National Research Council Canada | Conseil national de recherches Canada

Certificate of Analysis

Certified Reference Material

THCA-1

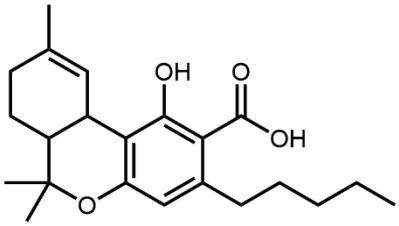
Delta-9-tetrahydrocannabinolic Acid Calibration Solution Certified Reference Material

THCA-1 is a calibration solution certified reference material (CRM) for the cannabinoid delta-9-tetrahydrocannabinolic acid (Δ^9-THCA), in acetonitrile. This material, distributed in 1 mL units, is intended for instrument calibration, method development, validation, and quantitation of Δ^9-THCA in cannabis, hemp, and other cannabis-derived products. Certified values for the mass fraction and mass concentration of delta-9-tetrahydrocannabinolic acid in THCA-1 have been established, as listed in Table 1. The information values for the mass fraction and mass concentration of minor impurities in THCA-1 are provided in Table 2.

The certified values of delta-9-tetrahydrocannabinolic acid in a solution of acetonitrile are based on results from data generated at the National Research Council of Canada (NRC) using quantitative proton nuclear magnetic resonance spectroscopy with internal calibration. The expanded uncertainty (U) for all values is equal to $U = ku_c$ where u_c is the combined standard uncertainty calculated according to the JCGM Guide [1] and k is the coverage factor of two ($k = 2$, 95 % confidence interval, CI). It is intended that the U for certified values accounts for every aspect that reasonably contributes to their uncertainties.

Table 1: Certified values and expanded uncertainties ($k = 2$, 95 % CI) for THCA-1

Substance	Symbol	Molecular formula	Mass fraction mg/g	Mass concentration at 21 °C mg/mL
delta-9-tetrahydrocannabinolic acid (a)	Δ^9-THCA	$C_{22}H_{30}O_4$	1.29 ± 0.05	1.01 ± 0.04



delta-9-tetrahydrocannabinolic acid (Δ^9-THCA)

CAS registry number: 23978-85-0
InChI Key: UCONUSSAWGCZMV-HZPDHXFCSA-N
Molecular formula: $C_{22}H_{30}O_4$
Molar mass: 358.47 ± 0.03 g/mol

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Table 2: Information values for THCA-1

Substance	Symbol	CAS number	Molecular formula	Mass fraction µg/g	Mass concentration at 21 °C µg/mL
cannabinolic acid (b)	CBNA	2808-39-1	$C_{22}H_{26}O_4$	6.4	5.0
tetrahydrocannabivarinic acid (b)	THCVA	39986-26-0	$C_{20}H_{26}O_4$	6.1	4.8
delta-9-tetrahydrocannabinol (b)	Δ^9-THC	1972-08-3	$C_{21}H_{30}O_2$	3.8	3.0

Coding

The coding refers to the instrument method used for value assignment:

- **a** Internal standard quantitative proton nuclear magnetic resonance spectroscopy with ^{13}C-decoupling ($^1H\{^{13}C\}$-qNMR)
- **b** Liquid chromatography – tandem mass spectrometry (LC−MS/MS)

Certified values

Certified values are considered to be those for which the NRC has the highest confidence in accuracy and that all known and suspected sources of bias have been taken into account and are reflected in the stated expanded uncertainties. Certified values are the best estimate of the true value and uncertainty (Table 1).

Information values

Information values are those for which insufficient data are available to provide a comprehensive estimate of uncertainty (Table 2).

Intended use

Distributed in 1 mL units, this certified reference material is primarily intended for use in method development and in the calibration of instrumentation for the quantitative analysis of delta-9-tetrahydrocannabinolic acid.

Storage

It is recommended that the material be stored in a controlled cold temperature environment such as a freezer at approximately –20 °C or below.

Instructions for use

Prior to opening, each ampule should be allowed to warm to room temperature and the contents should be thoroughly mixed. The ampule should be opened at the pre-scored mark immediately prior to use. The certified value is only guaranteed if the ampule is sampled immediately after opening in order to limit solvent evaporation.

For applications where metrological traceability is not required, users can consider transferring the content to a sealed glass vial and should take responsibility for demonstrating stability at appropriate storage conditions in their own laboratories.

Please note that the volume of the solution is not certified; only the concentration is certified. Therefore, the entire contents of the ampule should not be diluted to volume. It is recommended that the CRM solution should not be evaporated to dryness.

The mass concentration values reported were calculated from the mass fraction values using a density of 0.781 ± 0.004 g/mL (k = 2, 95 % confidence interval) at 21 °C determined at the NRC on the actual CRM solution. However, note that the density of acetonitrile changes by 0.14 % per degree Celsius (in the interval of 15 to 30 °C; decreasing density with increasing temperature).

Preparation of material

The calibration solution was prepared by dissolving a sample of solid delta-9-tetrahydrocannabinolic acid, provided by Canopy Growth Corporation (Ontario, Canada), in acetonitrile. The purity of the solid delta-9-tetrahydrocannabinolic acid was certified by $^{1}H\{^{13}C\}$-qNMR with an internal standard. The calibration solution was dispensed in 1 mL aliquots in clean amber glass ampules. The ampules were immediately flame-sealed in a controlled environment at 20 % relative humidity.

Stability

The transportation and long-term stability of THCA-1 was assessed using liquid chromatography with UV detection (LC–UV) at one-, two-, four-, and eight-week time points using an isochronous approach at +50, +20, +4, and –20 °C temperatures with reference to samples held at –80 °C. Degradation of Δ^9-THCA in acetonitrile was observed at temperatures over +4 °C after 2 weeks when compared to the reference samples, therefore it is advised to keep the material in a freezer until needed. A pseudo first-order degradation model was fitted to the data along with the Arrhenius model to make predictions for degradation of Δ^9-THCA in acetonitrile. The uncertainty due to transportation includes an estimate of instability at +20 °C for one-week to represent any significant shipping delays. The long-term stability was projected for five years at the recommended storage temperature of –20 °C.

Homogeneity

The material is expected to have a high degree of homogeneity as it is a pure solution. The homogeneity was tested at the NRC using LC–UV. Results from a representative number of ampules across the fill series were evaluated using the analysis of variance (ANOVA) random effects model [2, 3]. The between-unit variability was determined to be negligible, therefore, the material is deemed to be homogeneous.

Uncertainty

Included in the combined uncertainty estimate (u_c) are uncertainties in the batch characterization (u_{char}), uncertainties related to possible between-unit variation (u_{hom}), uncertainties related to stability ($u_{stability}$), and uncertainties related to the measurement of the density of the CRM solution ($u_{density}$). Expressed as standard uncertainties, these components are listed in Table 3.

Table 3: Uncertainty components for THCA-1

Substance	Unit	$U_{k=2}$	u_c	u_{char}	u_{hom}	$u_{stability}$	$u_{density}$
delta-9-tetrahydrocannabinolic acid	mg/g	0.05	0.025	0.008	0.000	0.024	NA
	mg/mL	0.04	0.02	0.007	0.000	0.019	0.003

Metrological traceability

Results presented in this certificate are traceable to the SI through gravimetrically prepared standards of NIST PS1 benzoic acid, which was used to assign purity to dimethyl terephthalate, employed as an internal standard for $^{1}H\{^{13}C\}$-qNMR. As such, THCA-1 serves as a suitable reference material for laboratory quality assurance programs, as outlined in ISO/IEC 17025.

Quality Management System (ISO 17034, ISO/IEC 17025)

This material was produced in compliance with the NRC Metrology Quality Management System, which conforms to the requirements of ISO 17034 and ISO/IEC 17025. The Metrology Quality Management System supporting the NRC Calibration and Measurement Capabilities, as listed in the *Bureau international des poids et mesures* (BIPM) Key Comparison Database (http://kcdb.bipm.org/), has been reviewed and approved under the authority of the Inter-American Metrology System (SIM), and found to be in compliance with the expectations of the *Comité international des poids et mesures* (CIPM) Mutual Recognition Arrangement. The SIM approval is available upon request.

Updates

Users should ensure that their certificate is current. For updates, please refer to doi.org/10.4224/crm.2023.thca-1.

References

[1] Evaluation of measurement data: Guide to the expression of uncertainty in measurement. JCGM 100:2008. https://www.bipm.org/en/publications/guides/gum.html

[2] T.P.J. Linsinger, J. Pauwels, A.M.H. van der Veen, H. Schimmel, A. Lamberty, Homogeneity and stability of reference materials, Accred Qual Assur (2001), 6: 20-25. https://doi.org/10.1007/s007690000261

[3] ISO (2017), Reference materials – Guidance for the characterization and assessment of homogeneity and instability. ISO Guide 35:2017.

Cited by

A list of scientific publications citing THCA-1 can be found at doi.org/10.4224/crm.2023.thca-1.

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Citation

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This Certificate is only valid if the corresponding material was obtained directly from NRC or an Authorized Reseller.

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