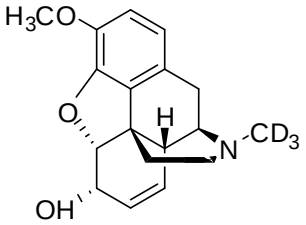
DEUTERATED INTERNAL STANDARD PRODUCT INFORMATION SHEET

NMIA D673: d_3-Codeine base



Report ID: D673.2023.01 (Ampouled 100803)

Chemical Formula: $C_{18}H_{18}D_3NO_3$

Molecular Weight: 302.3 g/mol

Property value

Batch No.	CAS No.	Mass per ampoule
01-D-02	**70420-71-2**	**1001 ± 5 µg**

IUPAC: (5α,6α)-3-Methoxy-17-($^2H_3$)methyl-7,8-didehydro-4,5-epoxymorphinan-6-ol

Expiration of certification: The property values are valid till 14th February 2028 i.e. five years from the date of re-certification provided the **unopened** material is handled and stored in accordance with the recommendations below. The material as issued in the unopened container and stored as recommended below should be suitable for use beyond this date, subject to confirmation of batch stability from the issuing body. The expiry date/shelf life does not apply to ampoules that have been opened. In such cases, it is recommended that the end-user conduct their own in-house stability trials.

Description: The compound is supplied as a dried aliquot in a sealed ampoule under an atmosphere of argon. The deuterated internal standard is intended for a single use to prepare a standard solution containing D673. The material was prepared by synthesis and characterised for identity and purity by NMIA. The main component of this material is d_3-codeine base. d_2-, d_1- and d_0-Codeine base are also present. The stated mass of the analyte per ampoule represents the approximate combined masses of deuterated (d_3, d_2 and d_1) and d_0- codeine base in the material.

Intended use: The isotopic purity of this material is an estimate only. This material should be considered for use as an internal standard only and is not intended for use as a calibrator. The material does not have certified reference material status as metrological traceability of the stated purity value to the SI unit for mass (kg) has not been established.

Instructions for use: Open the ampoule and carefully rinse the interior at least three times with a suitable organic solvent (e.g. Chloroform). This will transfer approximately 1001 µg of anhydrous codeine (d_3, d_2, d_1 and d_0). The mass of analyte in each ampoule is calculated from the assigned purity of the bulk and the concentration of bulk material in a stock solution used to prepare the ampoules.

Recommended storage: When not in use, this material should be stored at or below 4 ºC in a closed container in a dry, dark area.

Stability: At the recommended storage conditions this material has demonstrated stability over a minimum period of three years. The measurement uncertainty at the 95% coverage interval includes a stability component which has been estimated from annual stability trials. The long-term stability of the compound in solution has not been examined.

Homogeneity assessment: The homogeneity of the material was assessed using purity assay by GC-FID on seven randomly selected ampoules of the material. The material was judged to be homogeneous at this level of sampling as the variation in analysis results between samples was not significantly different at a 95% confidence level from that observed on repeat analysis of the same sample.

Safety: Treat as hazardous substance. Use appropriate work practices when handling to avoid skin or eye contact, ingestion or inhalation of dust. Refer to the provided safety data sheet.

S. R. Davies

Dr Stephen R. Davies,
Team Leader,
Chemical Reference Materials, NMI.
6 March 2023

This report supersedes any issued prior to 06 March 2023.

NATA Accreditation No. 198 / Corporate Site No. 14214.

Legal notice: Terms and Conditions associated with the provision of this reference material can be found on the NMIA website.

Characterisation Report:

GC-FID:	Instrument:	Varian 3800
	Column:	VF-1, 30 m × 0.32 mm × 0.25 μm
	Program:	200 °C (1 min), 8 °C/min to 230 °C (5 min), 10 °C/min to 290 °C (1 min)
	Injector:	250 °C
	Detector Temp:	320 °C
	Carrier:	Helium
	Split ratio:	20/1
	Relative peak area response of main component:	
	Initial-analysis:	Mean = 99.7%, s = 0.01% (7 ampoules in duplicate, August 2010)
GC-FID:	Instrument:	Agilent 6890/8890
	Column:	HP-1, 30 m × 0.32 mm × 0.25 μm
	Program:	200 °C (1 min), 8 °C/min to 230 °C (5 min), 10 °C/min to 300 °C (3 min)
	Injector:	250 °C
	Detector Temp:	320 °C
	Carrier:	Helium
	Split ratio:	20/1
	Relative peak area response of main component:	
	Initial-analysis:	Mean = 99.6%, s = 0.04% (5 ampoules in duplicate, August 2013)
	Re-analysis	Mean = 99.5%, s = 0.09% (5 ampoules in duplicate, June 2018)
	Re-analysis	Mean = 99.6%, s = 0.14% (5 ampoules in duplicate, February 2023)

The following analytical data was obtained on the bulk material subsequently used in the preparation of the ampoules.

The identity was confirmed by a range of spectroscopic techniques, NMR, IR and MS. The indicative purity value was obtained by mass balance from a combination of traditional analytical techniques, including GC-FID, thermogravimetric analysis, Karl Fischer analysis and ^{1}H NMR spectroscopy. The purity value was calculated using Equation 1.

Purity = (100 % - I_{ORG}) x (100 % - I_{VOL} – I_{NVR}) Equation 1

I_{ORG} = Organic impurities of related structure, I_{VOL} = volatile impurities, I_{NVR} = non-volatile residue.

Supporting evidence is provided by elemental microanalysis.

The main component of this material is d_3-codeine base with d_2-, d_1- and d_0- codeine base also present. The stated chemical purity represents the combined mass fraction of deuterated (d_3, d_2 and d_1) and d_0- codeine base in the material.

The isotopic purity of this material is an estimate only. This material should be considered for use as an internal standard only.

Isotopic purity:		$d_3 \approx 98.6$ % [= 100 × d_3 / (d_0 + d_1 + d_2 + d_3)]
		d_0 = 0.4 % [= 100 × (d_0 / d_3)]
GC-FID:	Instrument:	HP5890
	Column:	ZB-1 Capillary, 30 m × 0.32 mm I.D. × 0.25 μm
	Program:	220 °C (2 min), 10 °C/min to 260 °C (12 min)
	Injector:	250 °C
	Detector Temp:	320 °C
	Carrier:	Helium
	Split ratio:	20/1
	Relative peak area response of main component:	
	Initial analysis:	Mean = 99.7%, s = 0.02% (10 sub samples in duplicate, March 2001)
	Re-analysis:	Mean = 99.3%, s = 0.2% (3 sub samples in duplicate, July 2008)
GC-FID:	Instrument:	Varian 3800
	Column:	VF-1, 30 m × 0.32 mm × 0.25 μm
	Program:	200 °C (1 min), 8 °C/min to 230 °C (5 min), 10°C/min to 290°C (1 min)
	Injector:	250 °C
	Detector Temp:	320 °C
	Carrier:	Helium
	Split ratio:	20/1
	Relative peak area response of main component:	
	Initial analysis:	Mean = 99.7%, s = 0.01% (7 sub samples in duplicate, August 2010)
Thermogravimetric analysis:		Volatiles content < 0.1% and non-volatile residue < 0.2 % mass fraction (August 2010)
Karl Fischer analysis:		Moisture content <0.1% mass fraction (August 2010)

Spectroscopic and other characterisation data

GC-MS: Instrument: HP6890/5973

Column:	Zebron ZB-5, 30 m × 0.25 mm I.D. × 0.30 μm
Program:	160 °C (1 min), 12 °C/min to 280 °C (4 min)
Injector:	260 °C
Transfer line temp:	300 °C
Carrier:	Helium
Split ratio:	N/A

The retention time of the parent compound is reported along with the major peaks in the mass spectra. The latter are reported as mass/charge ratios and (in brackets) as a percentage relative to the base peak.

Parent (6.56 min): 302 (M^+, 100), 232 (20), 217 (14), 188 (11), 165 (30), 127 (14), 115 (12) *m/z*

Deuteration yield (by SIM analysis of the parent compound, mean of 7 sub samples)

Column:	Zebron ZB-5, 30 m × 0.25 mm I.D. × 0.30 μm
Program:	160 °C (1 min), 12 °C/min to 280 °C (4 min)
6.80 min:	(Deuteration state, % rel. to d_3-codeine at 302 *m/z*) 299 (d_0, 0.4), 300 (d_1, 0), 301 (d_2, 1.0), 302 (d_3, 100) *m/z*

TLC:	Conditions:	Kieselgel 60F_{254}. Chloroform/methanol/diethylamine (94:5:1) Single spot observed, R_f = 0.2
IR:	Instrument:	FT-IR, Biorad WIN FTS40
	Range:	4000-400 cm^{-1}, KBr powder
	Peaks:	3534, 2228, 2175, 2032, 1637, 1503, 1453, 1386, 1274, 1060 cm^{-1}
^{1}H NMR:	Instrument:	Bruker DMX-600
	Field strength:	600 MHz
	Solvent:	$CDCl_3$ (7.26 ppm)
	Spectral data:	δ 1.88 (1H, d), 2.07 (1H, dt), 2.31 (1H, dt), 3.03 (1H, d), 3.83 (1H, s), 4.89 (1H, d), 5.29 (1H, dt), 5.70 (1H, d), 6.56 (1H, d), 6.65 (1H, d) ppm
^{2}H NMR:	Instrument:	Bruker DMX-600
	Field strength:	77 MHz
	Solvent:	$CHCl_3$
	Spectral data:	δ 2.42 ppm
^{13}C NMR:	Instrument:	Bruker DMX-600
	Field strength:	151 MHz
	Solvent:	$CDCl_3$ (77.16 ppm)
	Spectral data:	δ 20.4, 35.6, 40.7, 42.8, 46.3, 56.2, 58.8, 66.3, 91.2, 112.8, 119.4, 126.9, 128.1, 130.9, 133.4, 142.1, 146.2 ppm
Melting point:		155-156 °C
Microanalysis:	Found:	C = 71.6 %; H/D = 7.9 %; N = 4.7 % (January 2001)
	Calculated:	C = 71.5 %; H/D = 8.0 %; N = 4.6 % (Calculated for $C_{18}H_{18}D_3NO_3$)