

## **“Legal Highs” – A UK Update**

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The supply of recreational drugs to users has changed over recent years, with increasing use of the Internet to source recreational drugs and / or purchase “legal highs” from high street head shops [1, 2]. These changes have been associated with a change in the types of compounds being used as recreational drugs, with increased use of novel compounds such as cathinones, piperazines and synthetic cannabinoid receptor agonists (“spice”) [3]. Until successive legislative changes, becoming effective from the 23<sup>rd</sup> December 2009 and 16<sup>th</sup> April 2010, all of these novel compounds have at some point been sold legally and were not controlled under the UK Misuse of Drugs Act (1971).

There is a general belief among users of these new, legal compounds that they are a ‘safe’ alternative to other illicit stimulants such as MDMA (methylenedioxymethamphetamine), amphetamine or cocaine. However there are numerous case reports of toxicity similar to that seen with classical recreational drugs in individuals using these “legal highs” [4-10]. As a result of the toxicity associated with some of these compounds, the UK Misuse of Drugs Act (1971) was amended to control piperazines as Class C compounds, and synthetic cannabinoid receptor agonists as Class B compounds [11]. Later, this was further updated to control the cathinone derivatives such as 4-methylmethcathinone (mephedrone) as Class B compounds [12].

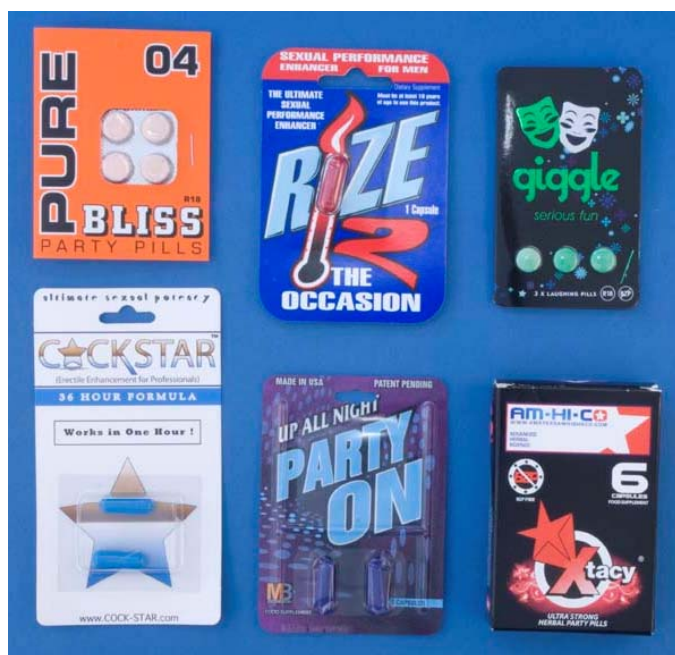
Despite these popular compounds becoming controlled in the UK, it is far from the end of “legal highs”, novel designer drugs and Internet drug shopping. Many more alternative stimulants are being prepared to replace those lost to government control and to keep this popular and lucrative market from crashing. This article aims to give an overview of how the legal high market has changed dramatically over recent months in the UK, and discusses how this chapter in our drug history is not over yet.

Studies used to monitor the drug dance scene market have previously analysed drugs removed from individuals entering nightclubs or large music festivals, which are deposited by security staff in “drug amnesty bins” [13, 14]. Analysis of drugs at turn of the century showed that tablets from both London and Manchester contained MDMA in >94% and >84% of tablets respectively. More recent studies have analysed drugs removed from / left by individuals presenting to the Emergency Department with acute recreational drug toxicity [15]. These have shown that the pattern of drugs used appears to have changed, with detection of a number of novel recreational drugs, including the piperazines.

Drug amnesty bin data from the 2009 Glastonbury Music Festival, a large outdoor music event that takes place over 4 days, also showed a distinct change in drug use patterns. The ecstasy tablets containing predominantly MDMA seen in previous years (2007 and 2008) had virtually disappeared (0.08% of amnesty bin tablets) and had been replaced by the then legal piperazine group of stimulants (38% of tablets). A large proportion of these were what appeared to be ‘ecstasy’ tablets with logos commonly seen on tablets containing MDMA. It is unknown whether such tablets were being sold as ecstasy or as legal highs. Coloured capsules containing piperazines and the Spice compounds were widely available on the festival site for sale through legal shop stalls.

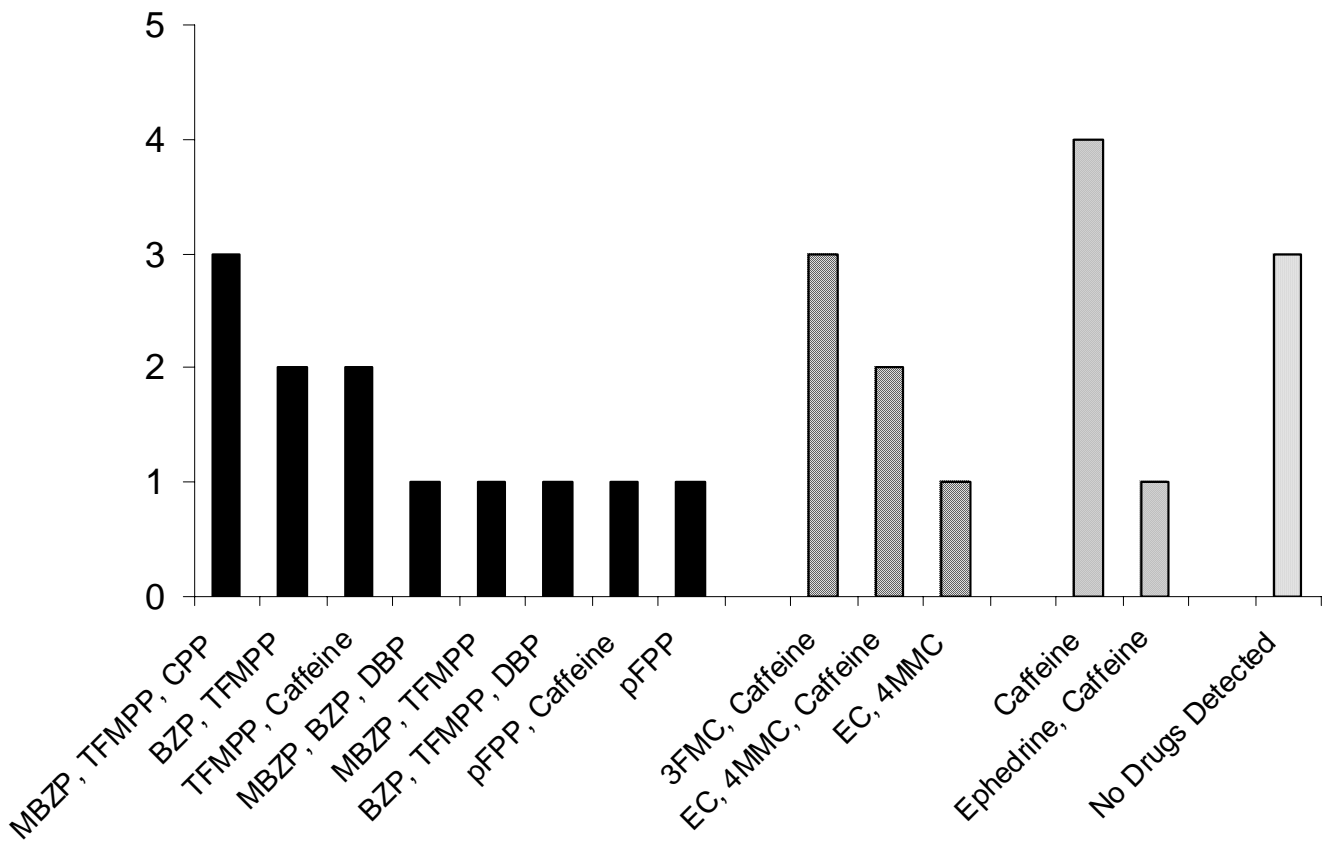
A significant proportion of amnesty bin items removed from people at the Glastonbury festival 2009 were found to be either multivitamin related products (10%) or fake ecstasy tablets containing no detectable drugs or made from Plaster of Paris (20%).

Legal highs sold over the Internet are often sold in packaging that does not provide detailed, if any, information on the contents of the tablets or capsules. No previous studies have comprehensively purchased items from the internet to ascertain their true contents, or determined whether the same named products change in content over time. Between January and June 2009, in a joint study between St George's University of London and Guy's and St Thomas's Clinical Toxicology Service, regular purchases were made from five different Internet sites well known for marketing and sale of "legal highs" [16]. 26 different products were purchased in month 1 and this was continued, with the same products purchased, where products were still available, through months 2 to 6. Some of these products are shown in Figure 1. Samples were subsequently qualitatively analysed by a previously described gas chromatographic assay with mass-spectrometric detection (GC-MS) [13]. Where standards were not available commercially, particularly for the piperazines and cathinones, standard drug mixtures of both piperazines and cathinone derivatives were used following in-house production of necessary standards in conjunction with Kingston University [17].



**Figure 1:** Shows some of the legal high products purchased from five popular websites.

The substances detected in the legal highs purchased over the 6 months broadly fell into the following drug classes: piperazines, cathinones, caffeine/ephedrine or no drugs detected; the number of legal high products in each of these classes is summarised in Figure 2.



**Figure 2.** Breakdown of active ingredients detected based on drug class: Piperazines ± caffeine ■, cathinones ± caffeine ▨, caffeine/ephedrine ☒ and no active ingredient detected ☐. (MBZP: 1-methyl-4-benzylpiperazine, TFMPP: 3-trifluoromethylphenylpiperazine, CPP: 3-Chlorophenylpiperazine, BZP: 1-benzylpiperazine, DBP: 1,4-Dibenzylpiperazine, EC: ethcathinone, 4MMC: 4-methylmethacathinone, 3FMC: 3-fluoromethcathinone, pFPP: 4-Fluorophenylpiperazine).

The number of products supplied after month 1 showed a steady decline. This was due to the products being no longer available and/or replacement products supplied. Some of the Internet sites only supplied in month 1. Out of the 26 products purchased in month 1, 20 products were supplied on one or more subsequent months. 15 (75%) of these contained the same active ingredient(s) throughout the study. It was found that each supplier sold at least one product that demonstrated a variation in content at some point during the 6 months of purchases. Three cases showed a substitution in the piperazine detected, changing between BZP and MBZP. Also, a product that had contained caffeine and pFPP, was found to only contain caffeine in one month. The same situation was found in a capsule containing caffeine and 3FMC in previous months.

Examination of the packaging, ingredient lists and information supplied showed no obvious differences between products labelling that were subsequently found to contain different compounds. This shows that the user could not have been aware of these substitutions.

Despite the popularity of “legal highs”, they remain relatively expensive when compared to illicit alternatives. The cost of individual products purchased in the Internet study ranged from £5.50 to £11.99 per pack and each pack contained between 1 and 6 tablets or capsules. Those purchased from one website were supplied in an 18 capsule multi-pack the cost of £99. For the products that contained an active drug ingredient, when the cost per individual capsule or tablet was calculated, based on the number of tables in each pack, there appeared to be an association between the cost per tablet/capsule and the active drug class detected. The most expensive products per single item were found to contain cathinones e.g. 4-methylmethcathinone (mephedrone) or 3-fluoromethcathinone, with a mean cost of £5.50 per item. Piperazine containing products followed at £4.62 per item. Where only caffeine or ephedrine was detected, the items were the cheapest at a mean cost of £2.97 per item.

Interestingly, of the three purchases where no active drug was detected, the mean price was £4.33 per tablet/capsule, which is comparable to the price for purchases containing cathinones or piperazines. These items appeared to be tailored towards the male market with product names such as ‘Cockstar’ and ‘Rise 2 the Occasion’. They were screened for and found not to contain any of the three main phosphodiesterase type 5 inhibitor drugs sildenafil, tadalafil or vardenafil.

In this 2009 test purchasing study and amnesty bin data, which took place before the two recent legislation changes in the UK, the most commonly seen active drug class was the piperazines. The test purchasing from Internet sites also showed the cathinones and caffeine/ephedrine were also commonly present, also indicating several inconsistencies between their true content. Although legislative changes are likely to cause further changes to the drug content of many of these products, there will remain a demand for related items. It is unclear if users repeat buy the same items to achieve the same effects, or vary their intake depending on availability and current legislative controls. It is clear, however, that product names and packing can not be relied upon to indicate likely contents or consistency. There is then the risk that individuals will be exposed to different active drugs than those that they are used to. Potentially, this could increase the risk of unwanted effects or lead to acute toxicity due to a difference in the relative amounts of active drug ingredient(s). There is the potential for significant toxicity associated with piperazine and cathinone drugs [1, 4, 5] and so the variation in the active drug in these compounds is significant enough to be of clinical relevance.

Despite a relationship between price per tablet/capsule and the active drug content, it is unlikely that given that there is significant variation seen in this relationship, that an individual will be able to predict what “legal high” they will be using based purely on purchase price.

Following the first legislative change after the initial Internet purchasing study, a small follow up study was conducted in February 2010. Similar products were purchased from the same websites, although the exact same products were generally not available or websites had stop supplying following the recent negative publicity surrounding legal highs in the UK. Purchases did show a reduction in piperazine containing products, although one product was found to still contain BZP and TFMPP. Compounds detected showed a slight change in trend towards the then still legal cathinone related compounds such as beta keto MBDB (1-(1,3-benzodioxol-5-yl)-2-(methylamino)butan-1-one), and the ecstasy related compound MDPV (methylenedioxypropylvalerone).

No further purchases could be made before the second legislative change was introduced on the 16<sup>th</sup> April 2010, which saw all cathinone derivatives, including mephedrone and beta keto MBDB, as well as MDPV, becoming Class B controlled under the UK Misuse of Drugs Act 1971. To determine the effects of this most recent set of changes to the UK legislation, further follow up purchasing studies are currently being conducted. It is predicted that NRG-1 (naphthylpyrovalerone) and MDAI (5,6-Methylenedioxy-2-aminoindane), which currently fall outside of UK control will take the place of the infamous BZP and mephedrone that have dominated the UK market, news and political headlines over the last 12 months.

## **References**

1. Wood DM *et al.* Irish Psychiatrist. 2008; 9: 223-228.
2. Schifano F *et al.* Prog Neuropsychopharmacol Biol Psychiatry. 2006; 30: 640-6.
3. Dick D *et al.* Drugs Survey. Mix Mag. 2010; 225: 44-53.
4. Wood DM *et al.* Lancet. 2007; 369: 1490.
5. Wood DM *et al.* J Med Toxicol. 2010; In press.
6. Ovaska H *et al.* Eur J Emerg Med. 2008; 15: 354-356.
7. Wood DM *et al.* J Med Toxicol. 2009; 5: 226-229.
8. Dargan PI *et al.* Eur J Clin Pharmacol. 2008; 64: 553-554.
9. Wood DM *et al.* J Med Toxicol. 2008; 4: 254-257.
10. Lidder S *et al.* J Med Toxicol. 2008; 4: 167-169
11. Statutory Instrument 2009 No.3209 Dangerous Drugs. Misuse of Drugs Act 1971 (Amendment) Order 2009 (accessed 26<sup>th</sup> February 2010). Available at [http://www.opsi.gov.uk/si/si2009/pdf/uksi\\_20093209\\_en.pdf](http://www.opsi.gov.uk/si/si2009/pdf/uksi_20093209_en.pdf)
12. Statutory Instrument 2010 No.1207 Dangerous Drugs. Misuse of Drugs Act 1971 (Amendment) Order 2010 (accessed 12<sup>th</sup> May 2010). Available at [http://www.opsi.gov.uk/si/si2010/pdf/uksi\\_20101207\\_en.pdf](http://www.opsi.gov.uk/si/si2010/pdf/uksi_20101207_en.pdf)
13. Kenyon SL *et al.* Ther Drug Monit. 2005; 793-798.
14. Ramsey JD *et al.* BMJ. 2001; 323:603
15. Wood DM *et al.* Emerg Med J. 2010; In Press.
16. Davies S *et al.*\_QJM. Published online doi: 10.1093/qjmed/hcq056
17. LTG website [www.ltg.uk.net](http://ltg.uk.net) <http://ltg.uk.net/pages/monographs/d-monographs.asp> Last accessed 12 May 2010.