Quantitative NMR:

An essential tool for the certification of Organic Reference Materials

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Background:

Modern day chemical analysis underpins such diverse activities as international trade, health, sport and the environment. One reliable pre-requisite for chemical measurement is the availability of fully certified reference materials (CRMs).

The Chemical Reference Materials team at NMI, Australia, currently assesses the purity of a ***"pure substance"*** organic compound using a combined approach comprising results from the following techniques, each analysing different components of a given material:

Organic: Analysis by GC-FID and/or HPLC with UV and ELSD detection.

Volatile(s): Analysis by TGA and Karl Fischer moisture.

Non-volatile residue: Analysis by TGA.

The sum of these is then taken as the certified purity.

The Advantage of QNMR:

In order to improve the characterisation and purity assessment of organic compounds, we have been using QNMR which has the distinct advantage of directly assessing the analyte of interest, both in terms of ***quality*** i.e. structural consistency, and ***quantity***, the amount of analyte present.

Reference: Wells, R J.; Cheung, J.; Hook, J.M. (2008) *NMR Spectroscopy in Pharmaceutical Analysis*, Holzgrabe, U., Wawer, I., Diehl, B., (Eds.) Elsevier, New York, pp. 219-315.

Aim:

In this work, the validity of QNMR has been tested with a variety of CRMs and the results compared directly to the purity assessment obtained by the "combined approach" detailed above.

Experimental and Results:

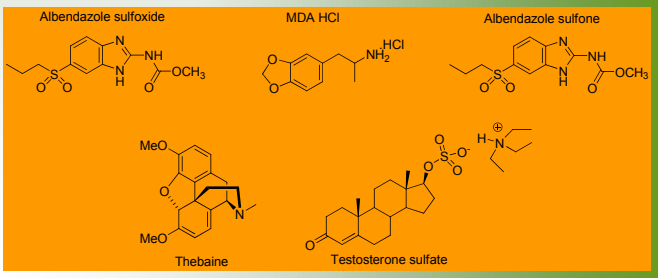
All ^{1}H NMR spectra were acquired on 400, 500 and 600 MHz NMR spectrometers, using either dimethylsulphone, sodium acetate trihydrate, trioxane or potassium hydrogen maleate as a standard.

Name	Purity (cert.)	s.d.	Purity (QNMR)	s.d.	Equivalent purity
MDMA HCl	99.98%	0.14%	99.9%	1.00%	YES
Androstendione	99.5%	0.11%	99.5%	0.32%	YES
Epitestosterone sulfate	>95%	0.26%	96.5%	0.70%	YES
Noretiocholanalone glucuronide (Na salt)	84.4%	0.48%	83.8%	0.63%	YES
Testosterone	99.2%	0.19%	99.0%	0.43%	YES
Carbophenothion sulfone	99.6%	0.22%	99.6%	0.80%	YES
Fentanyl	99.7%	0.13%	99.8%	0.35%	YES
Bromosafrole	92.4%	0.16%	92.6%	0.52%	YES
Testosterone glucuronide (free acid)	94.7%	0.49%	94.7%	0.38%	YES

Table 1: Comparison of analytical data from the combined approach and QNMR showing excellent agreement.

Name	Purity (cert.)	s.d.	Purity (QNMR)	s.d.	Equivalent purity
Albendazole sulfone	99.3%	0.17%	98.3%	0.44%	NO
MDA HCl	99.5%	0.37%	97.0%	0.97%	NO
Albendazole sulfoxide	97.0%	0.36%	95.3%	0.56%	NO
Thebaine	98.1%	0.50%	99.9%	0.45%	NO
Testosterone sulfate (NEt3 salt)	99.3%	0.25%	97.5%	0.20%	NO

Table 2: Comparison of analytical data from the combined approach and QNMR showing poor agreement.



Conclusions:

This work highlights the capability of QNMR spectroscopy for the evaluation of the quality and purity of organic reference materials. Three categories have been revealed:

1. Steroids, amphetamines and organophosphates as shown in Table 1. In many cases, QNMR complements the combined approach including GC-FID and HPLC-UV.

2. The combined approach and QNMR show high precision but unexplained differences shown in Table 2.

3. QNMR is the sole method of choice in some cases because of the overly sensitive nature of the substances.