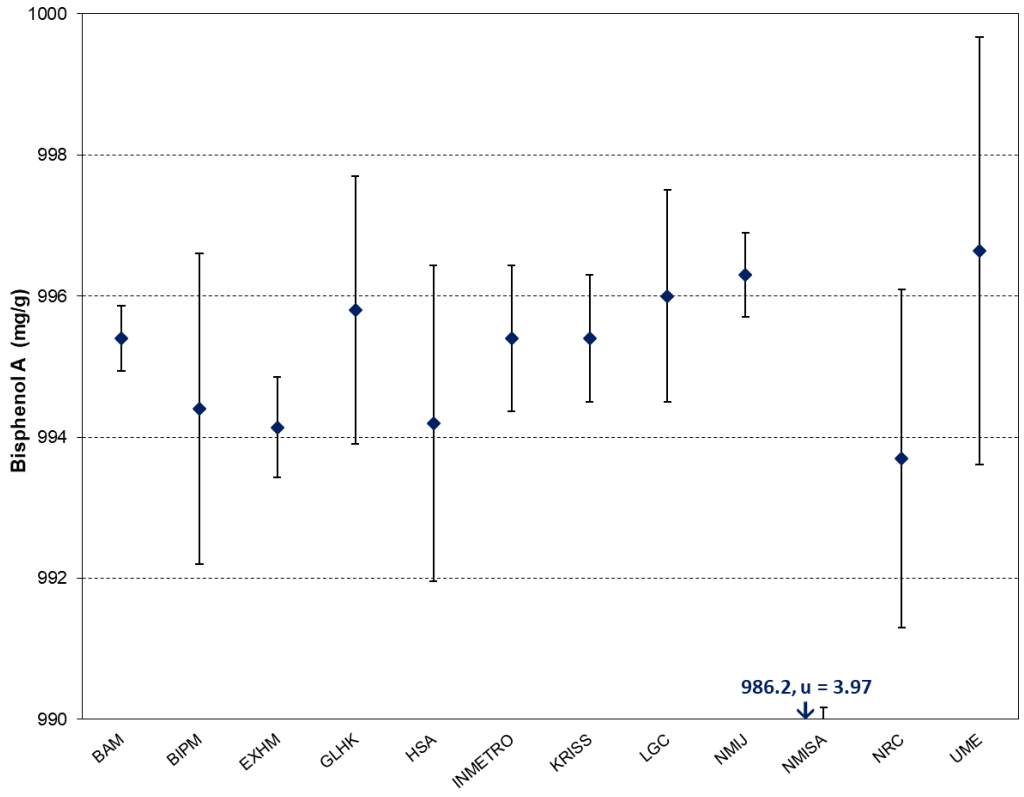


Figure 10: qNMR Results for BPA in CCQM-K148.a

Reported qNMR results for BPA content by participant in CCQM-K148.a.
Data points represent the reported value, x_i; bars the standard uncertainty, $u(x_i)$ in units of mg/g.

A summary of the qNMR method parameters used by each participant is given in Appendix L.

Footnotes in the summary of each participant's comparison assignment method in Appendix G indicate that EXHM, HSA, LGC and NRC corrected their direct qNMR value for contributions due to related structure impurities. The applied correction was either obtained by high resolution liquid chromatographic methods or directly from the qNMR data.

BPA content by DSC

Investigations of the main component content of the material by freezing point depression using a DSC instrument were undertaken by three participants. NMIJ analyzed four samples each of approximately 2 mg sample size using a Mettler DSC 822.e instrument operating in continuous scan mode. The temperature programme was 100 °C- (5 °C/min) - 165 °C (1st run) and 100 °C- (5 °C/min) - 140 °C (1 min)- (0.1 °C/min) - 158 °C for the 2nd run. They assigned a value for BPA content of 996.0 ± 2.1 mg/g after conversion of the original mole fraction value into a mass fraction equivalent with correction for contributions of impurities quantified by supporting techniques. An example of a DSC run used for the BPA analysis is shown in Figure 11.

INMETRO undertook the analysis of three hermetically sealed samples each of 3 mg sample size using a TA Instruments DSC Q2000 instrument. Their temperature programme was 130 °C- (2 min) - 161 °C at 0.5 °C/min. The value for BPA content reported as a mole fraction was 995.6 ± 4.0 mmol/mol. The DSC value was used in this case for comparison and confirmation of their reported value, derived separately from a combination of mass balance and qNMR data.

NMISA also undertook DSC analysis on three samples using a Mettler DSC 1 instrument. The temperature programme was 25 °C- 200 °C at 5 °C/min under nitrogen.

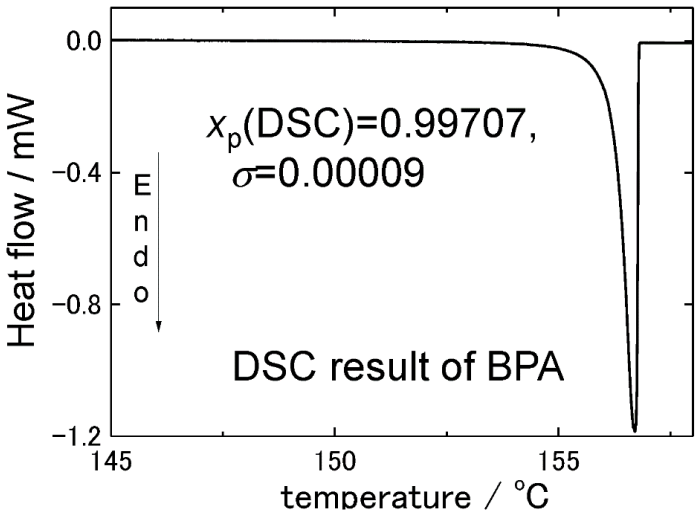


Figure 11: DSC data for CCQM-K148.a reported by NMIJ

KEY COMPARISON REFERENCE VALUE

The documents CCQM/11-18[12] and CCQM/13-22 *Guidance note: Estimation of a consensus KCRV and associated Degrees of Equivalence13*[11] describe recommended practice for the choice of estimators for a KCRV, depending on the range of participant results and their degree of consistency and taking into account their associated measurement uncertainty. The recommendations of the guidance document OAWG/19-064 *Decision guide for selecting CCQM Model 1 key comparison reference value estimation procedures* (version 1: 2019-09-23)[4] were followed to assign the KCRV for the BPA content of the CCQM-K148.a material.

Previous practice in comparisons of the CCQM-K55 series had been to assign the KCRV using a "consensus" mass balance value derived from the combined participant results. This approach was not followed for the CCQM-K55.d comparison on folic acid due to a lack of agreement between consensus results obtained by mass balance and qNMR approaches. However for this comparison that was not the case and the values obtained by qNMR and mass balance methods were shown to be in generally compatible and in close agreement.

After the initial result discussion and review of their data BIPM, NMISA and VNIMM requested to have their mass balance results removed from consideration for KCRV calculations. The outlier results from CENAM and NIMT were also not included for the KCRV calculation, with a plausible explanation for the discrepancy in the results reported for these participants being linked to artefact formation under the LC conditions used for the assignment of related structure impurity content.

A comparison of the DerSimonian Laird (DSL)-mean estimators for BPA content using qNMR alone (n = 11) and mass balance alone (n = 10) results is plotted in Figure 12, together with one result reported by NMIJ by FPD using DSC. These estimators for content of BPA do not incorporate the data withdrawn at the participant's request from consideration for inclusion in the KCRV assignment.

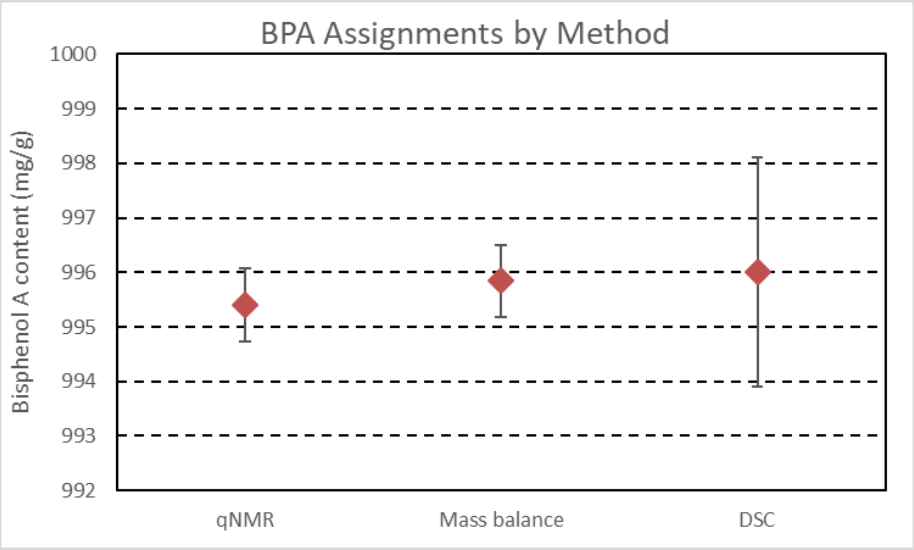


Figure 12: Consensus estimates for BPA content in CCQM-K148.a by method

As there was very good agreement between the consensus assignments obtained using either qNMR or mass balance methods, it was decided that for the KCRV calculation equal weight would

be given to each utilized approach (mass balance alone, qNMR alone or combination of values). Three candidate values for the BPA content in CCQM-K148.a, the simple mean, the DSL mean and the HB REM estimator were derived from the combination, following recommendations of the OAWG/19-064 guidance document,[4] of the twelve participant results listed in Table 4 retained for this purpose. The values derived from this revised data set are shown in Table 15.[14]

Estimator	*u*?[a]	*KCRV* (mg/g)	*KCRU* (mg/g)	U_{95}(*KCRV*) (mg/g)
Mean	No	995.7	0.28	0.6[b]
DSL-Mean	Yes	995.6	0.23	0.5
HB REM	Yes	995.6	0.3	0.6[c]

Table 15: Candidate estimators for BPA content in CCQM-K148.a

a) Utilizes information in the reported uncertainties?
b) $U_{95}(X) = t_s \cdot u(X)$, t_s is two-tailed Student's *t* critical value for 95 % coverage (2.20 where $n = 12$)
c) The dark uncertainty (tau) of the HB REM estimator for the KCRV is 0.41 mg/g

Both the DSL-mean and the HB REM value comply with recommendations for suitability for use as the KCRV estimate and it is evident that the values obtained for each estimator agree closely. The OAWG KCRV guidance document does not provide recommendations for selecting between the DSL and HB REM estimator where both are applicable and in this case the slightly more conservative HB REM estimator was proposed as the KCRV and KCRU. This proposal was agreed and confirmed during an OAWG video conference held on May 25th, 2020.[15]

A plot of participant results against the KCRV is provided in Figure 13 and the DoE values (d_i) with the expanded uncertainty of d_i (U_d) of each participant's reported value with respect to the KCRV are plotted in Figure 14.

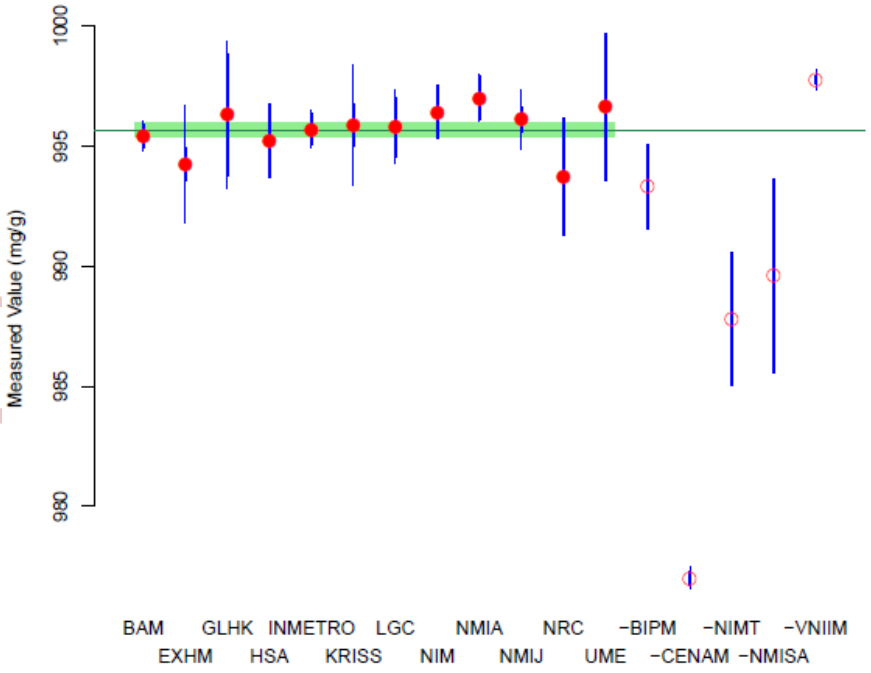


Figure 13: Participant results against the KCRV

Results for BPA content in CCQM-K148.a plotted against the KCRV of 995.6 mg/g which corresponds to the solid horizontal line. Dots represent the participant values, x; bars the standard uncertainty, u(x), in units of mg/g. The green band corresponds to the KCRV ± KCRU ($k = 1$). Only data points in red were used for the KCRV assignment.

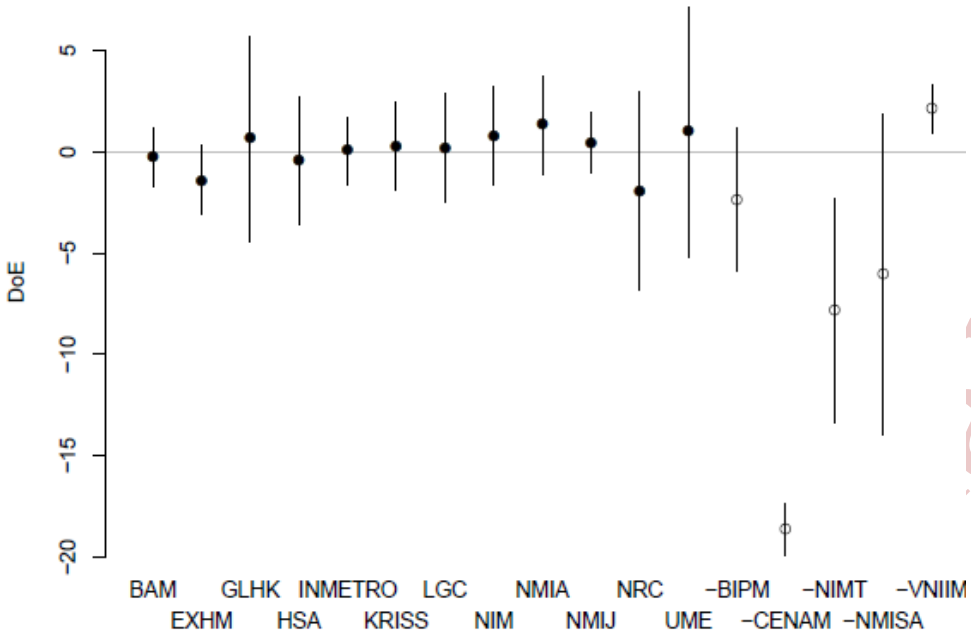


Figure 14: Unilateral DoE plot of participant results relative to the KCRV

The y-axis displays the absolute DoE, *d*, in units of mg/g. The dots represent the individual *d* values and the bars their associated 95 % expanded uncertainties, $U_{95}(d)$. The horizontal line denotes perfect agreement with the KCRV. The results from participant with DoE plotted in white were not included in the KCRV assignment.

The process, parameters used and results obtained for the calculation of HB REM as the KCRV are provided in Appendix M.The DoE of individual participant results against the KCRV is shown in Table 16.[14] A participant result is compatible with the KCRV when the DoE U_{95} of the result exceeds the absolute value of the DoE.

Participant	DoE (mg/g)	DoE (%)	DoE U_{95} (mg/g)	DoE U_{95} (%)
BAM	-0.214	-0.02	1.47	0.15
BIPM	-2.314	-0.23	3.50	0.35
CENAM	-18.59	-1.87	1.28	0.13
EXHM	-1.384	-0.14	1.73	0.17
GLHK	0.686	0.07	5.02	0.50
HSA	-0.414	-0.04	3.13	0.31
INMETRO	0.086	0.01	1.64	0.17
KRISS	0.256	0.03	2.15	0.22
LGC	0.186	0.02	2.68	0.27
NIM	0.796	0.08	2.42	0.24
NIMT	-7.814	-0.78	5.51	0.55
NMIA	1.386	0.14	2.39	0.24
NMIJ	0.486	-0.05	1.51	0.15
NMISA	-6.014	0.60	7.92	0.80
NRC	-1.914	-0.19	4.88	0.49
UME	1.026	0.10	6.12	0.62
VNIIM	2.136	0.21	1.31	0.13

Table 16: Unilateral DoE table for BPA content in CCQM-K148.a with HB REM KCRV

USE OF CCQM-K148.a IN SUPPORT OF CMC CLAIMS

How Far the Light Shines

Successful participation in CCQM-K148.a demonstrated measurement capabilities for assigning the mass fraction content of the primary component in a solid organic material where the primary component has a molar mass in the range 75 g/mol to 500 g/mol and is classified as non-polar, as defined by having an octanol-water partition coefficient (K_{ow}) such that $pK_{ow} < -2$.

Depending on the characterization procedure applied the participants demonstrated capabilities for organic purity assignment by a mass balance or qNMR approach or by the combination of results obtained using both methods. In addition three participants in the comparison investigated the use of freezing point depression measurement (FPD) by DSC for the assignment of BPA content although only one combined the value obtained by FPD into their final overall result.

In addition to the capability for purity assignment of the primary component, participants also demonstrated capabilities for the assignment of water content in a non-polar organic material having a water content of less than 2 mg/g.

CONCLUSIONS

Participants in CCQM-K148.a demonstrated and benchmarked their ability to assign the mass fraction content of a non-polar solid organic compound having moderate molecular complexity present as the primary component in an organic material. Five participant results were excluded from use in assigning the KCRV due to identified issues with their methodologies. All results used for the calculation of the KCRV as well as two of the excluded results were consistent with the KCRV within the combined 95 % expanded uncertainty range of the unilateral degree of equivalence of the result with the KCRV, taking into account the KCRU and the reported uncertainty of the individual result.

ACKNOWLEDGEMENTS

The study coordinators thank the participating laboratories for the extensive and comprehensive investigations undertaken to characterize the comparison material and their co-operation in checking the data and providing the information reported in this study in a timely manner. This greatly facilitated the preparation of this Report. The assistance of Michael Nelson and Antonio Possollo from NIST in calculation of the HB REM estimator for the KCRV and the associated unilateral DoEs of the individual participant results is gratefully recognized.

APPENDIX A: Homogeneity test: Candidate material

The results for the homogeneity of content of BPA and the two major impurities detected by LC-UV response at 280 nm for a set of vials selected across the candidate material production batch are summarized in Figure 15. For each component, the normalized mean value of triplicate analysis per vial is plotted with the associated trendline. There was no evidence of significant variation in the material content for either the principal component or the two major impurities across the batch. For each data point the error bar corresponds to the relative standard deviation of the contributing data points.

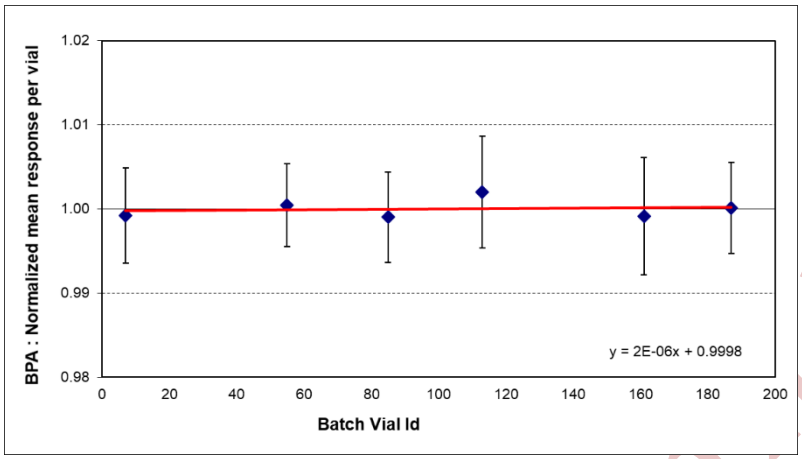


Fig. 15.a: Mean of normalized triplicate LC-UV response @ 280 nm for BPA per vial selected from the candidate batch of OGP.027

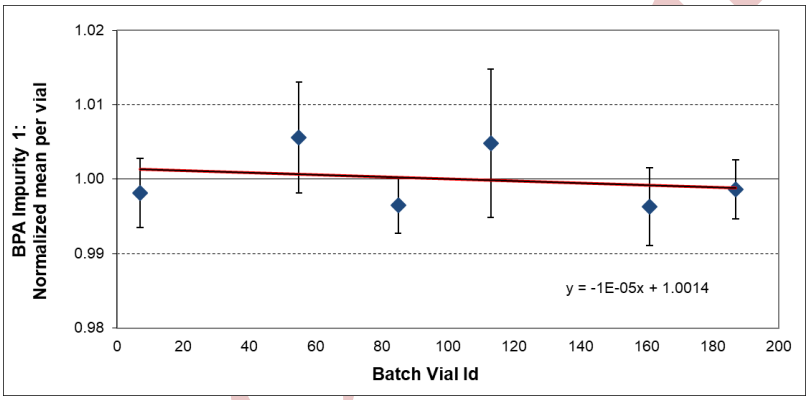


Fig. 15.b: Mean of normalized triplicate LC-UV response @ 280 nm for BPA Impurity 1 per vial of OGP.027

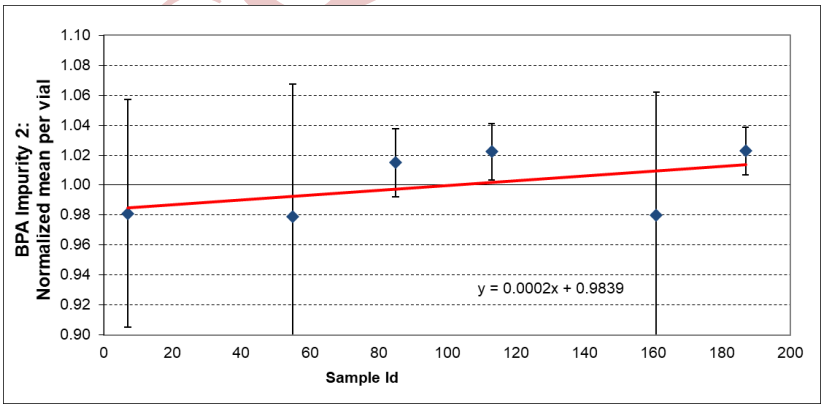


Fig. 15.c: Mean of normalized triplicate LC-UV response @ 280 nm for BPA Impurity 2 per vial of OGP.027

Note: for each data point shown above the bars corresponds to ± relative standard deviation of the triplicate data contributing to each reported value.

APPENDIX B: Stability test Candidate material

The trend results for storage stability at 40 °C are presented for BPA and the two main impurities as measured by LC-UV response at 280 nm relative to material stored at the reference temperature of -20 °C. For each time point the comparison of results of duplicate analysis of samples from each of two vials stored under the stated conditions are shown relative to the results of two samples from four vials stored continuously at the reference temperature. The trendlines for ongoing storage stability for each component at 40 °C are plotted. The corresponding plots for materials stored at 22 °C and 4 °C displayed smaller extent of deviation over time.

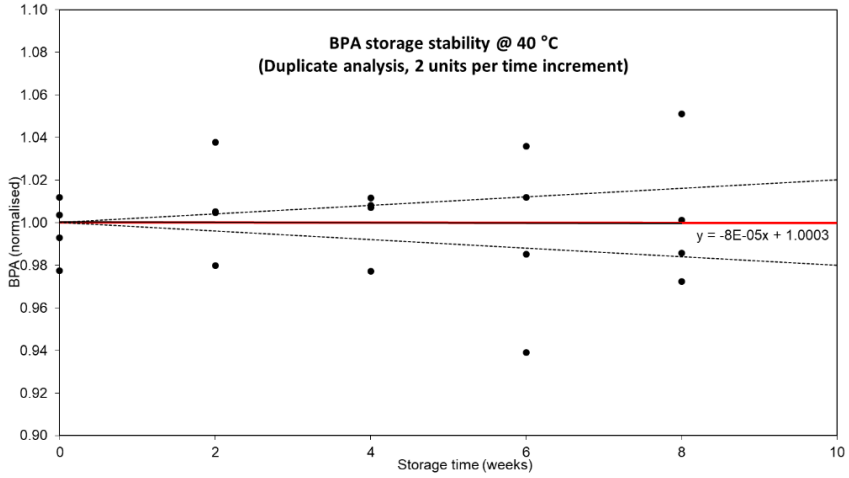


Fig. 16.a: LC-UV response (2 samples in duplicate) @ 280 nm, normalized against reference value, for BPA in OGP.027 after storage at 40 °C for indicated period.

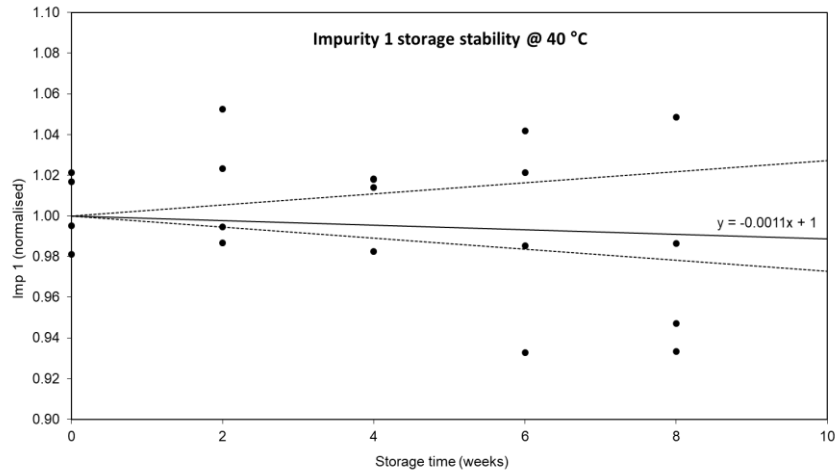


Fig. 16.b: LC-UV response (2 samples in duplicate) @ 280 nm, normalized against reference value, for Impurity 1 in OGP.027 after storage at 40 °C for indicated period.

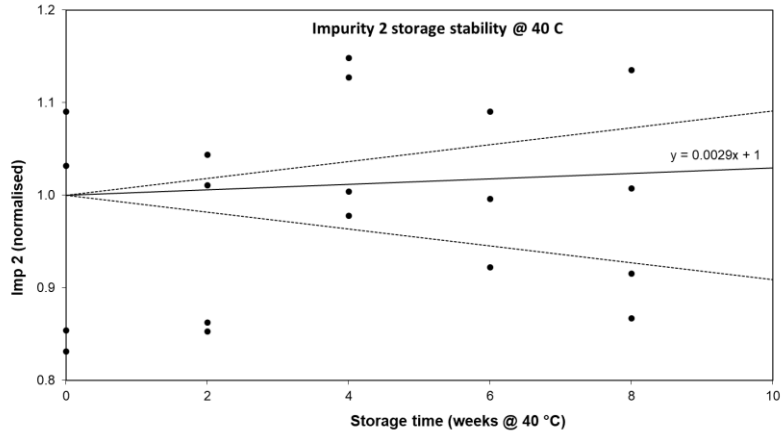


Fig. 16.c: LC-UV response (2 samples in duplicate) @ 280 nm, normalized against reference value, for Impurity 2 in OGP.027 after storage at 40 °C for indicated period.

APPENDIX C: Call for Participation and Comparison Protocol

INTRODUCTION

The ability to undertake a purity property value assessment on organic materials intended for use as a pure substance reference material by National Metrology Institutes (NMIs) and Designated Institutes (DIs) recognized under the CIPM Mutual Recognition Arrangement (MRA) is considered a core competency for the provision of SI-traceable measurement services in organic analysis. This comparison allows NMIs and DIs to provide objective evidence that the procedure(s) they use for purity assessment and the property value with its associated uncertainty that is assigned through their procedure are suitable for their intended purpose. Evidence of successful participation in relevant international comparisons is needed to document calibration and measurement capability claims (CMCs) made by NMIs and DIs under the MRA.[1]

CCQM-K148.a constitutes one of the "Track A" Key comparisons in the OAWG Strategic plan for the period 2017-2026 [2], intended to demonstrate and benchmark an NMI's core competencies for the delivery of measurement services in organic analysis.
The high-purity organics measurement space is defined by three sectors (X, Y and Z) which partition the organic purity space up to MW 1000 on the basis of molecular weight and polarity. The measurement space model is reproduced in Annex A:

CCQM-K148.a corresponds to the "X" sector of the model and intended to be representative for compounds with MW < 500 and pK_{OW} < -2. All NMIs with measurement capabilities in organic analysis requiring in-house assignment of primary calibrator materials classified within this sector are expected to participate in this key comparison. All institutes planning to submit broad claim CMCs for organic purity assignment are also recommended to participate.

TIMELINE

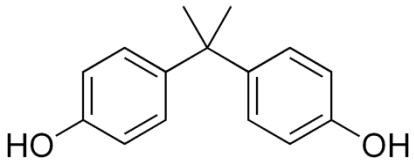
Table 1 lists the timeline for the proposed study.

Table 1

Date	Action
June 2016	Sample Preparation
June 2017	Homogeneity and Stability Testing
June 2018	Completion of Sample characterization
August 2018	Call for participation to OAWG members
October 2018	Sample Distribution
February 2019	Deadline for Submission of Results
April 2019	Preliminary Discussion of Results

MEASURAND

Participants are required to report the mass fraction of the major component, Bisphenol A (BPA. Figure 1), in one unit of the comparison study material. The units for reporting the mass fraction of BPA in the CCQM-K148.a comparison material are mg/g.



Bisphenol A (BPA)
Formula: $C_{15}H_{16}O_2$; Mol. Weight = 228.3 ; pK_{OW} = -3.3
Figure 1: Structure of BPA

For participants using a mass balance (summation of impurities) procedure to assign the BPA content are required to report the mass fraction assignment and associated combined standard uncertainty for each sub-class of impurity contributing to their result. The sub-classes of impurities to be quantified for a mass balance assignment of BPA will include some or all of the following:

1. total related structure organic substances;
2. water;
3. total residual organic solvent or volatile organic substances (VOCs);
4. total non-volatiles and inorganics.

For participants using a quantitative NMR (qNMR) procedure, information will be requested regarding the selection of standard (internal or external), solvent, sample preparation, NMR experimental conditions, quantification of signals and assignment of measurement uncertainty. The purpose of this comparison is to evaluate and benchmark the measurement procedure and uncertainty estimation for a qNMR assignment using a sample relevant to typical measurement made within an NMI.

All participants are required to describe their measurement equation and uncertainty budget used to assign the mass fraction content of BPA.

In addition to a KCRV for the BPA content of the comparison sample, KCRV values for each impurity class will also be assigned and degree of equivalence (DoE) plots will be prepared for each impurity class for each participant using the mass balance approach.

Participants are also encouraged to report their mass fraction determinations for all significant individual impurities identified in the comparison material. The ability to identify and quantify minor components is regarded as an important competency for the high-level characterization of organic materials.

INSTRUCTIONS AND SAMPLE DISTRIBUTION

Participants are requested to notify the comparison coordinator of specific requirements for shipment documentation required to facilitate customs clearance into their country and to liaise with the coordinating laboratory during the delivery process.

Participants will be notified by the coordinating laboratory in advance of the shipment of the materials and will be given details of the carrier used for the shipment.

Participants will be asked to return a form acknowledging receipt of the samples, to advise the comparison coordinator if any damage had occurred to the vials during shipping, and to indicate whether or not a monitoring strip inside the shipping container had registered a temperature in excess of 37 °C during the transport process.

RESULTS

Participants will be requested to report a single estimate of the mass fraction of BPA in mg/g.

An electronic data submission form will be supplied as an EXCEL spreadsheet. The draft result reporting spreadsheet is attached to this protocol (Annex B).

The following information **shall** be included in the result reporting form:

- Laboratory information;
- Names of staff for inclusion as contributing authors in the Final Report of the comparison;
- Temperature and relative humidity in area(s) where gravimetric operations are performed and water content measurements are undertaken;
- Main Component Result giving the mass fraction content of BPA (in mg/g) with the combined standard uncertainty and the expanded uncertainty at a 95% confidence range;
- Measurement equation and uncertainty budget for the BPA assignment.

For participants using a mass balance approach as either the sole or a contributing method to their overall value assignment **shall** in addition complete the Impurity Class Results providing the assigned values and the associated standard uncertainty for each sub-class of impurities contributing to the assignment of the mass fraction and standard uncertainty of BPA.

This table shall include assignments for some or all of:

- total related structure impurities
- water
- residual organic solvent
- total non-volatiles/inorganics
- representative chromatogram from analysis of a sample solution

Participants using a mass balance approach **may** provide further information:

- mass fraction content of each individual impurity component in the material (in mg/g).
- claim for a generic water content measurement competency

Participants using a qNMR approach as either their sole or as a contributing method to their final value assignment **shall** provide information on the:

- solvent(s) used;
- standard(s) (internal or external)
  - name and source
  - purity and associated uncertainty (in mg/g)

- basis for the traceability of the purity of the standard(s);
- balance for gravimetric sample preparation:
  - make, model and resolution
  - repeatability (standard deviation [SD_r] of at least ten repeat determinations of a reference mass [N] with tare)
  - minimum weight (mass for which $2*SD_r/N < 0.1\%$)
- sample preparation
  - smallest mass of analyte and standard used in sample preparation
  - lowest concentration of analyte and standard in sample solutions
- qNMR measurement parameters and data processing.
  - make, model and spectrometer frequency
  - qNMR experimental parameters
  - FT software, processing and parameters
- signal integration results
- representative spectrum of a qNMR sample solution and of the standard alone in solution

Participants using an approach other than mass balance or qNMR as either their sole or as a contributing method to their final value assignment shall also provide a brief outline of the procedure and all critical method parameters.

When a participant combines the results of two or more independent methods to obtain the final value reported for the comparison, the individual results for each method shall be reported. A compilation of all such contributing results, including their degree of equivalence with the KCRV, will be included in an Annex to the Final Report.

USE OF CCQM-K148.a IN SUPPORT OF CALIBRATION AND MEASUREMENT CAPABILITY (CMC) CLAIMS

How Far the Light Shines

Successful participation in CCQM-K148.a demonstrates generic measurement capabilities for assigning the mass fraction of the main component in solid organic compounds in the molecular weight range 75 to 500 and having a low polarity as indicated by a $pK_{ow} < -2$. If specifically requested, a CMC competency can also be demonstrated for the assignment of water content present at similar levels in comparable organic solids.

Core Competency Statements and CMC support

The template for the Core Competency claims arising from successful participation in CCQM-K148.a is provided.

REFERENCES

1. See CIPM MRA-D-05 Measurement comparison in the CIPM MRA: http://www.bipm.org/en/cipm-mra/cipm-mra-documents/
2. OAWG Practices and Guidelines Document: https://www.bipm.org/wg/CCQM/OAWG/Allowed/General_Documents/OAWG_18_004.pdf

APPENDIX D: Registration Form

Registration Form

CCQM-K148.a/CCQM-P187.a
Characterization of Organic Substances for Chemical Purity: Bisphenol A

REQUEST FOR REGISTRATION TO PARTICIPATE IN:

☐ **CCQM-K148.a**

☐ **CCQM-P187.a**

(Click to check your selection. Participation in the CCQM-K148.a comparison is only allowed for NMIs or Designated Institutes recognized under the CIPM MRA)

ORGANIZATION / DEPARTMENT / LABORATORY

FULL ADDRESS FOR SHIPMENT OF SAMPLES

CONTACT PERSON

E-MAIL, TELEPHONE and FAX

Date _____

Complete and return to steven.westwood@bipm.org **before September 28, 2018**

APPENDIX E: Reporting Form

CCQM-K148.a / CCQM-P187.a

Bisphenol A mass fraction in a high purity material

Data Submission Form

Please complete all pages of the reporting form and submit it by email before March 1 2019 to:
steven.westwood@bipm.org

Registered comparison participation:	**CCQM-K148.a**	**CCQM-P187.a**	(delete as appropriate)
Reporting Date			
Institute			
Submitted by (name)			
E-mail address			
Contributing authors for acknowledgement in Final Report			

CCQM-K148.a/CCQM-P187.a RESULTS

a. Mass Fraction assignment - main component

Measurand	Mass Fraction (mg/g)	Combined Standard Uncertainty (mg/g)	Coverage Factor (k)	Expanded Uncertainty (mg/g)
Bisphenol A				

b. Mass Fraction assignments - impurity components [required for participants using a mass balance procedure, optional otherwise]

Measurand	Mass Fraction (mg/g)	Combined Standard Uncertainty (mg/g)	Coverage Factor (k)	Expanded Uncertainty (mg/g)
Total related structure impurities				
Water				
Residual organic solvent				
Non-volatiles				

c. Mass Fraction assignments - individual impurity components [optional]

Measurand	Mass Fraction (mg/g)	Combined Standard Uncertainty (mg/g)	Coverage Factor (k)	Expanded Uncertainty (mg/g)
Impurity 1				
Impurity 2				
Impurity 3				
Impurity 4				
[additional entries as required]				

d. Environmental conditions

Measurement	Temperature (°C)	Relative Humidity (%)
Gravimetric operations		
Water content measurements		

Assignment method (e.g., relative response, external calibration, internal standard, IDMS)	
Reference standards used (if applicable) (Please specify the compounds, source and role)	
UV wavelength(s) monitored in LC-UV (if applicable)	
SIM/MRM(s) monitored in MS (if applicable)	
Assessment of response factors (as applicable) (Please describe assumptions or investigations into the relative response factors of impurities to the main component. If no information is provided, a 1:1 response factor will be assumed)	
Any other information	
[NB - To complete your entry, please use additional space as necessary]	

2.Water content

Sample amount per analysis (approximate)	mg
Number of samples analyzed	
Instrumentation (e.g., coulometric Karl Fischer titration, TGA)	
Analytical conditions	

3. Residual solvent content

Sample amount per analysis (approximate)	mg
Number of samples analyzed	
Instrumentation (e.g., headspace GC, NMR, etc)	
Analytical conditions	

4. Combined non-volatile content

Sample amount per analysis	mg
Number of samples analyzed	
Instrumentation (e.g., TGA, EA, ICP-MS)	
Analytical conditions	

Information about the qNMR procedure(s) used

Solvent(s) used			
qNMR procedure	Internal Standard	External Standard	Both
Name and source of standard(s)			
Purity and uncertainty of standard(s)			
Traceability source			

Gravimetry

Type of balance (make, model and resolution)		
Balance repeatability		(µg)
Minimum weight		(mg)

Sample preparation

Smallest mass of analyte		(mg)
Smallest mass of standard		(mg)
Number of samples prepared		
Number of replicate analyzes per sample		

qNMR parameters

Spectrometer	
Experimental parameters	
Processing software	
Integration parameters	
Lineshape (FWHM of solvent peak)	
Signal/Noise	
Standard peak	
Analtye peak	

[NB - To complete your entry, please use additional space as necessary]

Contributing results for Bisphenol A in CCQM-K148.a		
Mass balance result (if used)		mg/g
qNMR result (if used)		mg/g
Other results (if used)		mg/g
Final reported result (as entered in "Results" Worksheet)		mg/g
Measurement equation		
Describe both:		
1. Measurement equation for individual methods		
2. Measurement equation for combination of values if results of two or more methods were combined for the assignment		
Uncertainty budget		
(please include breakdown of the budget, describing major individual uncertainty contributions and how they were combined)		
[NB - To complete your entry, please use additional space as necessary]		

APPENDIX F: Core Competency Table Template

CCQM-K148.a (Bisphenol A)	***NMI/DI***	**Assignment of Mass fraction of Main Component in an Organic Solid**
Scope of comparison: The measurement results are representative of the laboratory's capability for the purity assignment of organic compounds in the molecular weight range 100 - 500 with pK_{OW} < -2.		
• Value assignment of Primary Reference: Main component mass fraction and uncertainty		
Competency	**✓,× or N/A**	**Specific Information**
Identity verification		*Summary of methods used to establish the qualitative identity (e.g., comparison with independent sample, mass spec., NMR, other)*
Assignment of main component mass fraction content of CCQM-K148.a		*Indicate method(s) used to quantify mass fraction of BPA in the material*
Bisphenol A content (mg/g)		*Reported comparison result (± $U_{95\%}$)*
• Value assignment of Primary Reference: Impurity class mass fraction and uncertainty (required if using a mass balance method, otherwise optional)		
Assignment of related structure impurity		*Indicate method(s) used to quantify mass fraction of related structure impurities in the material*
Related structure impurity (mg/g)		*Reported comparison result (± $U_{95\%}$)*
Assignment of water content		*Indicate method(s) used to quantify mass fraction water content in the material*
Category of water content assignment*		*Select from list below* the applicable category of general water content assignment competency*
Water content (mg/g)		*Reported comparison result (± $U_{95\%}$)*
Assignment of residual solvent content		*Indicate method(s) used to quantify mass fraction residual solvent content in the material*
Total residual solvent (mg/g)		*Reported comparison result (± $U_{95\%}$)*
Assignment of total non-volatiles content		*Indicate method(s) used to quantify mass fraction total non-volatile content in the material*
Total non-volatiles (mg/g)		*Reported comparison result (± $U_{95\%}$)*

General Instructions:

- Replace "*NMI/DI*" with the acronym for your institution in the first cell of the middle column
- Place a tick, cross or N/A (not applicable) in the middle column cell as appropriate for each competency
- In each right hand column cell replace the blue text with the relevant information for your comparison result

* To be completed by NMIs intending or anticipating to make CMC claims for the assignment of water content in solid organic materials. Choose one of the following general categories:

- non-polar organic solid, water content < 2 mg/g
- non-polar organic solid, water content > 2 mg/g, < 20 mg/g

The entry of information for this competency is optional but is encouraged for NMIs having or intending to submit CMCs for the assignment of the water content of organic solid material

APPENDIX G: Summary of Participants' Analytical Approach

a. Method(s) used for value assignment

NMI	Mass balance – related structure	Mass balance - water	Mass balance – VOC	Mass balance – Non-volatiles	qNMR (IS used)	Other
BAM					IS (BA)	
BIPM	LC-UV, LC-CAD	KFT	NMR	EA, TGA	IS (DMTP)	
CENAM	LC-UV	KFT	GC-FID	Ashing		
EXHM	LC-UV	KFT	HS GC-MS	ICP-MS	IS (BTFMBA)[a]	
GLHK	LC-UV	KFT	HS GC-MS	ICP-MS, ICP-OES, IC	IS (BA)	
HSA	LC-UV	KFT	HS GC-MS, TGA	TGA, ICP-MS ICP-HRMS	IS ($DMSO_2$)[a]	
INMETRO	LC-UV, GC-FID	KFT	HS GC-MS, TGA	ICP-MS, ICP-OES	IS (DMTP)	
KRISS	GC-FID	KFT	HS GC	TGA	IS (BA)	
LGC	LC-UV	KFT	qNMR, TGA	ICP-MS, TGA	IS (BA)[a]	
NIM	LC-UV	KFT	GC-FID	ICP-MS		
NIMT	LC-UV	KFT	TGA	TGA		
NMIA	GC-FID	KFT	HS GC-MS	qNMR		
NMIJ	LC-CAD, LC-UV	KFT	GC-FID	TGA	IS (BTFMBA)[a]	FPD
NMISA	LC-UV, GC-MS	KFT	HS GC-MS	TGA	IS (DMTP)	
NRC	LC-UV				IS (BA)[a]	
UME	LC-UV	KFT	HS GC-FID	TGA	IS (BA)	
VNIIM	LC-UV	KFT	HS GC-MS	ICP-MS		

[a] qNMR assignment after correction for BPA-related impurities estimated either by qNMR or by LC-based methods.

b. Method(s) used for value verification / control

NMI	Mass balance – related structure	Mass balance – water	Mass balance – VOC	Mass balance – Non-volatiles	qNMR	Other
BAM	LC-UV	KFT	HS GC-MS			
BIPM	LC-MS/MS	TGA, EA	GC-MS	EA		
EXHM	LC-MS/MS, LC-FLD, GC-FID, GC-MS					
GLHK	LC-MS/MS					
HSA	LC-CAD, LC-MS/MS, NMR					
INMETRO	LC-MS, GC-MS					FPD
KRISS	LC-UV					
LGC	LC-MS					
NIM	LC-MS/MS, GC-MS				IS (BA)	
NIMT						
NMIA	LC-MS			EA	IS (BA)	
NMIJ	LC-MS, GC-FID					
NMISA	LC-MS, GC-FID					FPD
NRC	LC-MS					
UME		TGA				
VNIIM	HS GC-MS					

APPENDIX H: Summary of Measurement Equations and Uncertainty Budget

Short summaries of the approach used for estimation of the comparison value and the associated uncertainty were provided by each participant. Although the specifics of the measurement equation(s), symbols, units and measurement uncertainty budget(s) varied between participants, one or more of three basic approaches were used to assign the BPA content of the comparison material. To provide a reference for discussion of individual assignments within the summary these three approaches are referred to as:

Method 2. Mass balance by direct summation of impurities

$$w_{\mathrm{BPA(MB1)}} = 1000 - (w_{\mathrm{RS}} + w_{\mathrm{W}} + w_{\mathrm{OS}} + w_{\mathrm{NV}})\ \mathrm{mg.g^{-1}} \qquad \text{(Eqn. 1)}$$

all units are in $\mathrm{mg.g^{-1}}$ and the symbols correspond as follows:

$w_{\mathrm{BPA(MB1)}}$ = mass fraction of BPA by method 1 approach;
w_{RS} = mass fraction of impurities related in structure to BPA ;
w_{W} = mass fraction of water content;
w_{OS} = mass fraction of residual organic solvent content;
w_{NV} = mass fraction of combined inorganic and non-volatile organic content.

The standard uncertainty of the result, $u(w_{\mathrm{BPA(MB1)}})$, is given by:

$$u(w_{\mathrm{BPA(MB1)}}) = \sqrt{u(w_{\mathrm{RS}})^2 + u(w_{\mathrm{W}})^2 + u(w_{\mathrm{OS}})^2 + u(w_{\mathrm{NV}})^2} \qquad \text{(Eqn. 2)}$$

Method 2. Mass balance via relative chromatographic response

$$w_{\mathrm{BPA(MB2)}} = \left(1000 - w_{\mathrm{RS,rel}}\right) \times \left(\frac{1000-(w_{\mathrm{W}}+w_{\mathrm{OS}}+w_{\mathrm{NV}})}{1000}\right) \mathrm{mg.g^{-1}} \qquad \text{(Eqn. 3)}$$

where the symbols correspond to Eqn. 1 except:

$w_{\mathrm{BPA(MB2)}}$ = mass fraction of BPA by method 2 approach
$w_{\mathrm{RS,rel}}$ = ratio of total peak area response from related structure impurities to combined peak area response of BPA and related structure impurities in per mille.

Note: using the relative area response, without further investigation, assumes equivalent relative response factors on mass fraction basis for the total related structure impurities content and BPA.

Method 3. BPA content by internal standard qNMR

$$w_{\mathrm{BPA(qNMR)}} = \frac{I_{\mathrm{BPA}}}{I_{\mathrm{S}}} \times \frac{N_{\mathrm{S}}}{N_{\mathrm{BPA}}} \times \frac{M_{\mathrm{BPA}}}{M_{\mathrm{S}}} \times \frac{m_{\mathrm{S}}}{m_{\mathrm{BPA}}} \times w_{\mathrm{S}} \quad \mathrm{mg.g^{-1}} \qquad \text{(Eqn. 4)}$$

where:

$w_{\mathrm{BPA(qNMR)}}$ = mass fraction ($\mathrm{mg.g^{-1}}$) of BPA by internal standard qNMR
w_{S} = mass-fraction ($\mathrm{mg.g^{-1}}$) content of internal standard S
I_{BPA} = integral of the quantified signal for BPA,
I_{S} = integral of the quantified signal for internal standard S,
N_{BPA} = number of ^{1}H nuclei, BPA quantification signal,
N_{S} = number of ^{1}H nuclei, internal standard quantification signal,
M_{BPA} = molar mass of BPA,
M_{S} = molar mass of internal standard S,
m_{BPA} = mass of CCQM-K148.a material
m_{S} = mass of internal standard.

The relative standard uncertainty of the qNMR result given by:

$$\frac{u(w_{\mathrm{BPA(qNMR)}})}{w_{\mathrm{BPA(qNMR)}}} = \sqrt{\left(\frac{u(I_{\mathrm{BPA}})}{I_{\mathrm{BPA}}}\right)^2 + \left(\frac{u(I_{\mathrm{S}})}{I_{\mathrm{S}}}\right)^2 + \left(\frac{u(M_{\mathrm{BPA}})}{M_{\mathrm{BPA}}}\right)^2 + \left(\frac{u(M_{\mathrm{S}})}{M_{\mathrm{S}}}\right)^2 + \left(\frac{u(m_{\mathrm{BPA}})}{m_{\mathrm{BPA}}}\right)^2 + \left(\frac{u(m_{\mathrm{S}})}{m_{\mathrm{S}}}\right)^2 + \left(\frac{u(w_{\mathrm{S}})}{w_{\mathrm{S}}}\right)^2} \qquad \text{(Eqn. 5)}$$

Participant final results for the BPA content in the comparison material (w_{BPA}) were generally reported as either the result using one of these three basic methods or as the combination of results obtained using mass balance (method 1 or 2) and internal standard qNMR (method 3).

Measurement equation(s) and uncertainty budgets for each participant are summarized below.

BAM

BPA content assignment:
Internal standard qNMR (Method 3) approach with the reported measurement equation:

$$P\,[\%] = \frac{n_{IC} \cdot Int_t \cdot MW_t \cdot m_{IC}}{n_t \cdot Int_{IC} \cdot MW_{IC} \cdot m_s} \cdot P_{IC}$$

Measurement uncertainty:
Components:

Weighing operations:	relative uncertainty (int. Standard): 2.389E-04 relative uncertainty (Analyte): 3.689E-04
Molar Mass Uncertainty:	relative uncertainty (int. Standard): 1.773E-05 relative uncertainty (Analyte): 1.375E-05
Internal Standard Purity:	relative uncertainty: 2.200E-05

Precision of replicate measurements: relative uncertainty: 1.282E-04

The relative uncertainty of the reported BPA value (4.62E-04) was the quadratic combination of the component relative uncertainties.

BIPM

BPA content assignment:
Combination of separate results by a mass balance (two method 1 applications with the total related structure impurities quantified by LC-UV and LC-CAD respectively) and qNMR (method 3).

As values were consistent within the uncertainty of one another the final value for BPA content in CCQM-K148.a was the uncertainty-weighted mean of each contributing result.

Measurement uncertainty:
The standard uncertainty of the final value was the root mean square of the contributing uncertainties

CENAM

BPA content assignment:

Result by mass balance (method 1) approach calculated using Eqn. 1.

The mass fraction of individual related structure impurities was assigned from the peak area relative response by LC-UV according to :

$$w_{impurity\ ,i} = \frac{A_{impurity\ ,i}}{A_{B-A} + \sum_i A_{impurity\ ,i}}$$

where $A_{impurity\ i}$ is the peak area for impurity *i* and $A_{B\text{-}A}$ is the peak area of the BPA component

Measurement uncertainty:

	Uncertainty value	Value,mg/g	Standard uncertainty	Expanded standard uncertity
Water	w_w	1.36000	0.03138680	0.063
inorganic impurities	w_{NV}	0.025821	0.007401674	0.015
related structure impurities	w_1	1.75416667	0.044811849	
	w_2	13.475	0.222932891	
	w_3	5.1875	0.113320056	
	w_4	1.208333	0.039381797	
∑related structure impurities	w_{RS}	21.625000	0.257098302	0.51
Bisphenol A		977.019148	0.259112819	0.52

EXHM

BPA content assignment:

Combination of a mass balance (method 2) and a qNMR (method 3) approach. For the mass balance method, the measurement equation corresponding to Eqn. 2 was:

$$w_{BPA(MB2)} = A_{BPA,n}\left(1 - \frac{w_w + w_{os} + w_{nv}}{1000}\right)$$

where $A_{(BPA,n)}$ was the normalized BPA peak area in the LC-UV chromatogram on a mass basis given by:

$$A_{BPA_n} = \frac{A_{BPA}\,\frac{mw_{BPA}}{Rf_{BPA}}}{A_{BPA}\,\frac{mw_{BPA}}{Rf_{BPA}} + \sum A_{SRI,i}\,\frac{mw_{SRI,i}}{Rf_{SRI,i}}}$$

A_{BPA}	:	BPA peak area in the HPLC- UV chromatogram
$A_{SRI,i}$	:	SRI_i peak area in the HPLC- UV chromatogram
SRI_i	:	i^{th} Structure Related Impurity
RF_{BPA}	:	BPA relative response factor (= 1)
$RF_{SRI,i}$	:	i^{th} SRI relative response factor to BPA
mw	:	molar mass

For the qNMR method the measurement equations corresponding to Eqn. 4 were:

$$P_A = \frac{I_s}{I_{Std}}\frac{n_{Std}}{n_s}\frac{M_s}{M_{std}}\frac{m_{Std}}{m}P_{std}$$

$$P_{BPA} = \left(\frac{P_{arom}}{mw_{arom}} - \frac{P_{BPA2,4'}}{mw_{P_{BPA2,4'}}} - \frac{P_{chrom}}{mw_{chrom}}\right) \times mw_{BPA}$$

where P_{Arom} is the purity calculated for the total aromatic compounds, $P_{BPA2,4}$ is the content due to the 2,4-BPA impurity and P_{chrom} the content of other related structure impurities. *mw* is the respective estimate of the molecular weights of each component.

The final reported value for BPA content in CCQM-K148.a was the arithmetic mean of the final mass balance and qNMR results.

Measurement uncertainty:

The uncertainty in the reported value was the root mean square of the individual uncertainties for the mass balance and qNMR results.

GLHK

BPA content assignment:

Combination of results obtained by a mass balance (method 2 type) and qNMR (method 3). The final reported value (w_{BPA}) was the arithmetic mean of the two results.

Measurement uncertainty:

1. Mass balance approach:

$U(X_{BPA})$ = U(Σ X_{IC}) where the major components of U(X_{IC}) include purities of reference standard, precision, recovery and estimation for unknown impurities

2. qNMR

U(X_{BPA}) = U(Σ X_{IC}) major components of U(X_{IC}) include CRM purity, integration, weight of analyte, weight of CRM, repeatability and impurity estimation

HSA

BPA content assignment:

By combination of results obtained by a mass balance (method 2-type) and qNMR (method 3).

The mass balance result was assigned according to the measurement equation:

$$m_{MB} = (1000 - I_{RSI}) \times (1000 - F_{Others})/1000$$

where m_{MB} was the BPA content by mass balance, I_{RSI} was the mass fraction of total related structure impurities determined by HPLC-DAD and F_{Others} was the sum of mass fraction of other impurities, all in units of $mg.g^{-1}$ and

$$I_{RSI} = I_{LC\text{-}DAD} + I_{NR} + I_{ND}$$

where $I_{LC\text{-}DAD}$ was the mass fraction (mg/g) of total related structure impurities detected by HPLC-DAD; I_{NR} was the mass fraction (mg/g) of non-resolved organic impurities in HPLC-DAD (has a value of zero but has an associated uncertainty estimated from LOQ) and I_{ND} was the mass fraction (mg/g) of non-detected organic impurities in HPLC-DAD (has a value of zero but has an associated uncertainty estimated from LOD).

$$F_{Others} = F_{VO} + F_{W} + F_{IR}$$

where F_{VO} was the mass fraction (mg/g) of residual organic solvent; F_W was the mass fraction (mg/g) of water; F_{IR} was the mass fraction (mg/g) of total non-volatiles/inorganics.

A qNMR (method 3) value for the total BPA and related structure impurities content was corrected for related structure impurities contributing to the peak selected for NMR quantification to give a final value for the BPA content only by qNMR

The qNMR measurement equation was a variation on equation 4:

$m_{qNMR} = P_{ISTD} \times (I_X/I_{ISTD}) \times (n_{ISTD}/n_X) \times (M_X/M_{ISTD}) \times (m_{ISTD}/m_X)$

where m_{qNMR} is the mass fraction of BPA by qNMR (mg/g) uncorrected for "overlapping impurities"; P_{ISTD} is the mass fraction of the internal standard; I_X is the combined integral area from 1.4-1.8 ppm for BPA and unresolved structure related impurities; I_{ISTD} is the integral area of the quantification peak of internal standard; n_{ISTD} is the number of protons of the quantification peak of internal standard; n_X: number of protons of the quantification peak of BPA ; M_X: molecular weight of BPA ; M_{ISTD} molecular weight of internal standard; m_{ISTD} mass of internal standard used; m_X: mass of BPA used.

The qNMR value for BPA was assigned after applying a correction for related structure impurity:

$m'_{qNMR} = m_{qNMR} - m_{(hydroxyphenyl)isopropyl]phenol} - m_{indanol} - m_{benzopyran} - m_{unknown\ impurity\ 1}$

where m'_{qNMR} is the final mass fraction of BPA in CCQM-K148.a obtained by subtracting mass fractions of structure related impurities having NMR absorptions that contribute to m_{qNMR} *via* a combination of results from qNMR and HPLC-DAD; $m_{(hydroxyphenyl)isopropyl]phenol}$ is the mass fraction of 2,4-bis[1-(4-hydroxyphenyl)isopropyl]phenol (HPIP) determined from HPLC-DAD; $m_{indanol}$ is the mass fraction of 3-(4-hydroxyphenyl)-1,1,3-trimethyl-5-indanol determined from HPLC-DAD; $m_{benzopyran}$ is the mass fraction of p-(3,4-dihydro-2,2,4-trimethyl-2H-1-benzopyran-4-yl) phenol determined from HPLC-DAD and $m_{unknown\ impurity\ 1}$ is the mass fraction of unknown impurity1 determined from HPLC-DAD.

The final reported value ($m_{combined}$) was the uncertainty-weighted mean of the two results.

$$m_{combined} = \sum_{i=1}^{N} w_i x_i$$

where w_i is the weight factor, x_i is the purity value of BPA and $w_i = \frac{1/u(x_i)^2}{\sum_{i=1}^{N} 1/u(x_i)^2}$

Measurement uncertainty:

For the mass balance method, the uncertainty contributors and final standard uncertainty were:

Parameter	Value (mg/g)	u (mg/g)
I_{RSI}	3.74	0.93
F_W	0.445	0.056
F_{VO}	0	0.66
F_{IR}	0	1.44
m_{MB}	**995.8**	**1.83**

For the qNMR method, the uncertainty contributors and final standard uncertainty were:

Parameter	Value (mg/g)	u (mg/g)
m_{qnmr}	995.39	2.013
m_{HPIP}	0.17	0.010
$m_{Indanol}$	0.063	0.007
$m_{benzopyran}$	0.059	0.013
$m_{mpurity1}$	0.92	0.051
m_{others}	0	0.356
F_M	994.2	0.908
m'_{qnmr}	**994.2**	**2.24**

Parameter	Mass balance (m_{MB})	qNMR (m'_{qNMR})
w_i	0.598	0.402
$m_{combined}$, mg/g	995.2	
$u(m_{combined})$, mg/g	1.5	

INMETRO

BPA content assignment:

Combination of results obtained by mass balance (variation on method 2) and qNMR (method 3). The reported value (w_{BPA}) for BPA in CCQM-K148.a was the arithmetic mean of the two results.

The mass balance result was assigned according to the measurement equation:

$$w_{BPA\ mass\ balance} = (1000 - w_{water} - w_{ROS} - w_{NV}) \times N_{BPA}$$

where N_{BPA} is the mean normalized area response for BPA relative to the combined response for BPA and related structure impurities as determined by LC-DAD and GC-FID as:

$$N_{BPA} = \left(N_{BPA\ HPLC-DAD\ Primesep} + N_{BPA\ GC-FID\ DB5}\right)/2$$

The qNMR balance result was assigned using the approach described in equation 4.

Measurement uncertainty:

Mass balance method

No impurity was detected by GC headspace, ICP OES and ICP MS. Impurity content (for residual organic solvents or non-volatiles) was considered zero and an allowance for uncertainty was included based on a rectangular distribution between zero and the limit of detection of the method, assuming that the sample could contain 5 impurities between zero and the LoD for each method.

Source	value	u	unit	Rel. cont (%)
TRSI	3.260	0.270	mg/g	92.42
Water	0.815	0.076	mg/g	7.37
ROS	0.000	0.004	mg/g	0.02
NV	0.000	0.014	mg/g	0.25
Overall	995.925	0.281	mg/g	

The assigned value for N_{BPA} was 0,9967 with an expanded uncertainty of 0,0003.

qNMR method:

Source	value	*u*	*u* component	unit	Rel. cont (%)
I_S/I_{IS} rep	0.9250	0.0002	0.1796	mg/g	3.05
M_S	228.2854	0.0088	0.0382	mg/g	0.14
M_{IS}	194.1833	0.0059	0.0302	mg/g	0.09
m_{IS}	9.7804	0.0070	0.7124	mg/g	48.03
m_S	10.6843	0.0070	0.6521	mg/g	40.25
IS purity	999.8800	0.3000	0.2987	mg/g	8.44
Overall	995.4		1.0279	mg/g	

KRISS

BPA content assignment:

Combination of results obtained by mass balance (method 2 approach) and an internal standard qNMR (method 3 approach). The final reported value was the arithmetic mean of the two results.

For the mass balance result the measurement equation was:

$$Purity = \left(1 - \sum P_{impurity\_not\text{-}detectable\_by\_chromatography}\right) \bullet P_{chromatography}$$

For the qNMR result the measurement equation was:

$$\text{Purity} = \frac{M_{IS}}{M_{analyte}} \times \frac{\text{Mmass}_{analyte}}{\text{Mmass}_{IS}} \times \frac{I_{analyte}}{I_{IS}} \times \frac{\rho_{IS}}{\rho_{analyte}} \times P_{IS}$$

ρ	number of NMR active nuclei per molecule that contributes to the measured NMR signal
I	integrated peak area
$P_{I.S.}$	mass fraction purity of the internal standard
Mmass	molar mass

Measurement uncertainty:

The pooled standard uncertainty of the mass balance result and qNMR result was calculated as:

$$u_{pool} = \sqrt{\frac{v_1 * u_1^2 + v_2 * u_2^2}{v_1 + v_2}}$$

v_1 degrees of freedom of the mass balance result

u_1 standard uncertainty of the mass balance result

v_2 degrees of freedom of the qNMR result

u_2 standard uncertainty of the qNMR result

The overall standard uncertainty (u_{comb}) in the BPA value for CCQM-K148.a was assigned as the quadratic combination of u_{pool} and the difference (d) between the mass balance and qNMR results.

$$u_{comb} = \sqrt{{u_{pool}}^2 + d^2}$$

LGC

BPA content assignment:

Combination of results by mass balance (variation on method 2) and qNMR (method 3).

The final reported value was the mean weighted for the standard uncertainty of the two contributing results.

The mass balance result was assigned according to the measurement equation:

$$P_{Total} = \left[1 - \left[\frac{\%water}{100} + \frac{\%IR}{100} + \frac{\%res\ solvent}{100} + \frac{\%rel\ imp}{100}\right]\right] \times P_{org}$$

The qNMR value was assigned using the measurement equation:

$$\%Purity_{Analyte} = \frac{m_{IS}}{m_{Analyte}} \times \frac{Mwt_{Analyte}}{Mwt_{IS}} \times \frac{I_{Analyte}}{I_{IS}} \times \frac{\rho_{IS}}{\rho_{Analyte}} \times 100 P_{IS}$$

where ρ represents the number of ^{1}H nuclei giving rise to each quantified signal. The raw qNMR value obtained was corrected for contributions from overlapping BPA isomers and other low level impurities contributing to the qNMR value and detected by UPLC-UV.

Measurement uncertainty:

Mass balance (indirect) approach

	UPLC-DAD	Water	Inorg. Residue	Residual solvent
u	2.00E-01	5.29E-02	2.55E-02	5.77E-02
u^4	1.60E-03	7.84E-06	4.25E-07	1.11E-05
n	32	33	1000	5
n-1 (DoF)	31	32	999	4
u^4/(n-1)	5.16E-05	2.45E-07	4.25E-10	2.78E-06

Purity (%) 99.53

Combined: u = 0.22 mg.g^{-1} ; v_{eff} = 40.06

qNMR (direct) approach

Quantity/units	Value	u	u_{rel} (%)
$P_{analyte,mean}$ / %	99.71	0.01	0.0053
ρ_{IS}	2	0	0
$\rho_{analyte}$	4	0	0
$P_{internal\ std.}$/ %	99.992	0.003	0.0030
$MW_{analyte}$	228.28634	0.012067079	0.0053
$MW_{internal\ std.}$	122.12134	0.00564769	0.0046
$m_{internal\ std.}$ / mg	11.2844667	0.00103	0.0092
$m_{analyte}$ / mg	11.6951333	0.00103	0.0088
***Purity*, u_c / %**	**99.71**	**0.016**	**0.016**

By LGC policy the minimal relative standard uncertainty of a qNMR mass purity value cannot be less than be 0.1%. This value was used for the combined uncertainty calculation rather than the direct value from the qNMR data. A correction to the raw qNMR result for a contribution of 0.11% from impurities, with an associated uncertainty, gave an overall impurity-corrected value for BPA content via qNMR of 99.6% with a standard uncertainty of 0.15%.

The reported value for BPA content in CCQM-K148.a was the mean of the two results weighted for the uncertainty of each:

$$\%Purity_{combined} = \frac{\sum_{i=1}^{N} w_i x_i}{\sum_{i=1}^{N} w_i}$$

Where w_i = weighting factor equal to $1/U_i^2$; x_i = purity of BPA by mass balance or qNMR, U_i = expanded uncertainty of x_i

The uncertainty of the combined value was calculated as:

$$U_{Combined} = \frac{1}{\sqrt{w_{\mathrm{qNMR}} + w_{\mathrm{Indirect}}}}$$

NIM

BPA content assignment:

Result by mass balance (method 1) approach calculated using Eqn. 1

Measurement uncertainty:

Calculated as described in Eqn. 2

NIMT

BPA content assignment:

Result by mass balance (method 1) approach calculated using Eqn. 1

Measurement uncertainty:

Calculated as described in Eqn. 2. The assigned values were:

Parameter	Source of uncertainty	xi	u(xi)	u(rel)
M(H_2O)	Mass fraction of H2O (mg/g)	3.854	2.117	0.549
M(IP1)	Mass fraction of impurity 1 (mg/g)	0.099	0.040	0.403
M(IP2)	Mass fraction of impurity 2 (mg/g)	0.085	0.055	0.645
M(IP3)	Mass fraction of impurity 3 (mg/g)	0.059	0.024	0.401
M(IP4)	Mass fraction of impurity 4 (mg/g)	0.012	0.005	0.406
M(IP5)	Mass fraction of impurity 5 (mg/g)	3.667	1.468	0.400
M(IP6)	Mass fraction of impurity 6 (mg/g)	1.488	0.598	0.402
M(IP7)	Mass fraction of impurity 7 (mg/g)	0.244	0.098	0.403
M(IP8)	Mass fraction of impurity 8 (mg/g)	0.065	0.026	0.401
M(IP9)	Mass fraction of impurity 9 (mg/g)	0.544	0.220	0.405
M(IP10)	Mass fraction of impurity 10 (mg/g)	0.088	0.035	0.401
M(IP11)	Mass fraction of impurity 11 (mg/g)	0.013	0.005	0.400
M(IP12)	Mass fraction of impurity 12 (mg/g)	1.799	0.720	0.400
M(IP13)	Mass fraction of impurity 13 (mg/g)	0.108	0.043	0.401
M(IP14)	Mass fraction of impurity 14 (mg/g)	0.021	0.008	0.403
M(IP15)	Mass fraction of impurity 15 (mg/g)	0.013	0.005	0.408
M(V)	Mass fraction of volatiles (mg/g)	0.000	0.415	0.415
M(NV)	Mass fraction of non-volatiles (mg/g)	0.000	0.415	0.415
Total impurities (mg/g)	12.159			
Bisphenol A content (mg/g)	987.8	2.75		
Expanded uncertainty (*k*=2) (mg/g)	5.6			

NMIA

BPA content assignment:

Result by mass balance (method 2) approach according to measurement equation:

$$\text{Purity} = (100\%\text{-}I_{GC\text{-}all}) \times (100\%\text{-}I_{OT})$$

where I_{OT} is the sum of all contributions from water, volatiles and total non-volatile residue and $I_{GC\text{-}all}$ is a measure of the content of total related structure impurities relative to BPA by GC-FID.

Measurement uncertainty:

$$U_{purity} = Purity \times \sqrt{\left(\frac{U_{GC-all}}{I_{GC-all}}\right)^2 + \left(\frac{U_{OT}}{I_{OT}}\right)^2}$$

The major components of the uncertainty budget are the components of the expanded uncertainty of I_{OT} (U_{OT}) due to the standard uncertainty (0.6 mg/g) associated with the result for water content from two samples analysed by Karl Fischer analysis and the standard uncertainty (0.3 mg/g) associated with the assessment of non-volatile residue using the qNMR result (999 mg/g) which supports zero NVR content. The latter uncertainty was taken as the standard error of the mean in the qNMR experiment.

NMISA

BPA content assignment:

Combination of results from a mass balance (method 1) approach:

$w_{BPA\ mass\ balance} = 1000 - (w_{imp\ LC\&GC} + w_{RS} + w_{H2O} + w_{NV})$

and a related-impurity corrected qNMR (method 3) approach using the measurement equation:

$$w_{BPA:QNMR} = P_{BPA\ QNMR} - w_{imp\ LC\&GC}$$

where $P_{BPA\ QNMR}$ is the value for BPA and related structure impurity content by qNMR and $w_{imp\ LC\&GC}$ is the mass fraction of total related structure impurities determined for the mass balance method and assumed to contribute to the qNMR quantification peak.

The final result for the BPA content in CCQM-K148.a was the mean of the two results.

Measurement uncertainty:

Expanded uncertainty of the final result ($\overline{Y}$) was calculated as:

$$U_{95}(\overline{Y}) = 2 \times \sqrt{\frac{\left(\sum_{j=1}^{N}(Y_j - \overline{Y})^2 / N-1\right) + \left(\sum_{j=1}^{N}\left(\frac{U_{95}(Y_j)}{2}\right)^2 / N\right)}{N}}.$$

where N = 2 and:

	BPA content (mg/g)	**U_{95} (mg/g)**
Y_{MB}	992.9	3.4
Y_{QNMR}	986.2	7.9
$\overline{Y}$	989.6	8.0

NMIJ

BPA content assignment

Combination of results obtained by mass balance (method 1), qNMR (modified method 3) and freezing point depression (FPD).

The final reported value for BPA content in CCQM-K148.a was the arithmetic mean of the three contributing results.

Mass balance (method 1 type):

$P_{MBA} = 1000 - (C_{\text{total related structure impurities}} + C_{\text{water}} + C_{\text{residual organic solvent}} + C_{\text{total non-volatiles}})$

qNMR (method 3 type):

$P_{NMR} = P_S \cdot \{S_x \cdot R_X \cdot I_X \cdot N_S \cdot m_S \cdot M_X\} / \{S_S \cdot R_S \cdot I_S \cdot N_X \cdot m_X \cdot M_S\}$

P_{NMR}: purity of BPA (from ANOVA of combined NMR results)
P_S: purity of internal standard
m: mass ($m_x = m_{x2} - m_{x1}$, $m_s = m_{s2} - m_{s1}$)
S: NMR signal area of sample
R: Signal recovery factor (measure of NMR peak saturation/NMR relaxation)
N: ^{1}H natural abundance
M: molar mass

Freezing point depression (FPD) method

1. $$x_p(\mathrm{DSC}) = 1 - \frac{\Delta_{fus}H}{R \cdot {T_0}^2} \cdot \Delta T$$

$x_{p(DSC)}$ amount of substance fraction of BPA in CCQM-K148.a from freezing point depression
$\Delta_{fus}H$: molar fusion enthalpy
R: gas constant
T_0 melting point (K) of pure BPA
ΔT : melting point depression

2. $$x_{p,w}(\mathrm{DSC}) = \frac{M_p \cdot x_p(\mathrm{DSC})}{M_p \cdot x_p(\mathrm{DSC}) + M_{ip} \cdot \{1 - x_p(\mathrm{DSC})\}}$$

$x_{p,w\ (DSC)}$ mass fraction of BPA in CCQM-K148.a from freezing point depression
M_p molar mass of BPA
M_{ip} average molar mass of related structure impurities quantified by freezing point depression

Measurement uncertainty

The uncertainty of the reported result was evaluated from the standard uncertainty of the three methods with an additional uncertainty contribution due to the difference between results obtained by the methods. The uncertainty due to difference between the methods was estimated by assuming a rectangular distribution between the arithmetic mean and the largest or smallest result (in this case, P_{NMR})
The sum of mass fractions of water, residual organic solvent and total non-volatiles (SC_{imp}) was considered as a common uncertainty factor for the mass balance and FPD methods.

Symbol	Source of uncertainty	Value (P_i)	Standard uncertainty u(P_i)	C_i ($=\partial f/\partial P_i$)	ui=$\lvert c_i \rvert$ $u(P_i)$ mg/g	Degree of freedom
P_{MBA}	mass balance	995.9 mg/g	0.54 mg/g	0.3	0.18	large
P_{NMR}	nuclear magnetic resunance	996.3 mg/g	0.60 mg/g	0.3	0.20	large
P_{fpd}	freezing-point depression method	996.0 mg/g	1.04 mg/g	0.3	0.35	large
ΣC_{imp}	common	(0.57) mg/g	0.07 mg/g	1.1	0.07	large
P_{method}	between method	996.1 mg/g	0.13 mg/g	1.0	0.13	large
	Combined standard uncertainty				0.46	
	Expanded uncertainty (k=2)	996.1			1.0	

$$u^2_{cP(K148.sample)} = \frac{u^2(P'_{MBA}) + u^2(R_{NMR}) + u^2(P'_{fpd}) + u^2(\sum C_{imp})}{3^2} + \left(\frac{\sum C_{imp}}{1000}\right)^2 \cdot u^2(P'_{fpd}) + \left(\frac{P'_{fpd}}{1000}\right)^2 \cdot u^2(\sum C_{imp}) + u^2_{method}$$

NRC

BPA content assignment

A qNMR (method 3) approach with the initial value corrected for total related structure impurities contributing to the peak selected for NMR quantification.

The general qNMR measurement equation applied was:

$$w_{an} = \frac{I_{an}}{I_c} \cdot \frac{N_c}{N_{an}} \cdot \frac{MW_{an}}{MW_c} \cdot \frac{m_c}{m_{an}} \cdot \frac{V_{an}}{V_c} \cdot w_c$$

The correction for total related structure impurity was calculated as:

$$w_{imp\,corr} = \frac{MW_{an}}{N_{an}} \cdot \sum_i \frac{w_{imp\,i} \cdot N_{imp\,i}}{MW_{imp\,i}}$$

Where for analyte (*an*, BPA), calibrant (*c*, benzoic acid) and BPA-related structure impurity (*imp*): w = mass fraction; I = signal area; N = number of protons integrated , MW = molar mass (g/mol); m = weighed mass (g); V = volume by mass (g). V_{an} and V_c are equivalent in this case as analyte and calibrant are present in the same solution in internal standard qNMR.

The final result for BPA ($w_{an\,corr}$)in CCQM-K148.a was given by:

$$w_{an\,corr} = w_{an} - w_{imp\,corr}$$

Measurement uncertainty

Uncertainty contribution	*u* (mg/g)
Repeatability of measurement (three replicates)	1.01
Signal recovery (9 x T_1)	0.08
Peak integration (incompleteness)	0.99
Peak integration between analyst	0.50
Method uncertainty due to different signals	1.75
Weighings of the analyte	0.31
Weighing of the calibrant	0.76
Molecular weight of calibrant	0.03
Purity of the calibrant	0.03
Molecular weight of analyte	0.03
Combined standard uncertainty	2.4

The major uncertainty contributions were due to the variability in the mass fraction of BPA obtained by two different NMR signals and the repeatability of the measurement of individual signals.

UME

BPA content assignment

Results by mass balance (method 1) approach following Eqn. 1

w_A = $m_A / (m_A + \sum m_x)$
= $n_A * M(A) / (m_A + \sum m_x)$
= $1000 - (w_{RS} + w_W + w_{VOC} + w_{NV})$

w_A : mass fraction of main component A in the material
m_A mass of A in an aliquot of the material
Σm_x summed mass of minor components (impurities) in the same aliquot
n_A moles of A in an aliquot of the material
M(A) Molar mass of A

Measurement uncertainty

Parameter	Value (X)	u(X)	$u_{rel}(x)$
Sample weight	5	6.33E-03	1.266E-03
Repeatability	100	2.76E-01	2.762E-03
Relative combined uncertainty			3.038E-03
Result (mg/g)	996.642		
Combined uncertainty (mg/g)		3.028	
Expanded uncertainty (k = 2)		6.056	
Reported value ± expanded uncertainty (k = 2)	996.642 ± 6.056		

VNIIM

BPA content assignment

Result of mass balance (method 1) type where the value in $mg.g^{-1}$ for the combined related structure and residual solvent impurity mass fraction content (w_{RI}) was calculated as:

$$\omega_{RI} = \frac{1000 * [(A_1 + A_2 + A_3 + A_4 + A_5) * RF_1 + (A_6 + A_7) * RF_4 + A_8 * RF_2 + (A_9 + A_{10}) * RF_5 + (A_{11} + A_{12}) * RF_3)]}{m_s}$$

and A_1, A_2, ...A_{12} are areas of related structure impurities and VOCs, RF_1 is the response factor of phenol, RF_2 is the response factor of 2,4'-BPA, RF_3 is the response factor of trisphenol, RF_4 is a response factor equal to the arithmetic average of response factors of BPA and 2,4-BPA and RF_5 is a response factor equal to the arithmetic average of response factors of 2,4-BPA and trisphenol and m_s is the mass of the sample in grams

Measurement uncertainty

The uncertainty was calculated using a variation on equation 2:

$$u_{BPA} = \sqrt{u_{H2O}^2 + u_{NV}^2 + u_{RI}^2 + u_{VOC}^2} = \sqrt{u_{H2O}^2 + u_{NV}^2 + u_{RI+VOC}^2}$$

and

$$u_{H2O} = \omega_{H2O} * \sqrt{(u_A/\omega_{H2O})^2 + (u_{SDst}/\omega_{STH2O})^2 + (u_{st}/\omega_{STH2O})^2 + \left(u_{bal}/m_{sample}\right)^2 + (u_{blank}/\omega_{H2O})^2}$$

where:

u_{A}	std. deviation of sample measurement results, mg/g
u_{SDst}	std. deviation of water CRM measurement results, mg/g
u_{st}	standard uncertainty of water CRM reference value, mg/g
u_{bal}	standard uncertainty of mass determination due to balance characteristics, mg
u_{blank}	standard uncertainty of uncertainty of method blank determination, mg/g
m_{sample}	mass of sample, mg
w_{STH2O}	reference value of water content in CRM, mg/g

$$u_{NV} = \frac{LOD}{4}$$

$$u_{RI+VOC} = \sqrt{\sum_{1}^{12} \omega_{Impi} \left(u_{Cali}^2 + u_{Sam}^2 + u_{\overline{Ai}}^2 + \frac{\sum_1^n (u_{Ail}^2)}{18} \right)}$$

where:

w_{Impi}	mass fraction of individual impurity i, mg/g
$u_{\mathrm{Cal\ i}}$	uncertainty of calibration
$u_{\mathrm{Cal\ i}}$	uncertainty of calibration
u_{Ai}	RSD of six independent measurements
u_{Ail}	RSD of 3 measurements per sample

$$u_{Cali} = \sqrt{u_{A_{RFi}}^2 + u_{Sti}^2 + \sum_{1}^{3} \left(u_{m_{st}}^2 + u_{m_{sol}}^2 \right)}$$

u_{ARFi}	RSD of three measurements of RFs
u_{Sti}	uncertainty of standard reference value
u_{mst}	uncertainty of standard mass determination
u_{msol}	uncertainty of standard solvent mass determination

$$u_{Sam} = \sqrt{\sum_{n=1}^{6} \left(u_{m_s}^2 + u_{m_{solv}}^2 \right)}$$

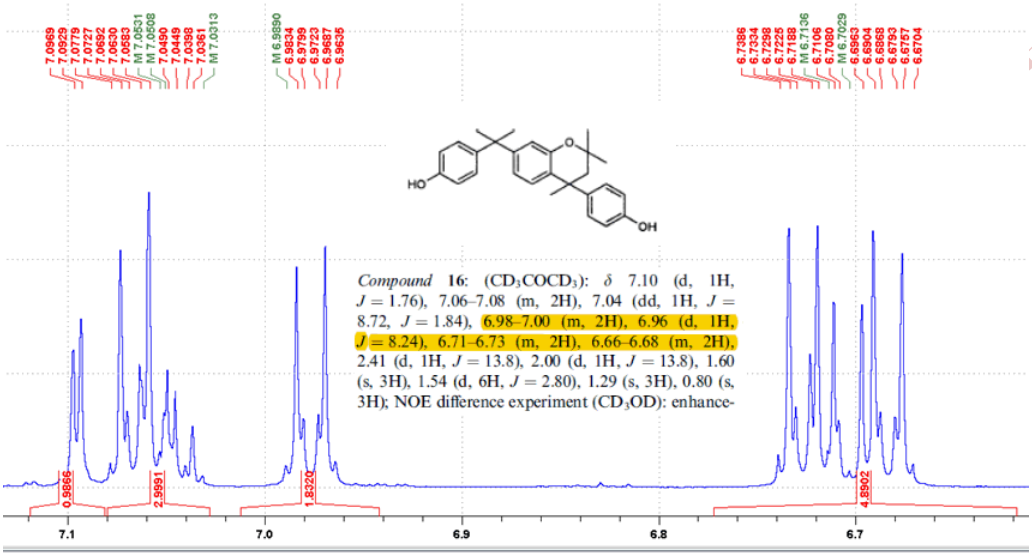
u_{ms}	uncertainty of sample mass determination
u_{msol}	uncertainty of sample solvent mass determination

The main contributors to the overall u_{BPA} (0.146 mg.g-^{1}) were the contribution of the uncertainty in the assignment of the 2,4'-BPA impurity content (0.133 mg.g^{-1}) to the combined value for $u_{\mathrm{RI+VOC}}$ and the uncertainty of the water content, u_{H2O} (0.04 mg.g^{-1}).

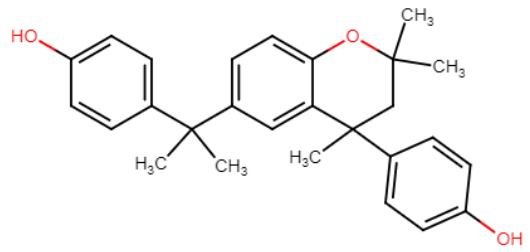
APPENDIX I

Correspondence from Dr Annie WF Wong, GLHK regarding the structure of the second significant related structure impurity in CCQM-K148.a:

"On page 14 of the Draft B report (ver 1.0), the second impurity was assigned as 4-hydroxy-phenyl(propan-2-yl)-2,3,4-trimethyl(chroman-4-yl)phenol with the NMR signal published in the quoted reference. I look deep into the 1H NMR spectrum of our test sample and find that the signals in the aromatic proton region (6-8 ppm) did not match with that quoted in the reference. The impurity was then isolated by LC and analysed again with 1H NMR to give a more clear picture of its identity. Below please find the spectrum of the isolated compound:



The signals in the quoted reference (highlighted in yellow) did not match with the signals of our isolated compound. From the 1H, 13C, DEPT, 2D COSY, NOESY, HSQC and HMBC NMR data of the impurity compound isolated, the structure of the impurity presented in the test sample with m/z 402 was proposed as follow:



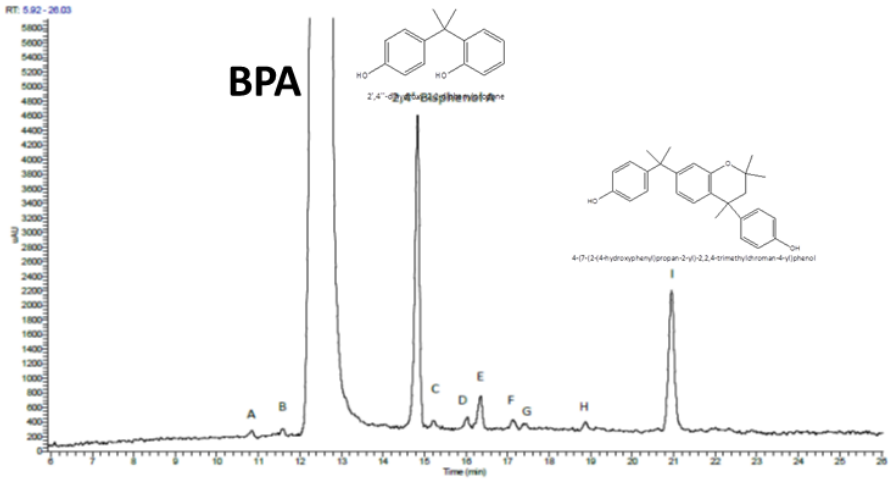
APPENDIX J: Key parameters of participant chromatographic methods

NMI	Method(s)	Column	Eluant A	Eluant B	Gradient	Detection
BAM	LC-UV	RP8 Lichrospher (125 x 4 mm)	H_2O	ACN	20% to 65% B (7 min)	210 & 225 nm
BIPM	LC-UV, LC-CAD	ODS Hypersil (250 x 4.6 mm)	H_2O	MeOH	60% to 95% B (35 min)	280 & 355 nm
CENAM	LC-UV	Kinetex 5 µm F5 (250 x 4.6 mm)	H_2O	ACN	30% to 80 % B (60 min)	225 nm
EXHM	LC-UV, LC-FLD, LC-MS/MS	Inertsil ODS-3 (250 x 2.1 mm)	H_2O	ACN	30% to 100% B (100 min)	280 nm (UV) 274/313 (FLD)
GLHK	LC-UV, LC-MS/MS	Phenom Aqua C18, (250 x 4.6 mm)	H_2O*	ACN		280 nm
HSA	LC-UV, LC-CAD LC-MS/MS	Phenom Gemini C18, (250 x 4.6 mm) ODS-3 (250 x 4.6 mm)	H_2O	ACN	50% to 90% B (80 min)	275 nm (1°) 260, 280 (2°)
INMETRO	LC-UV, LC-MS/MS	Primesep 100 (150 × 4.6 mm); Acquity HSS T3 (50 × 2.1 mm, 1.8 µm)	H_2O* H_2O	ACN* ACN	25% to 80% B (20 min) 20% to 80% B (12 min)	280 nm
	GC-FID	DB1 MS (30 m x 0.25 mm), BSTFA deriv.	200-224 °C at 2 °C/min, 224-300 °C at 30 °C/min			FID
KRISS	LC-UV	Waters BEH C18 & CSH Phenylhex	H_2O	ACN		278 nm (2°)
	GC-FID	DB5 (60 m, 0.53 mm, 1.5 µm)	50 - 230 °C at 20 °C/min, 230-300 °C at 1.5 °C/min			FID (1°)
LGC	LC-UV, LC-MS/MS	ACE Excel C18-FPF (100 x 3 mm, 1.7 µm)	H_2O*/ACN	H_2O* /ACN	40% to 70% B (22 min)	277 nm
NIM	LC-UV, LC-MS/MS	Inertsil ODS-SP (250 × 4.6 mm)	H_2O	MeOH	55% to 95% B (80 min)	215 nm
NIMT	LC-UV	Waters C-18 (250 x 4.6 mm)	H_2O	ACN	65% A (isocratic, 40 min)	190-800 nm
NMIA	GC-FID	HP-1/HP-5 (30 m x 0.32 mm); underivatised	120-230 °C at 10 °C/min, 230-300 °C at 30 °C/min			FID
NMIJ	LC-UV, LC-MS LC-CAD	Zorbax Eclipse C18 (150 x 2.1 mm, 1.8 µm) L-column2 ODS (150 x 2.1 mm, 2 µm)	H_2O*	ACN	20% to 100% B (15 min, UV, MS) 30% to 100% B (30 min, CAD) 50% to 100% B (30 min, CAD) 100% B (35 min, CAD)	220 & 254 nm
NMISA	LC-UV	Phenom. Kinetex C18 (250 x 4.6 mm)	H_2O	MeOH	50% to 100 % B (60 min)	280 nm (1°) 254, 210 (2°)
	GC-MS	Rxi-XLB (30 m x 0.25 mm); underivatized	80 - 340 °C at 5 °C/min			MSD (TIC)
NRC	LC-UV	Phenomx Synergi Fusion (150 x 2 mm)	H_2O*	ACN	30% to 84% B (31 min)	277 (BPA, I1) 279, 282 (other)
UME	LC-UV	Luna C18 (250 x 4.6 mm)	H_2O	ACN:MeOH	50% to 95% B (50 min)	280 nm
VNIIM	LC-UV	XDB-C18 (150 x 4.6 mm)	H_2O*	ACN	40% to 50% B (20 min)	275 nm

* Aqueous phase acidified using 0.05 – 0.1% formic or acetic acid or buffer (NH_4Ac, H_3PO_4)

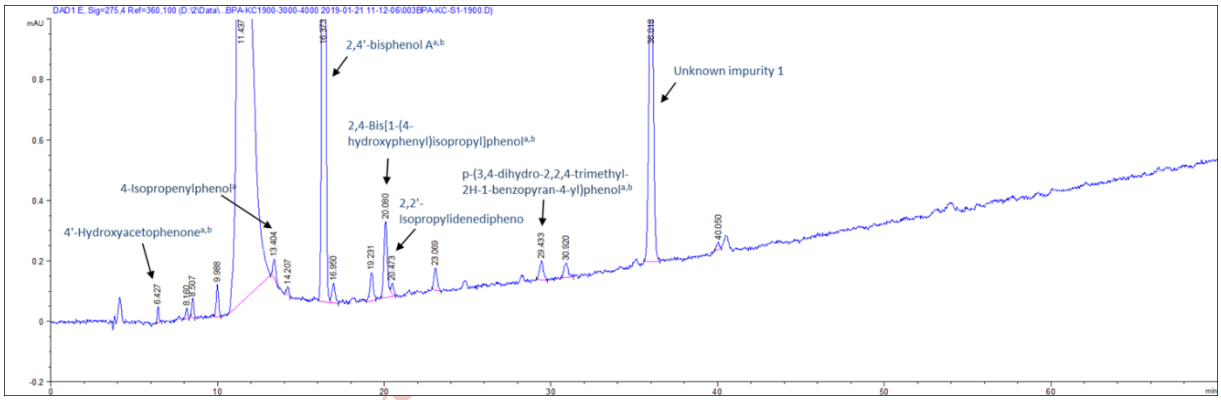
APPENDIX K: Representative chromatograms CCQM-K148.a

1.

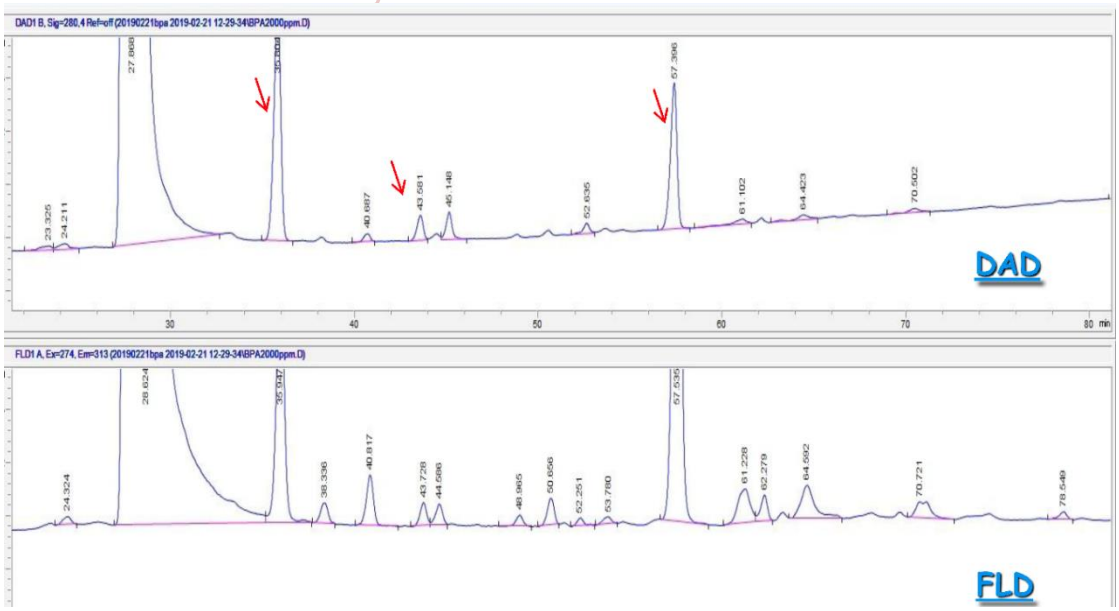


Representative LC-UV chromatograms of related structure impurity profile for the CCQM-K148.a material provided by GLHK (1), HSA (2) and EXHM (3) , which also shows the LC-FLD chromatogram.

2.



3.



APPENDIX L: Key parameters of qNMR methods

NMI	Result (mg/g)	NMR	Solvent	IS	Quantification Peak(s)	Delay (s)	SW (ppm)	Offset (ppm)	Integration
BAM	995.4 ± 0.91	Bruker 500	CD_3OD	BA	Me	42 (7*T1)	18	4.5	Manual
BIPM	994.4 ± 4.4	JEOL 400	Acetone-d_6	DMTP	Me	60 (15*T1)	400	5.5	Manual, > ^{13}C-sat
EXHM	994.14 ± 1.43	Bruker 500	DMSO-d_6	BTFMBA	Ar & Me	70	16	6	Manual, < ^{13}C-sat.
GLHK	995.8 ± 3.78	Bruker 600	DMSO-d_6	BA	Ar	60	25	7.4	Manual
HSA	994.2 ± 4.48	Bruker 500	CD_3CN	$DMSO_2$	Me	40	20	6.175	Manual
INMETRO	995.4 ± 2.06	Bruker 400	Acetone-d_6	DMTP	Me	41 (10*T1)	40	4.3	Manual, > ^{13}C-sat
KRISS	995.4 ± 1.8	Agilent 600	DMSO-d_6	BA	Me	60			
LGC	996 ± 3	Bruker 600	DMSO-d_6	BA	Ar	26	20		Manual, < ^{13}C-sat.
NIM *	996.5 ± 1.0	Bruker 800	CD_3OD	BA	Me	60	15	6	Manual
NIM (LC) *	994.5 ± 3.0	Bruker 800	CD_3OD	EHB	Ar	60	15	6	Manual
NMIA	997	Bruker 500	D_2O/NaOD	KHM	Ar	30			
NMIJ	996.3 ± 1.2	Varian 600	CD_3OD	BTFMBA	Me	60	99	5	Manual, > ^{13}C-sat
NMISA	986.2 ± 7.9	Varian 400	CD_3CN	DMTP	Ar & Me	60	100		Manual
NRC	993.7 ± 4.8	Bruker 600	DMSO-d_6	BA	Ar & Me	33 (9*T1)	30		Manual, > ^{13}C-sat
UME	996.64 ± 6.06	Varian 600	CD_3OD	BA	Ar	82	20	4.8	Manual
UME *	996.85 ± 2.10	Varian 600	CD_3OD, CD_3CN, Acetone-d_6 DMSO-d_6	BA, MA, DMTP, TMB	Ar	45	16-20	3.8 – 4.8	Manual

Note: All participants used a 90° degree excitation pulse

Key: BA = Benzoic acid ; BTFMBA = Bis(trifluoromethyl) benzoic acid; $DMSO_2$ = Dimethyl sulfone; DMTP = Dimethyl terephthalate; EHB = Ethyl hydroxybenzoate; KHM = Potassium hydrogen maleate; MA = Maleic acid; TMB = 1,3,5-Trimethoxybenzene

* Submitted for CCQM-P187.a

APPENDIX M: KCRV calculation parameters

The NIST Consensus Builder developed by Antonio Possolo -NIST, version of 2020-Aug-11, (https://consensus.nist.gov/) was used to implement the Hierarchical Bayes procedure as described in Koepke et al.[16]

The Heirarchical Bayes Random Effects Model (HB REM) estimator was calculated using as input the twelve participant results listed in Table 4 after excluding those of BIPM, CENAM, NMISA, NIMT and VNIIM.

The following (default) settings of the NIST Consensus Builder application were used:

- median of the absolute values of the differences between measured values and their median as the prior for between lab variance
- median of participant standard uncertainties as the prior for within lab variance
- total number of iterations = 250000
- length of burn in = 50000
- thinning rate = 25

This gave the following outputs for the BPA content, all in units of mg/g:

Content estimate = 995.6

Standard uncertainty = 0.29

95% confidence interval = 995.1 to 996.2

Dark uncertainty (tau) = 0.415

Variations in the number of iterations, length of burn in and thinning rate from the default values resulted in no significant change in the calculated outputs.

APPENDIX N: Core Competency Claims by Participant

CCQM-K148.a (Bisphenol A)	*BAM*	Assignment of Mass fraction of Main Component in an Organic Solid
Scope of comparison: The measurement results are representative of the laboratory's capability for the purity assignment of organic compounds in the molecular weight range 75 - 500 with pK_{ow} < -2.		
• Value assignment of Primary Reference: Main component mass fraction and uncertainty		
Competency	**✓,× or N/A**	**Specific Information**
Identity verification	✓	^{1}H NMR, LC-UV (comparison with independent Bisphenol A sample, retention time + UV spectrum)
Assignment of main component mass fraction content of CCQM-K148.a	✓	^{1}H qNMR
Bisphenol A content (mg/g)		995.4 ± 0.91
• Value assignment of Primary Reference: Impurity class mass fraction and uncertainty (required if using a mass balance method, otherwise optional)		
Assignment of related structure impurity	✓	LC-UV, 2 different columns, 2 wavelengths
Related structure impurity (mg/g)		5.67 ± 1.58
Assignment of water content	✓	Coulometric Karl-Fischer titration
Category of water content assignment*	✓	Non polar organic solid, water content < 2 mg/g
Water content (mg/g)		0.40 ± 0.03
Assignment of residual solvent content	✓	Headspace GC-MS
Total residual solvent (mg/g)		0.00011 ± 0.00004
Assignment of total non-volatiles content		
Total non-volatiles (mg/g)		

CCQM-K148.a (Bisphenol A)	*CENAM*	Assignment of Mass fraction of Main Component in an Organic Solid
Scope of comparison: The measurement results are representative of the laboratory's capability for the purity assignment of organic compounds in the molecular weight range 75 - 500 with pK_{ow} < -2.		
• Value assignment of Primary Reference: Main component mass fraction and uncertainty		
Competency	**✓,× or N/A**	**Specific Information**
Identity verification	✓	Mass spectrometry
Assignment of main component mass fraction content of CCQM-K148.a	✓	HPLC-DAD
Bisphenol A content (mg/g)		977.02 ± 0.52 mg/g
• Value assignment of Primary Reference: Impurity class mass fraction and uncertainty (required if using a mass balance method, otherwise optional)		
Assignment of related structure impurity	✓	HPLC-DAD, GC-MS, GC-FID on column
Related structure impurity (mg/g)		21.63 ± 0.51 mg/g
Assignment of water content	✓	Coulometric titration Karl Fischer
Category of water content assignment*		Non-polar organic solid, water content < 2 mg/g
Water content (mg/g)		1.360 ± 0.063 mg/g
Assignment of residual solvent content	✓	GC-FID on column
Total residual solvent (mg/g)		No detected residual solvent
Assignment of total non-volatiles content	✓	Ignition residual method by gravimetry
Total non-volatiles (mg/g)		0.0258 ± 0.015 mg/g

The result for CENAM was not consistent with the KCRV at the 95% confidence interval and the DoE did not cross zero. No information was provided to indicate the cause of this deviation.

CCQM-K148.a (Bisphenol A)	*EXHM*	Assignment of Mass fraction of Main Component in an Organic Solid
Scope of comparison: The measurement results are representative of the laboratory's capability for the purity assignment of organic compounds in the molecular weight range 75 -500 with pK_{ow}< -2.		
• Value assignment of Primary Reference: Main component mass fraction and uncertainty		
Competency	**✓,× or N/A**	**Specific Information**
Identity verification	✓	LC-MS/MS, LC-DAD, GC/MS, comparison NMIJ CRM 4030-a bisphenol A, qNMR,traceability NMIJ CRM 4601-b.
Assignment of main component mass fraction content of CCQM-K148.a	✓	LC-DAD, qNMR
Bisphenol A content (mg/g)		994.23 ± 0.75
• Value assignment of Primary Reference: Impurity class mass fraction and uncertainty (required if using a mass balance method, otherwise optional)		
Assignment of related structure impurity	✓	GC/MS, LC-DAD, LC-MS/MS, qNMR
Related structure impurity (mg/g)		4.68 ± 1.00
Assignment of water content	✓	Karl-Fischer Titration
Category of water content assignment*		non-polar organic solid, water content < 2 mg/g
Water content (mg/g)		0.993 ± 0.050
Assignment of residual solvent content	✓	Head Space-GC/MS, SPME-GC/MS, GC-FID, GC/MS, LC-FLD, LC-DAD, LC-MS/MS
Total residual solvent (mg/g)		< 0.02
Assignment oftotal non-volatiles content	✓	HR-ICP/MS
Total non-volatiles (mg/g)		< 0.02

CCQM-K148.a (Bisphenol A)	*GLHK*	Assignment of Mass fraction of Main Component in an Organic Solid
Scope of comparison: The measurement results are representative of the laboratory's capability for the purity assignment of organic compounds in the molecular weight range 75 - 500 with pK_{ow} < -2.		
• Value assignment of Primary Reference: Main component mass fraction and uncertainty		
Competency	**✓,× or N/A**	**Specific Information**
Identity verification	✓	IR, MS, NMR and chromatographic equivalence
Assignment of main component mass fraction content of CCQM-K148.a	✓	Mass-balance method and qNMR method
Bisphenol A content (mg/g)		996.3 ± 4.9 ($U_{95\%}$)
• Value assignment of Primary Reference: Impurity class mass fraction and uncertainty (required if using a mass balance method, otherwise optional)		
Assignment of related structure impurity	✓	LC-UV, LC-MS, LC-MS/MS
Related structure impurity (mg/g)		2.81 ± 1.41 ($U_{95\%}$)
Assignment of water content	✓	Coulometry Karl Fischer Titration
Category of water content assignment*	✓	non-polar organic solid, water content < 2 mg/g
Water content (mg/g)	✓	0.393 ± 0.041 ($U_{95\%}$)
Assignment of residual solvent content	✓	Headspace-GCMS
Total residual solvent (mg/g)		0 ± 2.0 ($U_{95\%}$)
Assignment of total non-volatiles content	✓	ICP-MS, ICP-OES and Ion Chromatography
Total non-volatiles (mg/g)		0 ± 2.0 ($U_{95\%}$)

CCQM-K148.a (Bisphenol A)	*HSA*	Assignment of Mass fraction of Main Component in an Organic Solid
Scope of comparison: The measurement results are representative of the laboratory's capability for the purity assignment of organic compounds in the molecular weight range 75 - 500 with pK_{ow} < -2.		
• Value assignment of Primary Reference: Main component mass fraction and uncertainty		
Competency	**✓,× or N/A**	**Specific Information**
Identity verification	✓	(1) Structural elucidation by NMR spectroscopy. The certified reference material of 4,4'-bisphenol A from NMIJ was also used to match each profile peak in the comparison material. (2) Comparison of retention time and UV absorption profile of the comparison material with those of the certified reference material of 4,4'-bisphenol A from NMIJ.
Assignment of main component mass fraction content of CCQM-K148.a	✓	Approach 1: Deduction of four classes of impurities from 1,000 mg/g using the mass balance approach. Approach 2: Direct determination of the main component using quantitative nuclear magnetic resonance spectroscopy *via* internal standard method.
Bisphenol A content (mg/g)	✓	995.2 ± 3.0
• Value assignment of Primary Reference: Impurity class mass fraction and uncertainty (required if using a mass balance method, otherwise optional)		
Assignment of related structure impurity	✓	(1) HPLC-DAD for identification and quantification of related structure impurities using relative peak area approach; (2) HPLC-CAD for estimation of measurement uncertainty due to difference in results from methods used in quantification of related structure impurities; and (3) LC-MS/MS, LC-QTOF and ^{1}H NMR for identification of related structure impurities.
Related structure impurity (mg/g)		3.74 ± 1.85
Assignment of water content	✓	Karl Fischer coulometry
Category of water content assignment*	✓	Non-polar organic solid, water content < 2 mg/g

(continues next page)

Core competency table for CCQM-K148.a – HSA (continued)

Water content (mg/g)	✓	0.445 ± 0.177
Assignment of residual solvent content	✓	(1) GC-MS for identification of residual organic solvent; and (2) TGA for quantification of total residual organic solvent.
Total residual solvent (mg/g)	✓	0 ± 2.11
Assignment of total non-volatiles content	✓	(1) TGA for quantification of total non-volatiles/inorganics; and (2) ICP-MS and ICP-HR-MS for identification and quantification of non- volatiles/inorganics.
Total non-volatiles (mg/g)	✓	0 ± 3.27

CCQM-K148.a (Bisphenol A)	*INMETRO*	Assignment of Mass fraction of Main Component in an Organic Solid
Scope of comparison: The measurement results are representative of the laboratory's capability for the purity assignment of organic compounds in the molecular weight range 75 - 500 with pK_{ow} < -2.		
• Value assignment of Primary Reference: Main component mass fraction and uncertainty		
Competency	**✓,× or N/A**	**Specific Information**
Identity verification	✓	MS (from LC-MS/MS and GC-MS) and NMR spectra according to bisphenol A structure; UV spectrum, LC and GC retention time according to a commercial reagent of bisphenol A.
Assignment of main component mass fraction content of CCQM-K148.a	✓	qNMR combined with mass balance Mass balance considered related structure substances, water, residual solvent and inorganics
Bisphenol A content (mg/g)		995.7 ± 1.2 mg/g (k = 2)
• Value assignment of Primary Reference: Impurity class mass fraction and uncertainty (required if using a mass balance method, otherwise optional)		
Assignment of related structure impurity	✓	Related structure impurities were quantified by area normalization both in LC-DAD and GC-FID as no reference standards for the relevant impurities were available.
Related structure impurity (mg/g)		3.26 ± 0.54 mg/g (k = 2)
Assignment of water content	✓	Coulometric Karl Fischer Titration and TGA
Category of water content assignment*	✓	non-polar organic solid, water content < 2 mg/g
Water content (mg/g)		0.82 ± 0.15 mg/g (k = 2)
Assignment of residual solvent content	✓	HS-GC-MS
Total residual solvent (mg/g)		0.0000 ± 0.0086 mg/g (k = 2)
Assignment of total non-volatiles content	✓	ICP-MS and ICP-OES
Total non-volatiles (mg/g)		0.000 ± 0.028 mg/g (k = 2)

CCQM-K148.a (Bisphenol A)	***KRISS***	**Assignment of Mass fraction of Main Component in an Organic Solid**
Scope of comparison: The measurement results are representative of the laboratory's capability for the purity assignment of organic compounds in the molecular weight range 75 - 500 with pK_{ow} < -2.		
• Value assignment of Primary Reference: Main component mass fraction and uncertainty		
Competency	**✓,× or N/A**	**Specific Information**
Identity verification	✓	Comparison with LC/UV, GC/MS and NMR
Assignment of main component mass fraction content of CCQM-K148.a	✓	Combining mass balance method and qNMR method
Bisphenol A content (mg/g)		995.87 ± 2.02 mg/g
• Value assignment of Primary Reference: Impurity class mass fraction and uncertainty (required if using a mass balance method, otherwise optional)		
Assignment of related structure impurity	✓	GC/FID
Related structure impurity (mg/g)		2.21 ± 0.051 mg/g (with 95 % of confidence level , *k*=2.26)
Assignment of water content	✓	KFT coulometry
Category of water content assignment*		non-polar organic solid, water content < 2 mg/g
Water content (mg/g)		0.79 ± 0.29 mg/g (with 95 % of confidence level , *k*=4.30)
Assignment of residual solvent content	✓	Headspace GC/MS
Total residual solvent (mg/g)		0.60 ± 1.36 mg/g (with 95 % of confidence level , *k*=2.20)
Assignment of total non-volatiles content	✓	TGA
Total non-volatiles (mg/g)		0.050 ± 0.11 mg/g (with 95 % of confidence level , *k*=4.30)

CCQM-K148.a (Bisphenol A)	*LGC*	Assignment of Mass fraction of Main Component in an Organic Solid
Scope of comparison: The measurement results are representative of the laboratory's capability for the purity assignment of organic compounds in the molecular weight range 75 - 500 with pK_{ow} < -2.		
• Value assignment of Primary Reference: Main component mass fraction and uncertainty		
Competency	**✓,× or N/A**	**Specific Information**
Identity verification	✓	NMR, HPLC-UV-MS/MS, comparison with independent sample
Assignment of main component mass fraction content of CCQM-K148.a	✓	Combination of mass balance approach (indirect) and qNMR approach (direct)
Bisphenol A content (mg/g)		**995.8, U = 2.5**
Assignment of related structure impurity	✓	qNMR, HPLC-UV-MS/MS
Related structure impurity (mg/g)		**2.8, U = 1.0**
Assignment of water content	✓	Coulometric Karl Fischer titration with oven transfer, TGA as supporting
Category of water content assignment*	✓	Non-polar organic solid, water content > 2 mg/g, < 20 mg/g
Water content (mg/g)		**0.87, U = 1.06**
Assignment of residual solvent content	✓	qNMR, TGA as supporting
Total residual solvent (mg/g)		**None detected, U = 1.16**
Assignment of total non-volatiles content	✓	ICP-MS, TGA as supporting
Total non-volatiles (mg/g)		**1.02, U = 0.51**

CCQM-K148.a (Bisphenol A)	*NIM*	Assignment of Mass fraction of Main Component in an Organic Solid
Scope of comparison: The measurement results are representative of the laboratory's capability for the purity assignment of organic compounds in the molecular weight range 75 -500 with pK_{ow}< -2.		
• Value assignment of Primary Reference: Main component mass fraction and uncertainty		
Competency	**✓,× or N/A**	**Specific Information**
Identity verification	✓	NMR, LC-MS/MS,GC-MS/MS,LC-DAD (retention time and UV-spectrum against commercial standard)
Assignment of main component mass fraction content of CCQM-K148.a	✓	Mass Balance
Bisphenol A content (mg/g)	996.41, *U*=2.17	Reported comparison result (± $U_{95\%}$)
• Value assignment of Primary Reference: Impurity class mass fraction and uncertainty (required if using a mass balance method, otherwise optional)		
Assignment of related structure impurity	✓	LC-MS/MS,GC-MS/MS,LC-DAD
Related structure impurity (mg/g)	3.21, *U*=2.16	Reported comparison result (± $U_{95\%}$)
Assignment of water content	✓	Volumetric Karl Fischer Titration
Category of water content assignment*		non-polar organic solid, water content < 2 mg/g
Water content (mg/g)	0.342, *U* =0.127	Reported comparison result (± $U_{95\%}$)
Assignment of residual solvent content	✓	QNMR,GC-FID
Total residual solvent (mg/g)	0.035, *U* =0.012	Reported comparison result (± $U_{95\%}$)
Assignment of total non-volatiles content	✓	ICP-MS
Total non-volatiles (mg/g)	0.0046, *U* =0.0028	Reported comparison result (± $U_{95\%}$)

CCQM-K148.a (Bisphenol A)	*NIMT*	Assignment of Mass fraction of Main Component in an Organic Solid
Scope of comparison: The measurement results are representative of the laboratory's capability for the purity assignment of organic compounds in the molecular weight range 75 - 500 with pK_{ow} < -2.		
• Value assignment of Primary Reference: Main component mass fraction and uncertainty		
Competency	**✓,× or N/A**	**Specific Information**
Identity verification	✓	comparison with commercial BPA standard (Dr.Ehrenstofer) using HPLC-PDA
Assignment of main component mass fraction content of CCQM-K148.a	✓	Mass balance approach
Bisphenol A content (mg/g)		987.8 ± 5.6 ($U_{95\%}$)
• Value assignment of Primary Reference: Impurity class mass fraction and uncertainty (required if using a mass balance method, otherwise optional)		
Assignment of related structure impurity	✓	HPLC-PDA
Related structure impurity (mg/g)		8.31 ± 3.52 ($U_{95\%}$)
Assignment of water content	✓	Karl Fischer Titration (KFT)
Category of water content assignment*		non-polar organic solid, water content > 2 mg/g, < 20 mg/g
Water content (mg/g)		3.85 ± 4.23 ($U_{95\%}$)
Assignment of residual solvent content	✓	Thermogravimetric Analysis (TGA)
Total residual solvent (mg/g)		0 ± 0.83 ($U_{95\%}$)
Assignment of total non-volatiles content	✓	Thermogravimetric Analysis (TGA)
Total non-volatiles (mg/g)		0 ± 0.83 ($U_{95\%}$)

The result reported by NIMT was not consistent with the KCRV at the 95% confidence interval and the DoE did not cross zero. No information was provided to indicate the cause of this deviation.

CCQM-K148.a (Bisphenol A)	*NMIA*	Assignment of Mass fraction of Main Component in an Organic Solid
Scope of comparison: The measurement results are representative of the laboratory's capability for the purity assignment of organic compounds in the molecular weight range 75 - 500 with pK_{ow} < -2.		
• Value assignment of Primary Reference: Main component mass fraction and uncertainty		
Competency	**✓,× or N/A**	**Specific Information**
Identity verification	✓	^{1}H NMR, GC-MS and LC-MS (ESI negative ion mode). Also comparison with independent sample sourced from Sigma Aldrich
Assignment of main component mass fraction content of CCQM-K148.a	✓	Mass balance: GC-FID to determine mass fraction of isomeric impurity, Karl Fischer, ^{1}H NMR for solvent content and a second (minor) impurity. Non-volatile residue (inorganics) was assessed by qNMR i.e. 1000 mg/g mass fraction of BPA and organic impurities was translated as zero NVR.
Bisphenol A content (mg/g)		997 ± 2 ($U_{95\%}$)
• Value assignment of Primary Reference: Impurity class mass fraction and uncertainty (required if using a mass balance method, otherwise optional)		
Assignment of related structure impurity	✓	GC-FID to determine mass fraction of isomeric impurity, ^{1}H NMR the second (minor) impurity. Supporting evidence provided by HPLC-UV.
Related structure impurity (mg/g)		3 ± 0.3 ($U_{95\%}$)
Assignment of water content	✓	Karl Fischer titration
Category of water content assignment*		non-polar organic solid, water content < 2 mg/g
Water content (mg/g)		0 ± 1.4 ($U_{95\%}$)
Assignment of residual solvent content	✓	^{1}H NMR with supporting evidence from qualitative HS-GC-MS
Total residual solvent (mg/g)		0 ± 0 ($U_{95\%}$)
Assignment of total non-volatiles content	✓	qNMR i.e. 1000 mg/g mass fraction of BPA and organic impurities was translated as zero NVR.
Total non-volatiles (mg/g)		0 ± 0.7 ($U_{95\%}$) The uncertainty was assigned as the standard error of the mean of the qNMR determined purity value.

CCQM-K148.a (Bisphenol A)	*NMIJ*	Assignment of Mass fraction of Main Component in an Organic Solid
Scope of comparison: The measurement results are representative of the laboratory's capability for the purity assignment of organic compounds in the molecular weight range 75 - 500 with pK_{ow} < -2.		
• Value assignment of Primary Reference: Main component mass fraction and uncertainty		
Competency	**✓,× or N/A**	**Specific Information**
Identity verification	✓	NMR, HPLC-UV, HPLC-CAD, LC/MS(qTOF)
Assignment of main component mass fraction content of CCQM-K148.a	✓	qNMR mass balance approach freezing point depression method
Bisphenol A content (mg/g)		996.1, *U* = 1.0
• Value assignment of Primary Reference: Impurity class mass fraction and uncertainty (required if using a mass balance method, otherwise optional)		
Assignment of related structure impurity	✓	HPLC-UV, HPLC-CAD, LC/MS(qTOF)
Related structure impurity (mg/g)		3.522, *U* = 1.082
Assignment of water content	✓	KFT
Category of water content assignment*		non-polar organic solid, water content < 2 mg/g
Water content (mg/g)		0.460, *U* = 0.098
Assignment of residual solvent content	✓	GC-FID
Total residual solvent (mg/g)		0.05, *U* = 0.05
Assignment of total non-volatiles content	✓	TGA
Total non-volatiles (mg/g)		0.056, *U* = 0.054

CCQM-K148.a (Bisphenol A)	*NMISA*	Assignment of Mass fraction of Main Component in an Organic Solid
Scope of comparison: The measurement results are representative of the laboratory's capability for the purity assignment of organic compounds in the molecular weight range 75 - 500 with pK_{ow} < -2.		
• Value assignment of Primary Reference: Main component mass fraction and uncertainty		
Competency	**✓,× or N/A**	**Specific Information**
Identity verification	✓	Identity verified through: 1. Retention time match with standards 2. EI-MS NIST library match 3. Proton NMR comparison with standard
Assignment of main component mass fraction content of CCQM-K148.a	✓	Combination of mass balance and QNMR. For mass balance approach: 1) structurally related impurities were determined using LC-UV and GC-MS/FID, 2) non-volatiles by TGA and EA, 3) residual solvent by GC-MS and 4) water by KF oven transfer coulometry For QNMR, the BPA fraction was determined by subtraction of structurally related impurities (determined by#1 above) from the Total BPA signal QNMR result
Bisphenol A content (mg/g)		**989.6 ± 8.0 mg/g**
• Value assignment of Primary Reference: Impurity class mass fraction and uncertainty (required if using a mass balance method, otherwise optional)		
Assignment of related structure impurity	✓	structurally related impurities determined using LC-UV and GC-MS/FID. RRF from calibration curves or estimated by retention time and mass spectra. LC and GC values were combined to provide the final result.
Related structure impurity (mg/g)		**7.1 ± 2.8 mg/g**
Assignment of water content	✓	Water content not detected below LOD of 100 ug water in 50 mg sample (2 mg/g).
Category of water content assignment*		non-polar organic solid, water content < 2 mg/g
Water content (mg/g)		**< 0.1 + 0.62/-0 mg/g**
Assignment of residual solvent content	✓	Headspace gas chromatography mass spectrometry
Total residual solvent (mg/g)		**0.00065 ± 0.00040 mg/g**
Assignment of total non-volatiles content	✓	Thermal Gravimetric Analysis
Total non-volatiles (mg/g)		**<1 +0.79/-0 mg/g**

CCQM-K148.a (Bisphenol A)	*NRC*	Assignment of Mass fraction of Main Component in an Organic Solid
Scope of comparison: The measurement results are representative of the laboratory's capability for the purity assignment of organic compounds in the molecular weight range 75 - 500 with pK_{ow} < -2.		
• Value assignment of Primary Reference: Main component mass fraction and uncertainty		
Competency	**✓,× or N/A**	**Specific Information**
Identity verification	✓	Based on LC-UV, LC-MS and ^{1}H-NMR as well as a comparison with an independent sample
Assignment of main component mass fraction content of CCQM-K148.a	✓	Internal standard ^{1}H-qNMR
Bisphenol A content (mg/g)		993.7 ± 4.8 mg/g
• Value assignment of Primary Reference: Impurity class mass fraction and uncertainty (required if using a mass balance method, otherwise optional)		
Assignment of related structure impurity	✓	Identification by LC-HRMS and quantitation by LC-UV
Related structure impurity (mg/g)		4.06 ± 0.80 mg/g
Assignment of water content	**N/A**	Indicate method(s) used to quantify mass fraction water content in the material
Category of water content assignment*	**N/A**	Select from list below* the applicable category of general water content assignment competency
Water content (mg/g)	**N/A**	Reported comparison result (± $U_{95\%}$)
Assignment of residual solvent content	**N/A**	Indicate method(s) used to quantify mass fraction residual solvent content in the material
Total residual solvent (mg/g)	**N/A**	Reported comparison result (± $U_{95\%}$)
Assignment of total non-volatiles content	**N/A**	Indicate method(s) used to quantify mass fraction total non-volatile content in the material
Total non-volatiles (mg/g)	**N/A**	Reported comparison result (± $U_{95\%}$)

CCQM-K148.a (Bisphenol A)	*UME*	Assignment of Mass fraction of Main Component in an Organic Solid
Scope of comparison: The measurement results are representative of the laboratory's capability for the purity assignment of organic compounds in the molecular weight range 75 - 500 with pK_{ow} < -2.		
• Value assignment of Primary Reference: Main component mass fraction and uncertainty		
Competency	**✓,× or N/A**	**Specific Information**
Identity verification	✓	HPLC-UV
Assignment of main component mass fraction content of CCQM-K148.a	✓	Mass Balance (HPLC-UV, TGA, Karl Fischer, TD GC-MS, HS GC-MS), qNMR
Bisphenol A content (mg/g)		996.4 ± 6.06
• Value assignment of Primary Reference: Impurity class mass fraction and uncertainty (required if using a mass balance method, otherwise optional)		
Assignment of related structure impurity	✓	Mass Balance (HPLC-UV, TGA, Karl Fischer, TD GC-MS, HS GC-MS), qNMR
Related structure impurity (mg/g)		2.89 ± 0.54 mg/g
Assignment of water content	✓	Coulometric Karl Fischer titration with oven transfer and Thermal Gravimetric Analysis
Category of water content assignment*		Non-polar organic solid, water content < 2 mg/g
Water content (mg/g)		$0.05 \pm 1.47 \times 10^{-6}$
Assignment of residual solvent content	✓	HS GC-MS and qNMR
Total residual solvent (mg/g)		0
Assignment of total non-volatiles content	✓	TGA
Total non-volatiles (mg/g)		0

CCQM-K148.a (Bisphenol A)	*VNIIM*	Assignment of Mass fraction of Main Component in an Organic Solid
Scope of comparison: The measurement results are representative of the laboratory's capability for the purity assignment of organic compounds in the molecular weight range 75 - 500 with $pK_{OW} < -2$.		
• Value assignment of Primary Reference: Main component mass fraction and uncertainty		
Competency	**✓,× or N/A**	**Specific Information**
Identity verification	✓	Comparison with library mass-spec. NIST 14; Comparison with Standard (UV, mass-spec. and RT)
Assignment of main component mass fraction content of CCQM-K148.a	✓	Mass balance approach: Related structure imp. - LC/MS, LC/DAD, LC/ELSD, GC/MS Residual solvent – GC/MS, LC/DAD; Water - KF titration with oven; Non-volatiles - ICP/MS/MS
Bisphenol A content (mg/g)		997.75 ± 0.29 [revised value = 996.42 ± 0.50]
• Value assignment of Primary Reference: Impurity class mass fraction and uncertainty (required if using a mass balance method, otherwise optional)		
Assignment of related structure impurity	✓	LC/MS, LC/DAD, LC/ELSD, GC/MS
Related structure impurity (mg/g)		1.89 ± 0.28 (including residual solvent) [revised value = 3.22 ± 0.49]
Assignment of water content	✓	KF titration with oven
Category of water content assignment*	N/A	
Water content (mg/g)		0.36 ± 0.08
Assignment of residual solvent content	✓	GC/MS, LC/DAD
Total residual solvent (mg/g)		measured as related structure impurities
Assignment of total non-volatiles content	✓	ICP/MS/MS
Total non-volatiles (mg/g)		≤ 0.001 ± 0.0005

The result initially reported by VNIIM was not consistent with the KCRV at the 95% confidence interval and the DoE did not cross zero. On investigation they identified the cause for this overestimation and reported a revised value of 996.42 ± 0.50 mg/g compatible with the KCRV.

REFERENCES

1 See discussion in Section 5.2.2 of Version 1.0 of the *CCQM Strategy Document for Rolling Programme Development 2017-2026*

2 See definition in ISO 17511: 2003; *In vitro diagnostic medical devices. Metrological traceability of values assigned to calibrators and control materials*

3 CIPM MRA-D-05 *Measurement comparison in the CIPM MRA*: see http://www.bipm.org/en/cipm-mra/cipm-mra-documents/

4 OAWG-19-064 in OAWG Meeting documents for October 2019

5 CCQM-18-39: *Report from the OAWG* presented at the 24th Meeting of the CCQM in 2018.

6 European Food Safety Authority document (https://www.efsa.europa.eu/en/topics/topic/bisphenol)

7 pK_{OW} value of BPA predicted using XLogP3 version 3.0 software (PubChem release 2019.06.18)

8 J. Poskrobko et al; *J. Chrom. A*, 2000, **883**, 291-297

9 L. E. Brydia, *Anal. Chem*., 1968, **40**, 2212-2215

10 CCQM-P187.a Final Report (*In preparation*)

11 M. Terasaki et al; *Chemosphere*, 2004, **55**, 927-931

12 CCQM-11-18, 17th CCQM meeting (https://www.bipm.org/cc/CCQM/Restricted/17/CCQM11-18.pdf)

13 CCQM-13-22, 19th CCQM meeting (https://www.bipm.org/cc/CCQM/Restricted/19/CCQM13-22_Consensus_KCRV_v10.pdf)

14 Assistance with the calculation of the HB REM values including estimates of the derived DoE values for results for participants whose values were not included in the KCRV calculation was provided by Michael Nelson and Antonio Possolo from NIST.

15 Minutes of OAWG meeting May 2020 (File OAWG/20-034 in the “May 2020” OAWG webfolder)

16 A. Koepke et al; *Metrologia*, 2017, **54**, S34-S62