

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	A chemical analysis examining the pharmacology of novel psychoactive substances freely available over the internet and their impact on public (ill)health. Legal Highs or Illegal Highs?
<b>AUTHORS</b>	Ayres, Tammy ; Bond, John

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Dr David Wood Guy's and St Thomas' NHS Foundation Trust
<b>REVIEW RETURNED</b>	22-Apr-2012

<b>THE STUDY</b>	<p>- It is not clear what the basis for the selection of the compounds to be analysed was</p> <p>- There are several key references from this manuscript missing which have already done considerably similar analysis in this area. These include: Davies S, Wood DM, Smith G, Button J, Ramsey J, Archer R, Holt DW, Dargan PI. Purchasing 'legal highs' on the Internet--is there consistency in what you get? QJM. 2010 Jul;103(7):489-93</p> <p>Brandt SD, Freeman S, Sumnall HR, Measham F, Cole J. Analysis of NRG 'legal highs' in the UK: identification and formation of novel cathinones. Drug Test Anal. 2011 Sep;3(9):569-75</p> <p>Brandt SD, Sumnall HR, Measham F, Cole J. Second generation mephedrone. The confusing case of NRG-1. BMJ. 2010 Jul 6;341:c3564</p> <p>Spiller HA, Ryan ML, Weston RG, Jansen J. Clinical experience with and analytical confirmation of "bath salts" and "legal highs" (synthetic cathinones) in the United States. Clin Toxicol (Phila). 2011 Jul;49(6):499-505.</p>
<b>RESULTS &amp; CONCLUSIONS</b>	<p>I think that the authors have failed to review the previously published work in this area, and I am unsure what this manuscript adds to the previous work.</p> <p>Additionally on Page 4, Lines 42-46 they state that the work was timed to be done to ensure that the legislation had taken effect - I am not clear as to how they determined this.</p>
<b>REPORTING &amp; ETHICS</b>	This article does not need research ethics as it is analysis of substances bought off the Internet.
<b>GENERAL COMMENTS</b>	1. The authors have failed to review and include / cite a number of studies that have done this type of work before. It is not clear as to what this latest manuscript adds to the already extensively

	<p>published research in this area from the UK and elsewhere.</p> <p>2. There is no clear strategy defined as to how the substances that were analysed were actually decided upon - greater transparency is needed with regards to this</p> <p>3. There are abbreviations (e.g. BZP, TFMPP) which MUST be defined in the manuscript</p> <p>4. The authors incorrectly cite the UK drugs legislation - this should be the "Misuse of Drugs Act, 1971"</p> <p>5. Do the authors have any comment on the quantitative amounts of the compounds detected in the samples purchased</p> <p>6. The discussion could be more focused and shortened significantly</p> <p>7. I think that the term "illicit" should be replaced with "controlled" or "illegal"</p> <p>8. It would be good to acknowledge that most people in the field refer to these types of substances as "novel psychoactive substances" or "new psychoactive substances" (the latter is the preferred term of the EMCDDA) - the term "legal high" is not really appropriate - please consider replacing in the manuscript as appropriate.</p> <p>9. The toxicity of benzocaine in relation to methaemoglobinaemia has been referenced to a topical exposure. It would have been more appropriate if the authors had cited a recently published review on recreational drug related methaemoglobinaemia:</p> <p>Hunter L, Gordge L, Dargan PI, Wood DM. Methaemoglobinaemia associated with the use of cocaine and volatile nitrites as recreational drugs: a review. Br J Clin Pharmacol. 2011 Jul;72(1):18-26. doi: 10.1111/j.1365-2125.2011.03950.x.</p> <p>10. It would be good to acknowledge that there are also legal implications of purchasing supposedly legal substances off the Internet for the individual if they are subsequently found to contain controlled substances.</p>
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<b>REVIEWER</b>	<p>Dr Mark Baron Principal Lecturer in Analytical Chemistry University of Lincoln UK</p> <p>I have no competing financial, professional or personal interests that might have influenced my review of this paper.</p>
<b>REVIEW RETURNED</b>	11-Apr-2012

<b>THE STUDY</b>	<p>There are no participants or patients in this study. Analytical techniques used are given (NMR, FTIR and Raman) but it is not clear how they have been used to provide the analytical results. Were all samples analysed by all three methods? Were they compared with reference standards and if so where were they obtained. Where contaminants were detected how was this achieved with the techniques used? What level of contaminant is detectable?</p>
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	<p>Could the benzocaine only samples also contain a low level of other active ingredient?  No statistical methods are used or are they necessary for this study. The recent changes in the UK legislation (Misuse of Drugs Act) should be discussed in the introduction. As it stands the comments are a little out of date given that the legislation change is an attempt to speed up response for action when new substances appear. Reference should also be made to the ACMD publication on Novel Psychoactive Substances october 2011.</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer 1 (Dr Mark Baron):

- Reviewer 1 said it was not clear how the analytical techniques were used to provide the results, which we have now clarified in the text (see page 6) by adding 'each product was analysed with FTIR, Raman Spectroscopy and Proton NMR. Additionally, where there was an indication from the spectroscopy that a product contained an illegal substance, that product was analysed with <sup>13</sup>C NMR'.
- Reviewer 1 asked if comparisons were made with reference standards and if so where were they obtained. Comparison to specific reference standards for the illegal chemicals identified was not undertaken and this has now been clarified in the text (see page 6).
- In response to reviewer 1's comments the level of contaminant detectable has been added to the text (see page 7) and the integrated intensities of Proton NMR evaluated and the relative concentration of 4-MEC to 4-MMC given.
- In response to reviewer 1's question asking whether the benzocaine only samples also contained a low level of other active ingredient, we found no indication of this from the analyses performed. However this is a valid point and has now been included in suggestions for future research on page 14.
- As recommended the recent changes in the UK legislation (Misuse of Drugs Act) have been discussed in the introduction. The authors included information on the banning of substituted cathinones on page 3, and the new temporary class orders on page 4, to address the reviewer's comments and bring the article up to date.
- We have also made reference to the ACMD's (2011) publication on Novel Psychoactive Substances, where applicable.

Reviewer 2 (Dr David Wood):

- Point 1 - Although reviewer 2 said there were several key references missing from the manuscript, two of the articles listed as missing were referenced in the original article (i.e. Brandt et al. 'Purchasing 'legal highs' on the Internet' and 'Analysis of NRG 'legal highs' in the UK'). Although reviewer 2 was right when he said we had excluded 'Brandt SD, Sumnall HR, Measham F, Cole J. Second generation mephedrone. The confusing case of NRG-1. BMJ. 2010 Jul 6;341:c3564', we had included 'Brandt SD, Sumnall HR, Measham F, Cole J. The confusing case of NRG-1. The Lancet 2010' instead. Since both were letters we did not think it mattered which one we included, but in the revised manuscript we have changed the Lancet reference for the British Medical reference. We have now included the Spiller et al., (2011) article recommended by reviewer 2 where relevant.
- In point one - Reviewer 2 said we had failed to adequately review the previous literature in this area. However on page 3 we discussed the findings from the only three UK studies relevant to this

research. A more detailed discussion seemed unnecessary and uncharacteristic for an academic journal article.

Reviewer 2 also commented that he failed to see what 'this late manuscript adds to the already extensively published research'. Although, we can see why reviewer 2 might describe our manuscript as late, it was purposefully timed for 18 months after the cathinone ban. One of the caveats attached to the research conducted immediately after the ban (see Brandt, Sumnall, Measham and Cole, 2010: 381) was 'the sudden ban on mephedrone and some of its derivatives might have caused some manufacturers and wholesalers to continue selling their banned products in order to reduce stock'. By conducting the research 18 months later this caveat no longer applies. Also despite reviewer 2 saying the research in this area is extensive, it is difficult to see how a handful of articles on this subject constitutes extensive research; surely any research in this area contributes to this burgeoning knowledge base?

This article also contributes in the following ways:

- 1) It brings the medical literature together with other research on this subject, in to one accessible article.
- 2) It satisfies the calls for 'further characterisation of these products' and the need for continuous monitoring since the chemical and ingredients are constantly changing.
- 3) It demonstrates legislation has not stopped the supply of mephedrone over the internet 18 months on.

- Page 4, Lines 42-46 – We have clarified this point by writing 'By conducting the research at this time we overcome the caveats associated with earlier research, as the 2010 legislative controls prohibiting cathinones should have taken effect and any old stock containing mephedrone should have been sold in the period immediately after the ban'.

- Point 2 – Except for Davies, et al.'s (2010) article 'Purchasing Legal Highs on the Internet – Is there Consistency in what you get?' none of the other articles explain how the substances or the websites were chosen. However, in line with the request made by reviewer 2 we have included this information on page 6, which hopefully makes it more transparent.

- Point 3 – Instead of defining BZP on page 3, it was supplemented for its chemical name piperazines due to word constraints. However, on page 4, BZP and 3-TFMPP were both defined as requested.

- Point 4 - The authors have changed the Misuse of Drugs Act, 1971 to the Misuse of Drugs Act (1971).

- Point 5 - The integrated intensities of Proton NMR has now been evaluated and the relative concentration of 4-MEC to 4-MMC given in both NRG-2 samples given. As only these banned substituted cathinones were detected in both NRG-2 samples, the quantity of these substances taken by a user is simply the amount of powder consumed. This has now been clarified in the text.

- Point 6 – We have tried to make the discussion more focused.

- Point 7 – We changed the term 'illicit' to 'illegal' as recommended, in most instances.

- Point 8 – The term used by the EMCDDA is 'new psychoactive substances' while the ACMD use 'novel psychoactive substances', the term legal highs is also used by the ACMD in their (2011) report. We have taken the reviewers comment on board and acknowledged the term 'novel psychoactive substances' which we have abbreviated to NPS in the manuscript, but we have also used the term legal highs since this term is widely recognised by lay people and used extensively throughout the literature.

- Point 9 – The reference for the toxicity of benzocaine was removed because it was for topical exposure. Although we have cited the review recommended by reviewer 2 (Hunter et al., 2011), the article did not contain the toxicity of benzocaine in relation to methaemoglobinaemia. Since all of the thresholds identified in the literature seem to relate to topical exposure of benzocaine, we have changed this section of the article slightly in accordance with the medical literature on this subject.
- Point 10 – Reviewer 2 asked us to acknowledge the legal implications of purchasing illegal substances off the internet, which we had briefly mentioned in the conclusion of the original manuscript. However, we have also added a sentence on this in the introduction (see page 5). It is felt providing any more detail on this topic is beyond the remit of this paper.

We would like to thank the reviewers for their helpful comments. We hope that we have satisfactorily addressed the recommendations made by the managing editor and the two reviewers. Therefore, we are resubmitting the article for your reconsideration.

If you have any questions please do not hesitate to contact us on the above number or by email. We look forward to hearing from you.

Kind regards,

Tammy Ayres and John Bond