



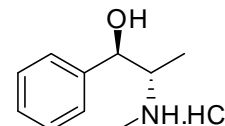
# CERTIFIED REFERENCE MATERIAL CERTIFICATE OF ANALYSIS

## NMIA M924b: (-)-Ephedrine hydrochloride

Report ID: M924b.2023.01 (Bottled 220105)

Chemical Formula:  $C_{10}H_{15}NO.HCl$

Molecular Weight: 201.7 g/mol (HCl), 165.2 g/mol (base)



### Certified value

| Batch No. | CAS No.                          | Purity (mass fraction) |
|-----------|----------------------------------|------------------------|
| 21-D-10   | 50-98-6 (HCl)<br>299-42-3 (base) | 99.6 ± 0.4%            |

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

**IUPAC name:** (1R,2S)-2-(Methylamino)-1-phenyl-1-propanol hydrochloride.

**Expiration of certification:** The property values are valid till 9 June 2026, three 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. The material will be re-tested on an annual basis to ensure that the property values are still valid. In the event a product fails the stability trial, notification will be sent to all impacted customers.

**Description:** White powder sourced from an external supplier, purified and certified for identity and purity by NMIA. Packaged in amber glass bottles with a septum and crimped aluminium 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%. Quantitative NMR provides an independent direct measure of the mass fraction of the analyte of interest, calibrated with an internal standard certified for purity (mass fraction).

**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 and accelerated stability trials, the latter conducted at 40 °C and 75% humidity for a 14 day period.

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.  
14 June 2023

This report supersedes any issued prior to 14 June 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.

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## 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 <sup>1</sup>H NMR spectroscopy. The purity value is calculated as per Equation 1.

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

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

Supporting evidence is provided by quantitative NMR (qNMR), qualitative headspace GC-MS analysis of occluded solvents and elemental microanalysis. The purity value obtained by qNMR was determined using combination of the three-proton singlet at 2.79 ppm, the one-proton multiplet at 3.58 ppm, and the five aromatic protons in the range 7.2-7.7 ppm were measured against a certified internal standard of potassium hydrogen maleate. Capillary electrophoresis confirmed the material is 100% (-)-ephedrine hydrochloride.

|                             |   |
|-----------------------------|---|
| GC-FID:                     | Instrument: Agilent 7890A or 8890<br>Column: HP-1MS, 30 m × 0.32 mm I.D. × 0.25 μm<br>Program: 60 °C (1 min), 15 °C/min to 165 °C, 30 °C/min to 300 °C (3 min)<br>Injector: 150 °C<br>Detector Temp: 320 °C<br>Carrier: Helium<br>Split ratio: 20/1   |
|                             | Relative mass fraction of the main component as the free base:<br>Initial analysis: Mean = 99.7%, s = 0.03% (10 sub samples in duplicate, September 2021)<br>Re-analysis: Mean = 99.8%, s = 0.02% (5 sub samples in duplicate, July 2022)<br>Re-analysis: Mean = 99.95%, s = 0.01% (5 sub samples in duplicate, June 2023)  |
| Karl Fischer analysis:      | Moisture content ≤ 0.2% mass fraction (September 2021 and June 2022)<br>Moisture content ≤ 0.1% mass fraction (March and June 2023)   |
| Thermogravimetric analysis: | Non-volatile residue < 0.2% mass fraction (September 2021)  |
| qNMR:                       | Instrument: Bruker Avance-III-500<br>Field strength: 500 MHz<br>Solvent: D <sub>2</sub> O (4.79 ppm)<br>Internal standard: Potassium hydrogen maleate (99.7% mass fraction)<br>Initial analysis: Mean (2.79 ppm) = 99.5%, s = 0.2% (5 sub samples, September 2021)<br>Initial analysis: Mean (3.57 ppm) = 99.5%, s = 0.1% (5 sub samples, September 2021)<br>Initial analysis: Mean (7.2-7.7 ppm) = 99.6%, s = 0.2% (5 sub samples, September 2021) |

## Spectroscopic and other characterisation data

|                      |   |   |
|----------------------|---|---|
| GC-MS:               | Instrument:   | Agilent 6890/5973   |
|                      | Column:   | DB-5MS, 30 m x 0.25 mm I.D. x 0.25 $\mu$ m  |
|                      | Program:  | 60 °C (1 min), 15 °C/min to 165 °C, 20 °C/min to 300 °C (3 min)   |
|                      | Injector:   | 250 °C  |
|                      | Split ratio:  | 20/1  |
|                      | Transfer line temp:   | 280 °C  |
|                      | Carrier:  | Helium, 1.0 mL/min  |
|                      | Scan range:   | 50-550 <i>m/z</i>   |
|                      | The retention time of (-)-ephedrine base is reported 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. |   |
|                      | Free base (8.6 min):  | 146 (2), 132 (2), 117 (9), 105 (7), 91 (5), 77 (13), 58 (100) <i>m/z</i>  |
| TLC:                 | Conditions:   | Kieselgel 60F <sub>254</sub> . Methanol/concentrated ammonia (98.5:1.5)<br>Single spot observed, R <sub>f</sub> = 0.2. Visualisation with ninhydrin.  |
| IR:                  | Instrument:   | Bruker Alpha Platinum ATR   |
|                      | Range:  | 4000-400 $\text{cm}^{-1}$ , neat  |
|                      | Peaks:  | 3325, 2959, 2906, 2837, 2756, 2467, 1589, 1453, 1389, 1353, 1238, 1048, 991, 751, 698, 595, 523, 449 $\text{cm}^{-1}$   |
| <sup>1</sup> H NMR:  | Instrument:   | Bruker Avance III-500   |
|                      | Field strength:   | 500 MHz   |
|                      | Solvent:  | D <sub>2</sub> O (4.79 ppm)   |
|                      | Spectral data:  | $\delta$ 1.16 (3H, d, <i>J</i> = 6.8 Hz), 2.79 (3H, s), 3.58 (1H, dq, <i>J</i> = 3.7, 6.8 Hz), 5.15 (1H, d, <i>J</i> = 3.6 Hz), 7.41-7.46 (3H, m), 7.47-7.52 (2H, m) ppm<br>Propan-2-ol was quantified at 0.2% mass fraction using <sup>1</sup> H NMR spectroscopy. |
| <sup>13</sup> C NMR: | Instrument:   | Bruker Avance III-500   |
|                      | Field strength:   | 126 MHz   |
|                      | Solvent:  | D <sub>2</sub> O  |
|                      | Spectral data:  | $\delta$ 9.7, 30.7, 59.9, 71.5, 126.1, 128.5, 128.8, 138.4 ppm  |
| Melting point:       | 219-220 °C  |   |
| Microanalysis:       | Found:  | C = 59.6%; H = 8.1%; N = 6.8% (September, 2021)   |
|                      | Calculated:   | C = 59.6%; H = 8.0%; N = 6.9% (Calculated for C <sub>10</sub> H <sub>15</sub> NO.HCl)   |