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Letter to the editor

Dear Editor,

We are writing with comment on the article "3,4-Methylenedioxymethamphetamine quantification via benchtop ^{1}H qNMR spectroscopy: Method validation and its application to ecstasy tablets collected at music festivals" by Abbate and co-workers [1]. Specifically, we would like to draw attention to the lack of appropriate referencing / acknowledgement of prior art, missing data, and improper validation procedures.

Firstly, Abbate *et al.* utilise an NMR method to quantify 3,4-methylenedioxymethamphetamine (MDMA) using an internal standard [IS, ethylene carbonate (EC)]. The spectrometer frequency and acquisition parameters are identical to those published in 2020 to quantify MDMA content of seized tablets [2], although an IS was not required. How do the authors suggest this is a better methodology?

Secondly, Abbate *et al.* do not acknowledge key literature, and as such, do not compare their work with the state-of-the-art. This is a key requirement of the journal's aims and scope in that "authors must address the question of how their proposed methodology compares with previously reported methods." Works by Almedia *et al.* [3], who published a validated NMR approach for MDMA quantification in 2018 and Naqi *et al.* [4], who detailed the quantitative NMR and UHPLC-MS analysis of seized MDMA / novel psychoactive mixtures and tablets from night club venues in 2019, have not been cited. Their need for their inclusion is clear. The limit of references cannot be used as an excuse. Reference to [2] is limited to a single broad statement regarding benchtop NMR in the introduction. This is not a meaningful comparison.

Furthermore, Abbate *et al.* [1] state that "All tablets included in the current study were considered to contain the HCl salt which was then calculated as free base to avoid confusion and be consistent with our previous work (8)." Reference (8) in this quoted sentence is ref. [5] herein, which is not the work of any of the authors of ref. [1] but is instead work published by authors (and their colleagues) of the present correspondence piece (and is patented [5]). This should be rectified accordingly.

Secondary analysis by Abbate *et al.* on the MDMA tablets analysed was limited to the statement "confirmed by GC-MS analysis" (no data provided). LC-MS data is reported for ten "randomly selected" samples – this data was reported as part of a previous project. The other 90 samples are not analysed by LC-MS. In addition, D_2O is used in the preparation of samples, to remove the broad amine peaks should they resonant at the same frequency as the IS or methylenedioxy protons of MDMA. Inspection of Fig. S2 of ref. [1] highlights that addition of D_2O does not completely remove key signals of lactate, potentially leading to under-reporting of MDMA for lactate adulterated samples. Similarly, Fig. S4 of ref. [1] highlights that key signals for benzocaine would lead to over-reporting. Based on this, how can Abbate and co-workers make the statement that "no overlapping signals with the MDMA peak of interest (methylene-dioxy) or the EC resonance were observed"?

Abbate *et al.* also investigate MDMA content in terms of batch variation. As refs. [2-4] all report batch analysis of MDMA tablets, why was there no comparison to prior, published, data? The absence of any direct comparison between refs. [2 – 5] and ref. [1] was, we suggest, because the similarity of the work with previous studies is too stark and would highlight the lack of scientific rigour and novelty in Abbate and co-workers' approach.

[1] A. Frinculescu, A. F.G. Maier, T. Shine, J. Ramsey, J. F. Araneda, S. D. Riegel, N. Frascione, V. Abbate, 3,4-Methylenedioxymethamphetamine quantification via benchtop ^{1}H qNMR

spectroscopy: Method validation and its application to ecstasy tablets collected at music festival J. Pharm Biomed. Anal. 214 (2022) 114728

[2] N. S. Almeida, L. E. C. Benedito, A. O. Maldaner, A. L. de Oliveira, A Validated NMR Approach for MDMA Quantification in Ecstasy Tablets, J. Braz. Chem. Soc. 29 (2018) 1944-1950

[3] H. A. Naqi, Stephen M. Husbands, I. S. Blagbrough, ^{1}H quantitative NMR and UHPLC-MS analysis of seized MDMA/NPS mixtures and tablets from night-club venues, Anal. Methods 11 (2019) 4795-4807

[4] J. H. Hussain, N. Gilbert, A. Costello, C. J. Schofield, E. K. Kemsley, O. B. Sutcliffe, R. E. Mewis, Quantification of MDMA in seized tablets using benchtop ^{1}H NMR spectroscopy in the absence of internal standards, Forensic Chem. 20 (2020) 100263.

[5] A method for screening psychoactive substances (GB1800377.2). Lodged 10th January 2019.

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