Australian Government
Department of Industry, Innovation and Science

National Measurement Institute

NATA
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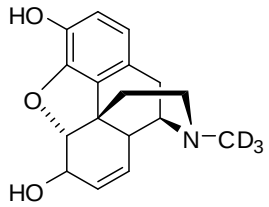
DEUTERATED INTERNAL STANDARD PRODUCT INFORMATION SHEET

NMIA D709: d_3-Morphine

Report ID: D709.2018.01 (Ampouled 091102B)

Chemical Formula: $C_{17}H_{16}D_3NO_3$

Molecular Weight: 288.4 g/mol



Certified value

Batch No.	CAS No.	Mass per ampoule
01-D-14	67293-88-3	928 µg

Expiration of certification: The property values are valid till 13th December 2023, 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 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 and is intended for a single use to prepare a standard solution containing D709. The main component of this material is d_3-morphine. d_2-, d_1- and d_0-Morphine are also present. The stated mass of the analyte per ampoule represents the combined masses of deuterated (d_3, d_2 and d_1) and d_0-morphine in the material. The material was prepared by synthesis or sourced from an external supplier, certified for identity and purity by NMIA.

Intended use: This reference material should be used as an internal standard only.

Instructions for use: Each ampoule contains approximately 928 µg of anhydrous morphine (d_3, d_2, $d_1$and d_0). Open the ampoule and carefully rinse the interior at least three times with a suitable organic solvent (chloroform/methanol 4:1).

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: This material has demonstrated stability over a minimum period of five years. The measurement uncertainty at the 95% confidence 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 sufficiently 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.
24 January 2019.

This report supersedes any issued prior to 17th December, 2018.

NATA logo notice: Accredited for compliance with ISO Guide 17034. Accreditation No. 198 / Corporate Site No. 20844. The results of the tests, calibrations and/or measurements included in this document are traceable to Australian/national standards.

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

Characterisation Report:

The identity was confirmed by a range of spectroscopic techniques, NMR, IR and MS. The certified 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 is calculated as per 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 qualitative elemental microanalysis.

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

Isotopic Purity: $d_3 \approx 98.6\%[= d_3 / (d_0 + d_1 + d_2 + d_3) \times 100]$
$d_0 < 0.4\%[= d_0 / (d_0 + d_1 + d_2 + d_3) \times 100]$

GC-FID:	Instrument:	Agilent 6890N
	Column:	HP-1 Capillary, 30 m × 0.32 mm I.D. × 0.25 µm
	Program:	200 °C (1 min), 10 °C/min to 220 °C (8 min), 30 °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 = 99.4%, s = 0.02% (7 ampoules in duplicate, November 2009)
	Re analysis:	Mean = 99.5%, s = 0.01% (5 ampoules in duplicate, September 2012)

GC-FID:	Instrument:	Varian CP-3820	
	Column:	HP-1 Capillary, 30 m x 0.32 mm I.D. × 0.25 µm	
	Program:	220 °C (1 min), 10 °C/min to 240 °C (8 min), 20 °C/min to 280 °C (10 min)	
	Injector:	250 °C	Detector Temp: 320 °C
	Carrier:	Helium	Split ratio: 20/1
	Relative peak area of main component as the *bis*-TMS derivative:		
	Initial analysis:	Mean = 99.4%, s = 0.02% (7 ampoules in duplicate, November 2018)	

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

Purity estimate obtained by subtraction from 100% of total impurities by GC-FID, thermogravimetric analysis, Karl Fischer and ^{1}H NMR. Supporting evidence provided by elemental microanalysis.

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 250 °C (10 min)
	Injector:	250 °C
	Detector Temp:	320 °C
	Carrier:	Helium
	Split ratio:	20/1
	Relative peak area response of main component:	
	Initial analysis:	Mean = 99.8%, s = 0.1% (10 sub samples in duplicate, February 2002)
	Re-analysis:	Mean = 99.4%, s = 0.1% (5 sub samples in duplicate, September 2006)

GC-FID:	Instrument:	Agilent 6890N
	Column:	HP-1 Capillary, 30 m × 0.32 mm I.D. × 0.25 µm
	Program:	200 °C (1 min), 10 °C/min to 220 °C (8 min), 30 °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:	
	Re-analysis:	Mean = 99.1%, s = 0.04% (5 sub samples in duplicate, September 2009)

Thermogravimetric analysis:	Volatiles content ca. 6%, non-volatile residue content ca.0.7% mass fraction (February 2002, September 2006 & September 2009)
Karl Fisher analysis:	Moisture content ca. 6.5% mass fraction (September 2009)

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:	200 °C (1 min), 10 °C/min to 250 °C (7 min)
	Injector:	250 °C
	Transfer line temp:	300 °C
	Carrier:	Helium, (0.8 mL/min)
	Split ratio:	20/1
	The retention time of the free base is reported along with the major peaks in the mass spectrum. The latter are reported as mass/charge ratios and (in brackets) as a percentage relative to the base peak.	
	9.5 min:	288 (M+, 100), 271 (14), 218 (25), 165 (35), 127 (17), 45 (18) *m/z*
	Deuteration yield (by SIM analysis of d3-codeine precursor, 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)
		(Deuteration state, peak intensity % rel. to d3-morphine at 288 *m/z*) 285 (d0, 0.4), 286 (d1, 0), 287 (d2, 1.0), 288 (d3, 98.6) *m/z*
TLC:	Conditions:	Kieselgel 60F254. Methanol/conc. $NH_{3(aq)}$ (100:1.5) Single spot observed, Rf = 0.4. Visualization with UV light (254 nm)
IR:	Instrument:	FT-IR, Biorad WIN FTS40
	Range:	4000-400 cm-1, KBr pellet
	Peaks:	3271, 2939, 2195, 2054, 1634, 1603, 1457, 1248, 1034, 798 cm^{-1}
^{1}H NMR:	Instrument:	Bruker DMX-500
	Field strength:	500 MHz
	Solvent:	MeOH-d_4 (3.31 ppm)
	Spectral data:	δ 1.85 (1H, bd), 2.11 (1H, dt), 2.39 (1H, dd), 2.49 (1H, dt), 2.64 (1H, dd), 2.70 (1H, bs), 3.06 (1H, d), 3.43 (1H, bdd), 4.22 (1H, dd), 4.84 (1H, d), 5.34 (1H, bd), 5.66 (1H, d), 6.48 (1H, d), 6.57 (1H, d) ppm
^{2}H NMR:	Instrument:	Bruker DMX-500
	Field strength:	77 MHz
	Solvent:	MeOH-d_4
	Spectral data:	δ 2.44 ppm
^{13}C NMR:	Instrument:	Bruker DMX-500
	Field strength:	126 MHz
	Solvent:	MeOH-d_4 (49 ppm)
	Spectral data:	δ 21.8, 36.5, 41.6, 44.6, 47.6, 60.3, 68.1, 93.1, 118.0, 120.7, 127.3, 129.6, 132.2, 134.1, 140.0, 147.6 ppm As a result of successful deuteration, no signal due to *N*-methyl (δ 43.0 ppm) is observed above baseline noise.
Melting point:		253 - 255 °C
Microanalysis:	Found:	C = 66.7%; H/D = 8.1%; N = 4.8% (February 2002)
	Calc:	C = 66.6%; H/D = 7.9%; N = 4.6% (Calculated for $C_{17}H_{16}D_3NO_3$)