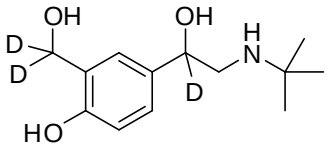
Australian Government
Department of Industry, Science and Resources

National Measurement Institute

NATA
WORLD RECOGNISED ACCREDITATION

DEUTERATED INTERNAL STANDARD PRODUCT INFORMATION SHEET

NMIA D939b: d3-Salbutamol



Report ID: D939b.2023.01 (Ampouled 221013)

Chemical Formula: $C_{13}H_{18}D_3NO_3$

Molecular Weight: 242.3 g/mol

Property value

Batch No.	CAS No.	Mass per ampoule
22-D-03	**1219798-60-3**	**952 ± 21 μg**

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

IUPAC name: 2-(1,1'-2H-Hydroxymethyl)-4-{1—hydroxy-1'-2H-2-[(2-methyl-2-propanyl)amino]ethyl}phenol.

Expiration of certification: The property values are valid till 11 October 2026, i.e. 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 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 D939b. The material was prepared by synthesis, and certified for identity and purity by NMIA. The main component of this material is d_3-salbutamol. d_2-, d_1- and d_0-Salbutamol 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-salbutamol 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. methanol). This will transfer approximately 954 μg of anhydrous salbutamol (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: In the absence of long term stability data the measurement uncertainty at the 95% coverage interval has been expanded to accommodate any potential change in the property value. The stability component has been estimated from stability trials conducted on similar materials by NMI Australia over the last ten years.

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 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.
19 October 2023.

This report supersedes any issued prior to 19 October, 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 CP-3800
	Column:	DB-17, 30 m × 0.32 mm I.D. × 0.25 μm
	Program:	150 °C (1 min), 10 °C/min to 300 °C (10 min)
	Injector:	250 °C
	Detector Temp:	320 °C
	Carrier:	Helium
	Split ratio:	20/1
	Relative peak area of the main component:	
	Initial analysis:	Mean = 98.4%, s = 0.2% (7 ampoules in duplicate, November 2022)
	Re-analysis:	Mean = 98.1%, s = 0.2% (5 ampoules in duplicate, October 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 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 elemental microanalysis.

The main component of this material is d_3-salbutamol. d_2-, d_1- and d_0-Salbutamol are also present. The stated chemical purity of the analyte represents the combined mass fractions of deuterium labelled (d_3, d_2 and d_1) and d_0-salbutamol 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 ≈ 94% [= $d_3/(d_3 + d_2 + d_1 + d_0)$ x 100]
	d_2 ≈ 5% [= $d_2/(d_3 + d_2 + d_1 + d_0)$ x 100]
	d_0 < 0.2% [= $d_0/(d_3 + d_2 + d_1 + d_0)$ x 100]

GC-FID:	Instrument:	Varian CP-3800
	Column:	DB-17, 30 m × 0.32 mm I.D. × 0.25 μm
	Program:	150 °C (1 min), 10 °C/min to 280 °C (10 min)
	Injector:	250 °C
	Detector Temp:	320 °C
	Carrier:	Helium
	Split ratio:	20/1
	Relative peak area of the main component:	
	Initial analysis:	Mean = 98.2%, s = 0.06% (7 sub samples in duplicate, August 2022)
Karl Fischer analysis:		Moisture content 0.4% mass fraction (August 2022)
Thermogravimetric analysis:		Volatiles content < 0.1% and non-volatile residue < 0.2% mass fraction (August 2022)

Spectroscopic and other characterisation data

GC-MS: The d_3-salbutamol free base was derivatised with non-activated MSTFA to afford the tris-TMS derivative.

Instrument:	Agilent 8890/5977B
Column:	HP5MS, 30 m x 0.25 mm I.D. x 0.25 μm
Program:	150 °C (1 min), 10 °C/min to 280 °C (10 min)
Injector:	250 °C
Split ratio:	20/1
Transfer line temp:	280 °C
Carrier:	Helium, 1.0 mL/min
Scan range:	50-550 *m/z*

The retention time of the d_3-salbutamol *tris*-TMS derivative 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.

Tris-TMS d_3-salbutamol (9.6 min): 443 (4), 372 (100), 297 (7), 210 (13), 147 (8), 86 (58), 73 (37) *m/z*

ESI-MS:

Instrument:	Micromass Quatro LC Micro
Operation:	Positive ion mode, direct infusion at 10 μL/min
Ionisation:	ESI spray voltage at 3.5 kV positive ion
EM voltage:	650 V
Cone voltage:	15 V
Peak:	243 ($M+H^+$) *m/z*

TLC:

Conditions:	Kieselgel 60F_{254}. Methanol Single spot observed, R_f = 0.4. Visualisation with UV at 254 nm.

IR:

Instrument:	Bruker Alpha Platinum ATR
Range:	4000-400 cm^{-1}, neat
Peaks:	3140, 2966, 1704, 1609, 1505, 1417, 1365, 1332, 1268, 1170, 1118, 1027, 977, 950, 921, 845, 818, 705, 601 cm^{-1}

^{1}H NMR:

Instrument:	Bruker Avance III-500
Field strength:	500 MHz
Solvent:	MeOH-d_4 (3.31 ppm)
Spectral data:	δ 1.12 (9H, s), 2.66 (1H, d, *J* = 11.4 Hz), 2.78 (1H, d, *J* = 11.4 Hz), 6.76 (1H, d, *J* = 8.2 Hz), 7.11 (1H, dd, *J* = 2.2, 8.1 Hz), 7.29 (1H, d, *J* = 2.4 Hz) ppm. ^{1}H NMR shows the presence of ethanol and ethyl acetate in 0.8% and 0.01% mass fractions respectively (August 2022)

^{13}C NMR:

Instrument:	Bruker Avance III-500
Field strength:	126 MHz
Solvent:	MeOH-d_4 (49 ppm)
Spectral data:	δ 28.7, 51.0, 51.5, 116.0, 127.1, 127.2, 128.6, 134.9, 156.2 ppm

Melting point: 157-158 °C

Microanalysis:

Found:	C = 64.6%; H = 7.6%; N = 5.9%; (August, 2022)
Calculated:	C = 64.4%; H = 7.5%; N = 5.8% (Calculated for $C_{13}H_{18}D_3NO_3$)