



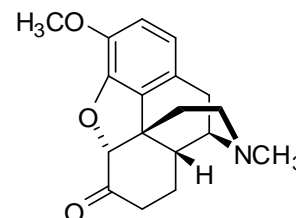
CERTIFIED REFERENCE MATERIAL CERTIFICATE OF ANALYSIS

NMIA D988: Hydrocodone

Report ID: D988.2021.03 (Bottled 160831)

Chemical Formula: C₁₈H₂₁NO₃

Molecular Weight: 299.4 g/mol



Certified value

| Batch No. | CAS No. | Purity (mass fraction) |
|-----------|----------|------------------------|
| 12-D-17 | 125-29-1 | 99.8 ± 0.4% |

The uncertainty has been calculated according to ISO Guide 35 and is stated at the 95% confidence limit (k = 2).

IUPAC name: (5 α)-3-Methoxy-17-methyl-4,5-epoxymorphinan-6-one

Expiration of certification: The property values are valid till 12 April 2031, i.e. ten 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 sample bottles that have been opened. In such cases it is recommended that the end-user conduct their own in-house stability trials.

Description: White powder sourced from an external supplier, and certified for identity and purity by NMIA. Packaged in amber glass bottles with a septum and crimped aluminium cap or screw top cap.

Intended use: This certified reference material is suitable for use as a primary calibrator.

Instructions for use: Equilibrate the bottled material to room temperature before opening.

Recommended storage: When not in use this material should be stored at or below 25 °C in a closed container in a dry, dark area.

Metrological traceability: The certified purity value is traceable to the SI unit for mass (kg) through Australian national standards via balance calibration. In the mass balance approach all impurities are quantified as a mass fraction and subtracted from 100%.

Stability: This material has demonstrated stability over a minimum period of three 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 ten randomly selected 1-2 mg sub samples 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 a 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.
21 September 2022

This report supersedes any issued prior to 21 September 2022.

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:

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 ¹H NMR spectroscopy. The purity value is calculated as per Equation 1.

$$\text{Purity} = (100\% - I_{\text{ORG}}) \times (100\% - I_{\text{VOL}} - I_{\text{NVR}}) \quad \text{Equation 1}$$

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

Supporting evidence is provided by qualitative headspace GC-MS analysis of occluded solvents and elemental microanalysis.

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|-----------------------------|---|
| GC-FID: | Instrument: Varian CP-3800 or Agilent 7890 Column: VF-1MS or HP-1MS, 30 m × 0.32 mm I.D. × 0.25 μm Program: 200 °C (1 min), 4 °C/min to 260 °C, 20 °C/min to 300 °C (3 min) Injector: 250 °C Detector Temp: 320 °C Carrier: Helium Split ratio: 20/1 Relative mass fraction of the main component: Initial analysis: Mean = 99.9%, s = 0.01% (10 sub samples in duplicate, September 2012) Re-analysis: Mean = 99.9%, s = 0.01% (5 sub samples in duplicate, July 2013) Re-analysis: Mean = 99.9%, s = 0.004% (5 sub samples in duplicate, June 2014) Re-analysis: Mean = 99.8%, s = 0.117% (5 sub samples in duplicate, July 2015) Re-analysis: Mean = 99.8%, s = 0.007% (5 sub samples in duplicate, May 2018) Re-analysis: Mean = 99.9%, s = 0.01% (5 sub samples in duplicate, April 2021) |
| GC-FID: | Instrument: Varian CP-3800 Column: HP-5, 30 m × 0.32 mm I.D. × 0.25 μm Program: 200 °C (1 min), 4 °C/min to 260 °C, 20 °C/min to 300 °C (5 min) Injector: 250 °C Detector Temp: 320 °C Carrier: Helium Split ratio: 20/1 Relative mass fraction of the main component: Initial analysis: Mean = 99.8%, s = 0.01% (10 sub samples in duplicate, September 2012) |
| Thermogravimetric analysis: | Volatile content < 0.1% and non volatile residue < 0.2% mass fraction (September 2012) |
| Karl Fischer analysis: | Moisture content ≤ 0.1% mass fraction (September 2012, July 2013, June 2014, June 2015, May 2018 and March 2021) |

Spectroscopic and other characterisation data

| | | |
|----------------------|---|--|
| GC-MS: | Instrument: | Agilent 6890/5973 |
| | Column: | TG-1MS, 30 m x 0.25 mm I.D. x 0.25 μ m |
| | Program: | 200 °C (1 min), 4 °C/min to 260 °C, 20 °C/min to 300 °C (3 min) |
| | Injector: | 250 °C |
| | Transfer line temp: | 280 °C |
| | Carrier: | Helium, 1.0 mL/min |
| | Split ratio: | 20/1 |
| | The retention time of the parent compound 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. | |
| | Parent (11.5 min): | 299 (M^+ , 100), 242 (47), 214 (21), 185 (21), 96 (17) m/z |
| HS-GC-MS: | Instrument: | Agilent 6890/5973/G1888 |
| | Column: | DB-624, 30 m x 0.25 mm I.D. x 1.4 μ m |
| | Program: | 50 °C (5 min), 7 °C/min to 120 °C, 15 °C/min to 220 °C (8.3 min) |
| | Injector: | 150 °C |
| | Transfer line temp: | 280 °C |
| | Carrier: | Helium, 1.2 mL/min |
| | Split ratio: | 50/1 |
| | Solvents detected: | Toluene |
| TLC: | Conditions: | Kieselgel 60F ₂₅₄ . TBME/diethyl ether/diethylamine (45/45/10) Single spot observed, R_f = 0.27. Visualisation with UV at 254 nm |
| IR: | Instrument: | Biorad FTS3000MX FT-IR |
| | Range: | 4000-400 cm^{-1} , KBr powder |
| | Peaks: | 2932, 2833, 2790, 2697, 1717, 1607, 1501, 1441, 1271, 1059, 962, 800 cm^{-1} |
| ¹ H NMR: | Instrument: | Bruker Avance-400 |
| | Field strength: | 400 MHz |
| | Solvent: | CDCl ₃ (7.26 ppm) |
| | Spectral data: | δ 1.24 (1H, dddd, J = 4.0, 13.2, 13.2, 13.2 Hz), 1.78-1.86 (2H, m), 2.05 (1H, ddd, J = 4.8, 12.0, 12.0 Hz), 2.19 (1H, ddd, J = 3.6, 12.0, 12.0 Hz), 2.26-2.44 (3H, m), 2.42 (3H, s), 2.52-2.59 (2H, m), 3.02 (1H, d, J = 18.4 Hz), 3.17 (1H, dd, J = 2.8, 5.2 Hz), 3.90 (3H, s), 4.64 (1H, s), 6.22 (1H, d, J = 8.0 Hz), 6.69 (1H, d, J = 8.0 Hz) ppm |
| ¹³ C NMR: | Instrument: | Bruker Avance-400 |
| | Field strength: | 100 MHz |
| | Solvent: | CDCl ₃ (77.0 ppm) |
| | Spectral data: | δ 20.2, 25.6, 35.6, 40.2, 42.8, 42.9, 46.8, 46.9, 56.9, 59.2, 91.4, 114.9, 119.7, 126.4, 127.3, 142.9, 145.5, 207.6 ppm |
| Melting point: | | 199-200 °C |
| Microanalysis: | Found: | C = 72.4%; H = 7.2%; N = 4.7% (September, 2012) |
| | Calculated: | C = 72.2%; H = 7.1%; N = 4.7% (Calculated for C ₁₈ H ₂₁ NO ₃) |