

# 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?

Tammy C Ayres,<sup>1,2</sup> John W Bond<sup>3</sup>

**To cite:** Ayres TC, Bond JW. 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? *BMJ Open* 2012;**2**:e000977. doi:10.1136/bmjopen-2012-000977

► Prepublication history for this paper is available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2012-000977>).

Received 8 March 2012  
Accepted 18 June 2012

This final article is available for use under the terms of the Creative Commons Attribution Non-Commercial 2.0 Licence; see <http://bmjopen.bmj.com>

<sup>1</sup>Department of Criminology, University of Leicester, Leicester, UK

<sup>2</sup>School of Psychology, University of Leicester, Leicester, UK

<sup>3</sup>Department of Chemistry, University of Leicester, Leicester, UK

## Correspondence to

Tammy Ayres; [tca2@le.ac.uk](mailto:tca2@le.ac.uk)

## ABSTRACT

**Objectives:** Public Health England aims to improve the nation's health and acknowledges that unhealthy lifestyles, which include drug use, undermine society's health and well-being. Recreational drug use has changed to include a range of substances sold as 'research chemicals' but known by users as 'legal highs' (legal alternatives to the most popular illicit recreational drugs), which are of an unknown toxicity to humans and often include prohibited substances controlled under the Misuse of Drugs Act (1971). Consequently, the long-term effects on users' health and inconsistent, often illegal ingredients, mean that this group of drugs presents a serious risk to public health both now and in the future. Therefore, the aim of this study was to ascertain what is in legal highs, their legality and safety, while considering the potential impact, these synthetic substances might be having on public health.

**Design:** A total of 22 products were purchased from five different internet sites, 18 months after the UK ban on substituted cathinones, like mephedrone, was introduced in April 2010. Each substance was screened to determine its active ingredients using accepted analytical techniques.

**Setting:** The research was conducted in Leicestershire but has implications for the provision of primary and secondary healthcare throughout the UK.

**Results:** Two products, both sold as NRG-2 from different internet suppliers, were found to contain the banned substituted cathinones 4-methylethcathinone (4-MEC) and 4-methylmethcathinone (4-MMC), the latter being present in much smaller quantities. Although sold as research chemicals and labelled 'not for human consumption', they are thinly disguised 'legal highs', available online in quantities that vary from 1 g to 1 kg.

**Conclusions:** Despite amendments to legislation, prohibited class B substances are still readily available in large quantities over the internet. The findings suggest that these prohibited substances are being manufactured or imported into the UK on a large scale, which has serious implications for public health and clinicians who are ill equipped to deal with this newly emerging problem.

## ARTICLE SUMMARY

### Article focus

- To analyse the chemical composition of substances bought over the internet, including the legality of the active ingredients and if products differ between retailers.
- To consider the medical implications and adverse health risks associated with legal highs bought over the internet.

### Key messages

- The most recent examination of the composition of 'legal highs', conducted 6 months after the introduction of the ban, found no presence of banned cathinones.
- Our study shows that, 18 months after the introduction of the ban, illegal cathinone substitutes are readily available for purchase in the UK in large (1 kg) quantities with little known about their clinical effects.

### Strengths and limitations of this study

- The small number of products tested (22 products) and the limited number of retailers sampled are limitations of this study. However, this study does show that despite being banned, illegal cathinones remain readily available over the internet, despite their potential harmfulness.

## INTRODUCTION

Public health is inadvertently connected to wider society and the cultural nuances that influence individual health and well-being, which include drug use. From the public health implications arising from increased heroin use in the 1980s to the more recent furore surrounding legal highs, pharmacological leisure has always impacted on public health and medical practitioners. The noughties are no different, as the culture of

## The pharmacology of novel psychoactive substances

recreational drug use has changed to include a group of substances known by users as 'legal highs' but referred to in the literature as 'novel psychoactive substances' (NPSs)<sup>1</sup>—a range of chemical and herbal substitutes marketed as legal alternatives to the most popular but illicit recreational drugs. Although herbal products (ie, *Salvia Divinorum*, *Damiana* and *Kratom*) are widely available, this research will focus on synthetic substances since their increased popularity has caused a furore in the media and problems for the authorities who are unable to act quickly enough to monitor and legislate on the vast array of new substances being created in this burgeoning market. According to the International Narcotic Control Board, the growth in production and distribution of these new designer drugs is 'escalating out of control'<sup>2</sup> with their availability growing at an unprecedented pace.<sup>3</sup> Unlike traditional recreational drugs, little is known about the chemical composition of these new substances, their toxicity or the long-term effects associated with their use, meaning they pose a serious challenge to public health agencies and has the potential to undermine the objectives of Public Health England. Many first-generation legal highs (eg, mephedrone, piperazines and spice) have been brought under the Misuse of Drugs Act (1971), the most recent being mephedrone, which was banned in April 2010, when the Misuse of Drugs Act, 1971 (Amendment) Order categorised mephedrone and other substituted cathinones as a class B controlled drug. However, despite introducing legislative controls over these drugs, there is some evidence to suggest little has changed and banned substances are still being sold online under a new guise. Products are frequently given new names and marketed as superior, but legal, alternatives to the banned substances they purport to replace.<sup>4–7</sup> It is not known how many of these new products contain newly synthesised and legal chemicals and how many continue to contain illegal substances like mephedrone, which has been linked to a number of deaths.<sup>1</sup> In an effort to protect the public from the harmfulness of NPSs, a new temporary class order has been introduced, which prohibits the manufacture and supply of temporary class drugs for 12 months, while the Advisory Council on the Misuse of Drugs assess it for permanent control under the Misuse of Drugs Act (1971) (eg, methoxetamine was temporarily classified in March 2012).

Despite the rapid growth in the production and sale of these synthesised chemical products, there is a dearth of research in this area. Excluding the recent research on synthetic cannabinoids,<sup>6</sup> only three studies have analysed the chemical composition of legal highs: two<sup>5,7</sup> within 6 weeks of the 2010 ban on substituted cathinones and one conducted 6 months later.<sup>4</sup> The research conducted immediately after cathinones was brought under the Misuse of Drugs Act in April 2010 found prohibited cathinone derivatives, including mephedrone in 62.5%<sup>5</sup> and 83%<sup>7</sup> of the legal highs tested. The same research also found that 70% of the new generation of legal highs

purporting to contain naphyrone (ie, NRG-1 and NRG-2) and marketed as a legal alternative to mephedrone, actually contained a mixture of banned cathinones, including mephedrone; the drug it was claiming to replace. Only one of the NRG products tested contained naphyrone as advertised,<sup>5</sup> illustrating that although marketed as legal products, many of the substances sold were actually illegal. Although research conducted immediately after the ban<sup>5,7</sup> found cathinones in the products they tested, it is possible that these findings merely reflect retailers' response to the ban and their attempts to sell off surplus stock containing the prohibited cathinones,<sup>5</sup> rather than their widespread availability. Supporting this supposition and in contrast to the research conducted immediately after the ban, research conducted 6 months later by Baron and colleagues<sup>4</sup> found no cathinones in the NRG products tested. Instead, the products contained piperazines (BZP: 1-benzylpiperazine and 3-TFMPP: 3-trifluoromethylphenylpiperazine), a substance banned in December 2009. Although this provides erudite evidence that illegal substances continue to be mis-sold as legal highs, it also demonstrates the inconsistent and varied ingredients found in these products.<sup>8</sup>

Therefore, the purpose of this study is to develop previous research and ascertain whether cathinones, such as mephedrone, are still being sold under the guise of newly labelled legal highs 18 months after they were banned. 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 during this period. The emergence of 41 new products in the last year<sup>3</sup> and demands for 'further characterisation of these products'<sup>5</sup> also indicates a prerequisite for continually analysing these substances to facilitate a better understanding of these products, particularly their chemical composition and their potential impact on public health. Although health professionals are aware of the problems associated with new drugs, the evidence suggests that they are not equipped to deal with these largely unknown synthetic substances. However, before considering the potential impact legal highs might be having on public health, our discussion commences with an overview of the research methods and the chemical analyses employed to ascertain the active ingredients present in each substance. Subsequently, this is followed by a discussion of the results, before considering the medical implications of mislabelling and selling unknown, often illegal substances. Although these findings have implications for the criminal justice system and the prosecution of users under the Misuse of Drugs Act (1971), this is beyond the remit of this paper, which focuses on the medical implications and adverse health risks associated with legal highs.

### METHODS

The research investigated a range of second- and third-generation legal highs (products created after the

chemical structure of banned substances were modified to bypass the legislation), which are available to purchase online. A total of 22 products marketed as research chemicals, plant food or bath salts were purchased from five different internet sites. The five internet sites were randomly selected from an online list generated using the terms 'buying research chemicals', 'buying plant food' and 'buying NRG-2'; the list was generated from the first 10 results on each page. A list of products available from more than two of the sites (to facilitate comparisons) was generated, and eight products were randomly chosen for this research. All the products were purchased 18 months after the April 2010 UK ban on cathinone substitutes and 15 months after the July 2010 ban on naphyrone. The products were handled and tested by an analyst with a Chief Officer of Police's delegated authority to be in possession of controlled substances. The substances were stored in the secure drug store of a local police force and retained by them for destruction at the conclusion of the experiments.

Information concerning the marketing, packaging, ingredients, method of use, dosage and warnings over use was noted. Each product was, in turn, analysed qualitatively using a combination of the techniques outlined in [box 1](#). Each product was analysed with Fourier Transform Infrared Spectroscopy, Raman Spectroscopy and Proton Nuclear Magnetic Resonance (NMR). Additionally, where there was an indication from the spectroscopy that a product contained an illegal substance and that product was analysed with  $^{13}\text{C}$  NMR. For the Fourier Transform Infrared Spectroscopy and Raman Spectroscopy, the products were analysed in solid form. Those products supplied as a tablet were ground to

a powder, while those supplied as a capsule were emptied. For both NMR, 0.1 gm of the powder was dissolved in 0.6 ml of deuterated chloroform ( $\text{CDCl}_3$ ) for analysis. All instruments were calibrated using calibration sources and correction software supplied by the manufacturers. No specific comparison with reference standards for the illegal chemicals identified was undertaken.

## RESULTS

The results of the analyses were compared with the information provided by the suppliers and the legality of the active ingredients ascertained. This information is summarised in [table 1](#). Although methoxetamine was legal when the research was conducted, it was classified as a temporary class drug in March 2012, making its supply illegal.

### Advertised active ingredients: consistency in what you get?

The majority of products purchased (91%) provided information pertaining to the active ingredients present in each substance (either on the website or packaging, or both), although products purchased from three of the suppliers (A, B and D) did not adhere to the advertised ingredients. Out of the 22 products supplied and analysed, 9% did not list the active ingredients (Jolly Green Granules) and 23% did not contain the active ingredients listed on the website or package. Instead of containing 17- $\alpha$ ,21-Dihydroxy-16- $\alpha$ -methylpregna-1,4,9(11)-triene-3,20-dione-21-acetate, both of the NRG-3 products contained benzofuran (1-benzofuran-6-ylpropan-2-amine). This suggests that the benzofuran mixture is being sold as a number of different products (benzofuran and NRG-3), thus supporting previous research.<sup>4</sup> Benzofuran was found in 27% of the products, and although it is chemically similar to amphetamines and MDMA, there is little scientific information on its toxicity, its psychoactive properties or its effect on humans and their health. Instead of the advertised ingredients, benzocaine was found in three of the products (MDAI and both Jolly Green Granules). Benzocaine is a local anaesthetic and a popular cutting agent for cocaine. In contrast to earlier research,<sup>5</sup> there were no traces of mephedrone in either of the Jolly Green Granules. However, both NRG-2 products contained 4-methylethcathinone (4-MEC) with a smaller, trace, amount of 4-methylmethcathinone (4-MMC) or mephedrone, possibly as an unwanted contaminant, making them illegal. By measuring the integrated intensities of the Proton NMR resonances,<sup>9</sup> the relative concentration of 4-MEC was approximately 35 times that of 4-MMC. Consistent with the findings of Brandt *et al*,<sup>5</sup> no other compounds were found in either NRG-2 samples. Therefore, the product being sold is of a high purity and the amount of illegal cathinone taken is simply the quantity of powder consumed.

### Legal highs or illegal highs?

The majority of products (91%) were identified as containing either the active ingredients stated on the

## Box 1 Analysis techniques

### Fourier Transform Infrared Spectroscopy

Fourier Transform Infrared Spectroscopy analyses the composition of a substance by measuring how much infrared energy is absorbed by different molecules, thereby enabling the molecules present to be determined.

### Raman Spectroscopy

Raman Spectroscopy uses inelastic scattering of monochromatic light (usually a laser) to excite vibrational modes of bonds in the sample that result in a frequency shift of the emitted light, thereby enabling the composition of the sample to be determined.

### Proton Nuclear Magnetic Resonance ( $^1\text{H}$ NMR)

Proton Nuclear Magnetic Resonance uses the absorption of electromagnetic waves by protons ( $\text{H}^+$  ions) in a magnetic field that results in a frequency shift of the emitted electromagnetic waves to enable the composition of the sample to be determined.

### Carbon-13 NMR ( $^{13}\text{C}$ NMR)

Carbon-13 NMR employs the same principle as proton NMR but uses resonance of the C13 atom rather than the proton.

## The pharmacology of novel psychoactive substances

**Table 1** Summary of the 22 legal highs purchased via the internet, including the compounds detected, the accuracy of their description and their legal status

	Product	Compounds detected	As described	Status
Supplier A	Benzofury	1-Benzofuran-6-ylpropan-2-amine (6-APB)	Yes	Legal
	Jolly Green Granules	Benzocaine	Did not specify contents	Legal
	MDAI	5,6-Methylenedioxy-2-aminoindane	Yes	Legal
	Methoxetamine	2-(3-Methoxyphenyl)-2-(ethylamino) cyclohexanone	Yes	Legal*
	MPA	N-methyl-1-(thiophen-2-yl)propan-2-amine	Yes	Legal
	NRG-2	4-Methylethcathinone (4-MEC). Contaminant mephedrone	No	Illegal
	NRG-3	1-Benzofuran-6-ylpropan-2-amine (6-APB)	No	Legal
Supplier B	5-IAI	5-Iodo-2-aminoindane	Yes	Legal
	Benzofury	1-Benzofuran-6-ylpropan-2-amine (6-APB)	Yes	Legal
	MDAI	Benzocaine	No	Legal
Supplier C	5-IAI	5-Iodo-2-aminoindane	Yes	Legal
	Benzofury	1-Benzofuran-6-ylpropan-2-amine	Yes	Legal
Supplier D	Methoxetamine	2-(3-Methoxyphenyl)-2-(ethylamino) cyclohexanone	Yes	Legal*
	Jolly Green Granules	Benzocaine	Did not specify contents	Legal
Supplier E	MDAI Gold	5,6-Methylenedioxy-2-aminoindane	Yes	Legal
	MPA	N-methyl-1-(thiophen-2-yl) propan-2-amine	Yes	Legal
	NRG-2	4-Methylethcathinone (4-MEC). Contaminant mephedrone	No	Illegal
	NRG-3	1-Benzofuran-6-ylpropan-2-amine (6-APB)	No	Legal
	5-IAI	5-Iodo-2-aminoindane	Yes	Legal
	Benzofury	1-Benzofuran-6-ylpropan-2-amine (6-APB)	Yes	Legal
	MDAI Gold	5,6-Methylenedioxy-2-aminoindane	Yes	Legal
	Methoxetamine	2-(3-Methoxyphenyl)-2-(ethylamino) cyclohexanone	Yes	Legal*

\*Legal—methoxetamine was legal when this research was initially conducted; however, it has since (March 2012) been classified as a temporary class drug making its supply illegal.

packet or a chemical that is not controlled in the UK. Of the four NRG products analysed further by  $^{13}\text{C}$  NMR to confirm their contents, only two were found to contain the illegal compounds 4-methylethcathinone and 4-methylmethcathinone (mephedrone). 4-Methylethcathinone (4-MEC) is classified as a class B controlled substance in the UK. Even though it is not named specifically on the class B drug list, it is a substituted cathinone and therefore subject to the 2010 Misuse of Drugs Act (Amendment) Order. 4-MEC is structurally derived from cathinone by substitution in the phenyl ring with an alkyl substituent and by substitution at the nitrogen atom with an alkyl group (see [figures 1 and 2](#)).

The contaminant 4-methylmethcathinone (mephedrone) in NRG-2 is also a substituted cathinone and a class B controlled substance in the UK, subject to the 2010 Misuse of Drugs Act (Amendment) Order (see [figure 3](#)).

These findings show illegal cathinones are still being sold online as legal alternatives to illegal substances, which was also a marketing tool used by all the suppliers in this research. Analogies were made between the substances for sale and the recently banned cathinone,

mephedrone or illegal drugs like amphetamine, ecstasy (MDMA) or ketamine.

### Variation between retailers

The chemical composition of the products purchased from supplier A and supplier D were identical, as was the packaging, indicating that either two websites are fronting the same company or that both companies purchase goods from the same source. Specifically, the NRG-2 products tested from suppliers A and D and the relative concentration of each chemical suggested that they originated from the same source. If both suppliers A and D obtained NRG-2 from the same source, this suggests that, given the large quantities available to purchase (up to 1 kg), the scale of production or importation of these substances is alarming.

Suppliers varied on the information they provided in terms of contents, instructions on use and whether the drug was labelled 'not fit for human consumption'. Of the 22 products purchased, 68% contained the warning 'not fit for human consumption' on the internet site but all contained this warning on the packaging. Although 23% had information on how to use the product, this

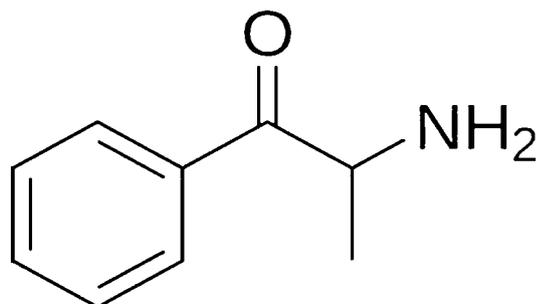
was of little use if the user intended to ingest it, as it related to feeding plants or conducting research (see [table 1](#)). The information provided included 'doses of 0.05 g will give your plants incredible growth ... to be dissolved in water' and 'very small doses of this research chemical are required for legitimate research, it is essential that your lab has access to scales that can weigh in increments of ten milligrams (0.01 g)'. The majority of websites and drug packets contained no safety information (77%) explaining how to use the substance or the recommended dose, which is concerning since many of the substances purchased could be bought in amounts that varied from 1 g to 1 kg.

## DISCUSSION

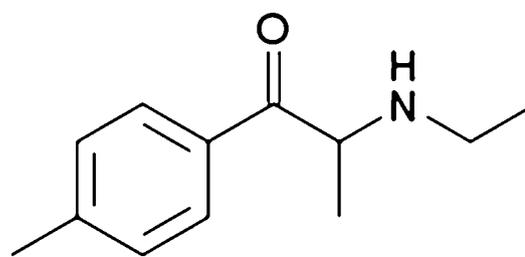
This study has shown that substituted cathinones continue to be freely available for purchase over the internet, 18 months after being classified as a class B drug. Two products, both sold as 'NRG-2' from different internet suppliers, were found to contain the banned substituted cathinones 4-methylethcathinone (4-MEC) and 4-methylmethcathinone (4-MMC), the latter being present in trace quantities. The physical appearance, packaging, labelling (not for human consumption) and chemical analysis of these products suggest that they originated from the same source, although neither product contained the ingredients listed. In contrast to previous research,<sup>5 7</sup> the majority (68%) of substances tested in this study contained the stated active ingredients. Of the 22 products supplied and analysed, 9% did not list the ingredients and 23% did not contain the ingredients listed on the website or package, which means consumers are putting their health at risk. The inconsistent ingredients, varied chemical composition and unknown subsequent drug interactions are potentially harmful to the user, particularly since these substances are of a high purity and available to buy in large quantities (up to 1 kg).

### Strengths and weaknesses of this study in the wider context

Our study employed a range of recognised analytical techniques to identify the active ingredients in each of the products purchased. While the analysis carried out here is not in itself a weakness, a limitation of this study



**Figure 1** Structure of cathinone (2-amino-1-phenyl-1-propanone).

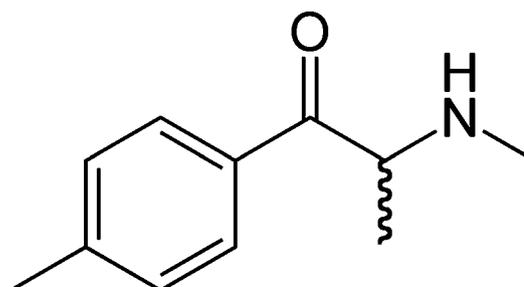


**Figure 2** Structure of the banned substituted cathinone 4-MEC (4-Methylethcathinone).

is the relatively small sample size. Our study purchased and analysed 22 random products from five internet suppliers and, from the packaging and chemical analyses, two of these suppliers appeared to be selling products from the same source. Thus, at best, we have analysed products from four different sources and only found banned substances in two of the products. However, this is the first analysis of the composition and legal classification of substances, sold under the banner of research chemicals, to be carried out within the past 12 months. Also, the number of products tested here (22) is far in excess of the number tested in the previous most recent study (seven),<sup>4</sup> which failed to find cathinones in any of their products. Our research also overcomes the caveats associated with the previous work carried out within 6 weeks<sup>5 7</sup> or 6 months<sup>4</sup> of the 2010 amendment. Our findings show that research conducted immediately after the 2010 ban, which found cathinones in a number of legal highs,<sup>4 6</sup> was not merely indicative of the retailers' attempts to sell off surplus stockpiles of mephedrone. Instead, this research indicates that despite being brought under the Misuse of Drugs Act (1971), substituted cathinones are still being sold illegally over the internet. Although the extent to which substituted cathinones are supplied is still unknown, finding cathinones in the small sample of products tested here indicates that the widespread distribution of cathinones over the internet is highly probable.

### Implications for clinicians and policy makers

Despite the perception that 'legal' means 'safe' to some users,<sup>10 11</sup> NPSs appear to be more harmful than many of



**Figure 3** Structure of the banned substituted cathinone 4-MMC or mephedrone (4-methylmethcathinone).

their more traditional illegal counterparts. Even though drugs like benzofuran, bromo-dragonFLY and MPA (N-methyl-1-(thiophen-2-yl)propan-2-amine) are legal to buy, little is known about the safety of these substances, how they interact with other drugs, their long-term effects (psychologically and behaviourally) on humans or their toxicity. This also applies to the banned drugs naphyrone,<sup>12 13</sup> synthetic cannabinoids<sup>14</sup> and mephedrone.<sup>15–17</sup> Users of substituted cathinones like mephedrone are presenting to hospitals with tachycardia (rapid heart rate), hypertension, chest pains, myoclonus (muscle contractions), hallucinations, paranoia, violence and sympathomimetic syndrome.<sup>17</sup> Although there is emerging medical research documenting the harmfulness of NPSs,<sup>12–18</sup> there is also evidence pertaining to the emergent health risks associated with legal anaesthetics, like benzocaine and lidocaine, which are being sold in their place.<sup>5</sup> Allergic reactions to benzocaine are common and ingesting more than the recommended amount can cause an overdose, particularly in susceptible individuals because there is 'no therapeutic window' (between the doses required to produce a therapeutic effect and those producing toxicity).<sup>19</sup> Benzocaine has also been linked to a toxic blood disorder methemoglobinemia in adults who take small quantities medicinally<sup>20</sup> and unknown quantities illicitly in adulterated cocaine.<sup>21</sup> The presence of benzocaine in legal highs is well documented.<sup>5 22</sup> However, it is never listed as one of the active ingredients meaning each product contains indefinite quantities, which is disturbing since research estimates that benzocaine induced methemoglobinemia only requires a small amount to cause cyanosis<sup>19 23</sup> (a bluish discoloration of the skin caused by a deficiency of oxygen in the blood). Although there have been no known deaths from benzocaine, the death of a teenager was attributed to cocaine containing four times the toxic dose of lidocaine,<sup>24</sup> illustrating the potential health risks arising from the varied composition of these products.

The arbitrariness of the advertised ingredients and mislabelling of products exacerbates the detrimental consequences for the health of the user. Products do not always contain the advertised active ingredients,<sup>8</sup> even those with the same name. The contents of the NRG products have varied substantially from one type of cathinone, to a combination of cathinones, to banned piperazines, and to inorganic material or benzocaine.<sup>4 5 7 25 26</sup> Users are inadvertently being exposed to unidentified drugs in unknown concentrations, which increase the risk of toxicity and overdose. Those repeatedly buying the same product and expecting the same effects may actually be taking a completely different and more potent substance. The user is also exposed to the risks arising from the potentiating effect of any drug interactions and their subsequent metabolites produced inside the body. However, any adverse effects brought on by these drugs are unlikely to be identified by clinicians, as drug screening

does not identify these new and unique compounds,<sup>27</sup> and despite recent publications examining specific toxicity case studies,<sup>28</sup> their toxicological detection in biological specimens is challenging.<sup>29</sup> Since only a small amount is need to elicit an effect and the minimum amount that can be purchased is 1 g, users will continue to present themselves to A&E departments across the country. Medical practitioners need to be made more aware of these substances, their effects and potential health risks. The healthcare professionals who are aware of the problems associated with NPSs are ill equipped to deal with them due to the paucity of scientific and medical research in this area. Since Public Health England recognises the 'importance of having an effective, highly trained and professionally skilled Public Health workforce',<sup>30</sup> this is an area that needs addressing. Research and reliable medical data on NPSs are sparse, and despite requests, there is no 'centralised system ... linking for instance toxicology and forensics across the country to collate information'.<sup>31</sup>

The public health risks associated with these drugs are compounded by the lack of safety guidance (ie, use and dosage information) provided by websites. All substances are labelled as not fit for human consumption, with some advocating medical assistance if swallowed. While this does not seem to deter use, it means that NPSs can be sold having undergone no checks and adhering to no regulations, which means that they could contain anything. Therefore, the growth in NPSs poses insurmountable challenges to clinicians attempting to identify and diagnose the adverse health effects arising from the ingestion of un-researched, unknown and unidentifiable chemicals.

### Unanswered questions and future research

The small sample (22 products) analysed in this study means the question of how many sites are selling products containing banned substances, how widespread the purchase of these substituted cathinones actually is and the extent to which they are being taken by unsuspecting consumers remains unknown. Since there is an estimated 314 online shops,<sup>32</sup> about 80 of which are based in the UK, we sampled products from <2% of these online suppliers. Therefore, future research should investigate a much wider range of internet suppliers and their products to establish the chemical composition of these substances and to help identify which products contain prohibited substances like mephedrone. Future research could also usefully investigate low-level contaminants in these substances, not least as a possible means of linking sites of manufacture. There is a need for more medical research to be conducted in this area examining the potential impact NPSs have on public health. This article illustrates more training for clinicians is required and demonstrates the need for a centralised system, which collates and stores information that medical practitioners can draw on when faced with a suspicious case. Surprisingly, there has been no public

health campaign highlighting the risks associated with NPSs to raise awareness among the public or the medical profession, despite the potential risks to health.

## CONCLUSIONS

Illicit cathinones continue to be sold online under the guise of 'legal highs'. The imposition of legislative controls banning certain substances has had little effect on the chemical composition of NPSs or their availability, indicating that bringing in new laws on drugs as quickly as they emerge is not tackling the problem of supply (or demand). Instead, it displaces the problem and invites chemists to modify the molecular structure of chemicals to create legal alternatives to the newly banned substances. The continual evolution of chemical compounds designed to evade the law is potentially creating more dangerous and unknown synthetic substances than the ones currently being legislated on. Although these substances are potentially more harmful than their illegal counterparts, many remain legal to buy and consume, thus undermining the scientific calculation of harm that underpins drug legislation, a calculation, which has come under increasing criticism in recent years.<sup>33 34</sup> It also poses an infinite challenge to mainstream healthcare professionals dealing with the adverse health effects arising from these substances.

Although new substances are constantly being created to evade the law, illegal ones are also being sold openly on the internet, indicating that the police are unable to enforce current legislation and prohibit supply. Unsuspecting buyers are breaking the law and are buying substances that are potentially harmful. NPSs have the potential to cause serious public health problems to a new generation of drug users who see them as a safer alternative to their illicit counterparts.<sup>10 11</sup> The public health costs of treating users in the short- and long-term comes at a time of economic paucity and cut backs in the public health sector. The medical profession are facing a new genre of NPS induced illnesses and an increase in toxicity cases but lack the methodology required to detect these drugs (and their metabolites) in biological samples or recognise the symptoms of toxicity. Prohibition is intended to protect public health by limiting the availability and use of drugs like substituted cathinones. However, legislation would appear to be failing and is simply displacing drug use. Users continue to consume an array of unknown synthetic compounds and can easily purchase large amounts (1 kg) of illegal substances, despite—and perhaps entirely unaware of—the unpredictable consequences it may have on their health.

**Acknowledgements** The authors would like to thank Amy Miller for assisting JWB with the analysis in the laboratory and Dr David Wood for the helpful advice he provided at the outset of this research project; it was much appreciated. We would also like to thank Yvonne Jewkes for reading and commenting on this paper. We would also like to thank the two reviewers for their helpful comments.

**Contributors** TCA conceptualised the paper and applied for funding to conduct the research. JWB conducted the chemical analysis of the substances. Both

authors contributed to the writing, argument and structure of the article including any revisions that have been made.

**Funding** This study was funded by the University of Leicester, College of Social Sciences research grant. The funding source had no role in the study design, analysis or in the writing up of the research.

**Competing interests** None.

**Ethics approval** This research received ethical approval (reference tca2-88995) from the Criminology Department's ethics committee.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** There are no additional data available.

## REFERENCES

1. Advisory Council on the Misuse of Drugs. *Consideration of the Novel Psychoactive Substances (Legal Highs)*. London: ACMD, 2011.
2. International Narcotic Control Board. *Annual Report*. New York: United Nations, 2011.
3. European Monitoring Centre for Drugs and Drug Addiction. *Europol 2010 Annual Report on the Implementation of Council Decision 2005/387/JHA*. Lisbon: EMCDDA, 2011.
4. Baron M, Eile M, Eile L. Analysis of legal highs—do they contain what it says on the tin? *Drug Test Anal* 2011;3:576–81.
5. Brandt SD, Sumnall HR, Measham F, *et al*. Analyses of second-generation 'legal highs' in the UK: initial findings. *Drug Test Anal* 2010;2:377–82.
6. Dargan PI, Hudson S, Ramsey J, *et al*. The impact of changes in UK classification of the synthetic cannabinoid receptor agonists in 'Spice'. *Int J Drug Policy* 2011;22:274–7.
7. Ramsey J, Dargan PI, Smyllie M, *et al*. Buying legal recreational drugs does not mean that you are not breaking the law. *QJM* 2010;103:777–83.
8. Davies S, Wood DM, Smith G, *et al*. Purchasing legal highs on the internet—is there consistency in what you get? *QJM* 2010;103:489–93.
9. Pauli GF, Jaki BU, Lankin DC. A routine experimental protocol for qHNMR illustrated with Taxol. *J Nat Prod* 2007;70:589–95.
10. Measham F, Moore K, Newcombe R, *et al*. Tweaking, bombing dabbing and stockpiling: The emergence of mephedrone and the perversity of prohibition. *Drugs Alcohol Today* 2010;10:14–21.
11. Sheridan J, Butler R. They're legal so they're safe right? *Int J Drug Policy* 2010;21:77–81.
12. Advisory Council on the Misuse of Drugs. *Consideration of the Naphthylpyrovalerone Analogues and Related Compounds*. London: ACMD, 2010.
13. De Paoli G, Maskell PD, Pounder DJ. Naphyrone: analytical profile of the new "legal high" substitute for mephedrone. *J Forensic Leg Med* 2011;18:93.
14. EMCDDA. *Understanding the Spice Phenomenon*. Lisbon: EMCDDA, 2009.
15. Gibbons S, Zloh M. An analysis of the legal high mephedrone. *Bioorg Med Chem Lett* 2010;20:4135–9.
16. Vardakou I, Pistos C, Spiliopoulou C. Drugs for youth via Internet and the example of mephedrone. *Toxicol Lett* 2011;201:191–5.
17. Spiller HA, Ryan ML, Weston RG, *et al*. Clinical experience with and analytical confirmation of "bath salts" and "legal highs" (synthetic cathinones) in the United States. *Clin Toxicol (Phila)* 2011;49:499–505.
18. Wood DM, Looker JJ, Shaikh L, *et al*. Seizures associated with recreational use of Bromo-dragonFLY. *J Med Toxicol* 2009;5:226–9.
19. Guay J. Methemoglobinemia related to local anaesthetics: a summary of 242 episodes. *Anesth Analg* 2009;108:837–45.
20. Osterweil N. Topical Benzocaine associated with methemoglobinemia. *Medscape Today* 2011.
21. Hunter L, Gordge L, Dargan PI, *et al*. Methemoglobinemia associated with the use of cocaine and volatile nitrates in recreational drugs: a review. *Br J Clin Pharmacol* 2011;72:18–26.
22. Power JD, McGlynn P, Clarke K, *et al*. The analysis of substituted cathinones. Part 1: chemical analysis of 2-,3- and 4-methylmethcathinone. *Forensic Sci Int* 2011;212:6–12.
23. McKinney CD, Postiglione KF, Herold DA. Benzocaine-adulterated street cocaine in association with methemoglobinemia. *Clin Chem* 1992;38:596–7.
24. SOCA. *Drug Profits Take a Hammering as Benzocaine Haul is Burned*. London: Stationary Office, 2010. <http://www.soca.gov.uk/news/260-drug-profits-take-a-hammering-as-benzocaine-haul-is-burned-> (accessed 25 Sep 2011).

## The pharmacology of novel psychoactive substances

25. Brandt SD, Freeman S, Sumnall HR, *et al.* Analysis of NRG 'legal highs' in the UK: identification and formation of novel cathinones. *Drug Test Anal* 2011;3:569–75.
26. Brandt SD, Sumnall HR, Measham F, *et al.* Second generation mephedrone: the confusing case of NRG-1. *BMJ* 2010;341:3564.
27. Smith CPT, Cardile AP, Miller M. Bath salts as a "legal high". *Am J Med* 2011;124:e7–8.
28. Salmner EM, Foley PL, Lauder GD, *et al.* A harmless high? *Lancet* 2010;376:742.
29. Houston S. *Forensic Magazine. Detecting Bath Salts*. 25 Oct 2011. <http://www.forensicmag.com/news/detecting-bath-salts>
30. Marshland A. *Public Health England: A Letter*. London: Department of Health, 2011. <http://bhamcf.files.wordpress.com/2010/10/nhs-pblchlhtr-11-3.pdf> (accessed 20 Dec 2011).
31. Boyce N. Health warnings for people who use heroin. *Lancet* 2011;377:193–4.
32. EMCDDA. *Annual Report 2011: The State of the Drugs Problem in Europe*. Lisbon: EMCDDA, 2011.
33. Nutt D, King L, Phillips L. Drug harms in the UK: a multicriteria decision analysis. *Lancet* 2010;376:1558–65.
34. Rolles S, Measham F. Questioning the method and utility of ranking drug harms in drug policy. *Int J Drug Policy* 2011;22:243–6.



# 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?

Tammy C Ayres and John W Bond

*BMJ Open* 2012 2:

doi: 10.1136/bmjopen-2012-000977

---

Updated information and services can be found at:

<http://bmjopen.bmj.com/content/2/4/e000977.full.html>

---

*These include:*

**Data Supplement**

*"Supplementary Data"*

<http://bmjopen.bmj.com/content/suppl/2012/08/04/bmjopen-2012-000977.DC1.html>

**References**

This article cites 24 articles, 4 of which can be accessed free at:

<http://bmjopen.bmj.com/content/2/4/e000977.full.html#ref-list-1>

**Open Access**

This is an open-access article distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license. See:

<http://creativecommons.org/licenses/by-nc/2.0/> and <http://creativecommons.org/licenses/by-nc/2.0/legalcode>.

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

---

To request permissions go to:

<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:

<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:

<http://group.bmj.com/subscribe/>

**Topic  
Collections**

Articles on similar topics can be found in the following collections

[Addiction](#) (34 articles)  
[Global health](#) (82 articles)  
[Health policy](#) (125 articles)  
[Pharmacology and therapeutics](#) (167 articles)  
[Public health](#) (436 articles)

---

**Notes**

---

To request permissions go to:

<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:

<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:

<http://group.bmj.com/subscribe/>