Assessment of the chemical and enantiomeric purity of organic reference materials

Yiu-chung Yip, Siu-kay Wong, Sik-man Choi

This review evaluates commonly used methodologies for assessing the chemical purity of organic reference materials. Direct assay of the principal component can be established by methodologies such as gas chromatography, liquid chromatography (LC), quantitative nuclear magnetic resonance (NMR), elemental analysis and titrimetry. Measurements of detectable impurity components mainly include determination of water or moisture content, and analysis of residual solvents, and organic and inorganic impurities. To complete assessment of chemical purity, it is necessary to determine the enantiomeric purity of chiral organic reference materials. Promising methodologies for analysis include LC with chiral stationary phases, capillary electrophoresis using chiral selectors, and NMR with chemical-shift reagents.

Keywords: Chemical purity; Differential scanning calorimetry; Enantiomeric purity; Gas chromatography; Inductively coupled plasma mass spectrometry; Ion chromatography; Karl Fischer titration; Liquid chromatography; Organic reference material; Quantitative nuclear magnetic resonance

Yiu-chung Yip*, Siu-kay Wong
Government Laboratory, Ho Man Tin Government Offices, 88 Chung Hau Street, Kowloon, Hong Kong, Hong Kong Special Administrative Region, China

Sik-man Choi
Centre for Food Safety, Food and Environmental Hygiene Department, 43/F, Queensway Government Offices, 66 Queensway, Hong Kong, Hong Kong Special Administrative Region, China

*Corresponding author.
Tel.: +852 27623862;
Fax: +852 27151737;
E-mail: ycyip@govtlab.gov.hk

1. Introduction

Participation of national metrology institutes/designated institutes (NMIs/DIs) in international intercomparisons (both pilot studies and key comparisons) serves three metrological purposes [1,2]:

(1) fulfilling the essential requirements of the Mutual Recognition Arrangement of the International Committee for Weights and Measures (CIPM MRA) for the demonstration of technical competence and capability;
(2) demonstrating the degree of equivalence of national measurement standards maintained by NMIs; and,
(3) providing the technical basis for confidence in declarations of calibration and measurement capabilities (CMCs) as shown in the key comparison database (KCDB) [3].

Purity assessment is one of the crucial steps for the production of organic reference materials, whose certified values should be reported with a credible statement of measurement uncertainty. The Organic Analysis Working Group (OAWG) of the *Comité Consultatif pour la Quantité de Matière* (CCQM) has been organizing a series of international intercomparisons relating to the characterization of organic substances for chemical purity since 2001 (Table 1) [4–9]. To demonstrate technical competence and capability on purity assignment, NMIs/DIs have made great efforts to develop methodologies for the following aspects (Table 2):

(1) direct estimate of the principal component; and,
(2) estimates of impurity components (e.g. water, residual solvents, organic and inorganic impurities).

This eventually allows NMIs/DIs to assess the purity of their own standards that are used for subsequent calibration purposes. In other words, participation in those intercomparisons serves as an effective means of demonstrating the degree of equivalence of the calibration standards that they produced. Also, this provides convincing evidence to underpin their CMC claims on the provision of organic reference materials.

To avoid confusion, definitions of the two commonly encountered terms, namely ''reference material'' and ''certified reference material'' respectively, are given in ISO Guide 30 ''Terms and Definitions

0165-9936/$ - see front matter © 2011 Elsevier Ltd. All rights reserved. doi:10.1016/j.trac.2010.12.003

Table 1. CCQM pilot studies/key comparisons relating to the characterization of organic substances for chemical purity

CCQM pilot study/key comparison	Organic substance	Coordinating laboratory	Start date	Status	Ref.
CCQM-P20.a	Tributyltin chloride	National Measurement Institute, Australia	2001	Completed	[4]
CCQM-P20.b	*o*-Xylene	National Institute of Standards & Technology	2002	Completed	
CCQM-P20.c.1 & CCQM-P20.c.2	Atrazine	National Measurement Institute, Australia	2003 2004	Completed Completed	[5]
CCQM-P20.d	Chlorpyrifos	National Measurement Institute, Australia	2003	Completed	[6]
CCQM-P20.e	Theophylline	Bureau International des Poids et Mesures/Laboratory of the Government Chemist	2006	Completed	[7]
CCQM-P20.f	Digoxin	Bureau International des Poids et Mesures/Laboratory of the Government Chemist	2007	Draft A summary report available	[8]
CCQM-K55.a/P117.a	17β-Estradiol	Bureau International des Poids et Mesures/National Metrology of Institute of Japan	2008	Preliminary result summary available	[9]

Table 2. Commonly used methodologies for the assessment of chemical purity

Property of organic substance	Methodology commonly used for giving direct estimate of the principal component
GC-detectable organic substance	• Gas chromatography-flame ionization detection (GC-FID)
UV/Vis-active organic substance	• Liquid chromatography-ultraviolet spectroscopy (LC-UV/Vis)
Integrated intensity of a resonance due to the analyte nuclei (e.g. ^{1}H)	• Quantitative nuclear magnetic resonance (qNMR)
Elemental carbon, hydrogen and nitrogen	• Elemental analysis (EA)
Possible impurity	**Methodology commonly used for giving estimates of impurity components**
Impurities that dissolve in the melt and are insoluble in the crystal	• Differential scanning calorimetry (DSC)
Water/moisture	• Loss on drying at a specified temperature • Karl-Fischer titration
Residual solvents	• Gas chromatography (GC-FID, GC-MS) • Nuclear magnetic resonance (NMR)
Inorganic impurities Anions (e.g., chloride and nitrate)	• Ion chromatography (IC)
Metallic impurities (e.g., Fe, Al, Ni, Cr)	• Inductively coupled plasma-mass spectrometry (ICP-MS) • Inductively coupled plasma-atomic emission spectrometry (ICP-AES) • X-ray fluorescence spectrometry (XRF)
Unidentified UV-active materials	• LC-UV

Used in Connection with Reference Materials'' [10], which is prepared by ISO REMCO (International Organization for Standardization Committee on Reference Materials). The definitions are as follows: