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Analyses of second-generation 'legal highs' in the UK: Initial findings

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In the UK, mephedrone and other so-called 'legal high' derivatives have recently been classified as Class B, Schedule I under the Misuse of Drugs Act 1971. Since then, alternative products have been advertised on a number of websites. In order to obtain an immediate snapshot of the situation, 24 products were purchased online from 18 UK-based websites over a period of 6 weeks following the ban in April 2010. Qualitative analyses were carried out by gas chromatography ion trap mass spectrometry using electron- and chemical ionization modes, nuclear magnetic resonance spectroscopy, and comparison with reference standards. Overall, the purchased products consisted of single cathinones or cathinone mixtures including mephedrone, butylone, 4-methyl-*N*-ethylcathinone, flephedrone (4-fluoromethcathinone) and MDPV (3,4-methylenedioxypyrovalerone), respectively. Benzocaine, caffeine, lidocaine, and procaine were also detected. The emphasis was placed on 'Energy 1' (NRG-1), a product advertised as a legal replacement for mephedrone-type derivatives usually claiming to contain naphyrone (naphthylpyrovalerone, O-2482). It was found that 70% of NRG-1 and NRG-2 products appeared to contain a mixture of cathinones banned in April 2010 and rebranded as 'new' legal highs, rather than legal chemicals such as naphyrone as claimed by the retailers. Only one out of 13 NRG-1 samples appeared to show analytical data consistent with naphyrone. These findings also suggest that both consumers and online sellers (unlike manufacturers and wholesalers) are, most likely unknowingly, confronted with the risk of criminalization and potential harm.

Keywords: naphyrone; legal high; NRG-1; NRG-2; mass spectrometry; forensic; clinical; cathinones

Introduction

The current debate on so-called 'legal highs'[1,2] has highlighted the difficulties encountered in the assessment of the motivations for and consequences of psychoactive drug use, alongside the broader issues of regulation, enforcement, and harm reduction in the current policy context. Earlier studies[3] exploring the motivation for use of legal highs suggested that the consumer's quest for legal psychoactive drugs reflected their perception that these substitutes were more likely to be of higher purity than street drugs, carry a lower risk of physical harm, and not face the possibility of criminal sanctions associated with the consumption of drugs controlled under the Misuse of Drugs Act 1971. In the UK, mephedrone and other cathinone derivatives were classified as Class B, Schedule I on 16 April 2010 by way of a generic definition.

As a consequence of this recent legislative change, commonly accessible cathinones such as mephedrone, MDPV (3,4-methylenedioxypyrovalerone) and butylone should have been removed from the product range offered on the Internet. In response to the recent ban, a number of alternative products have been promoted such as *Energy 1* (NRG-1), NRG-2, DMC (dimethocaine), and MDAI (5,6-methylenedioxy-2-aminoindane). These products have been marketed as legal substitutes for the recently criminalized first-generation legal highs, the mephedrone derivatives. One of the most prominently discussed of these second-generation products, at least in the UK media, is NRG-1, also advertised as naphyrone (naphthylpyrovalerone, O-2482), reflecting the presence of a naphthalene moiety instead of a substituted benzene ring commonly associated with cathinone drugs (see Figure 1 for structural representations).

The immediate introduction of alternative legal highs such as NRG-1 in mid-April 2010 raised questions about the identity of these novel derivatives which meant that initial qualitative determinations were warranted. Analyses of 24 purchased Internet products were carried out by gas chromatography ion trap mass spectrometry (GC-IT-MS) and nuclear magnetic resonance spectroscopy (NMR). Ionization methods used involved electron ionization (EI-IT-MS) and low-pressure chemical ionization (CI-IT-MS) with internal ionization using methanol as the CI reagent. Compound identifications were also supported by comparison with standards.

Experimental

Legal high products

A total number of 24 products were purchased online from 18 UK-based websites over a period of 6 weeks following the introduction of the ban on mephedrone and other substituted cathinones. Samples were dissolved in methanol at a concentration of 0.50 mg/mL and subjected to GC-(EI/CI)-IT-MS analysis. Qualitative analyses were based on the implementation of previously established methods employed for the profiling of

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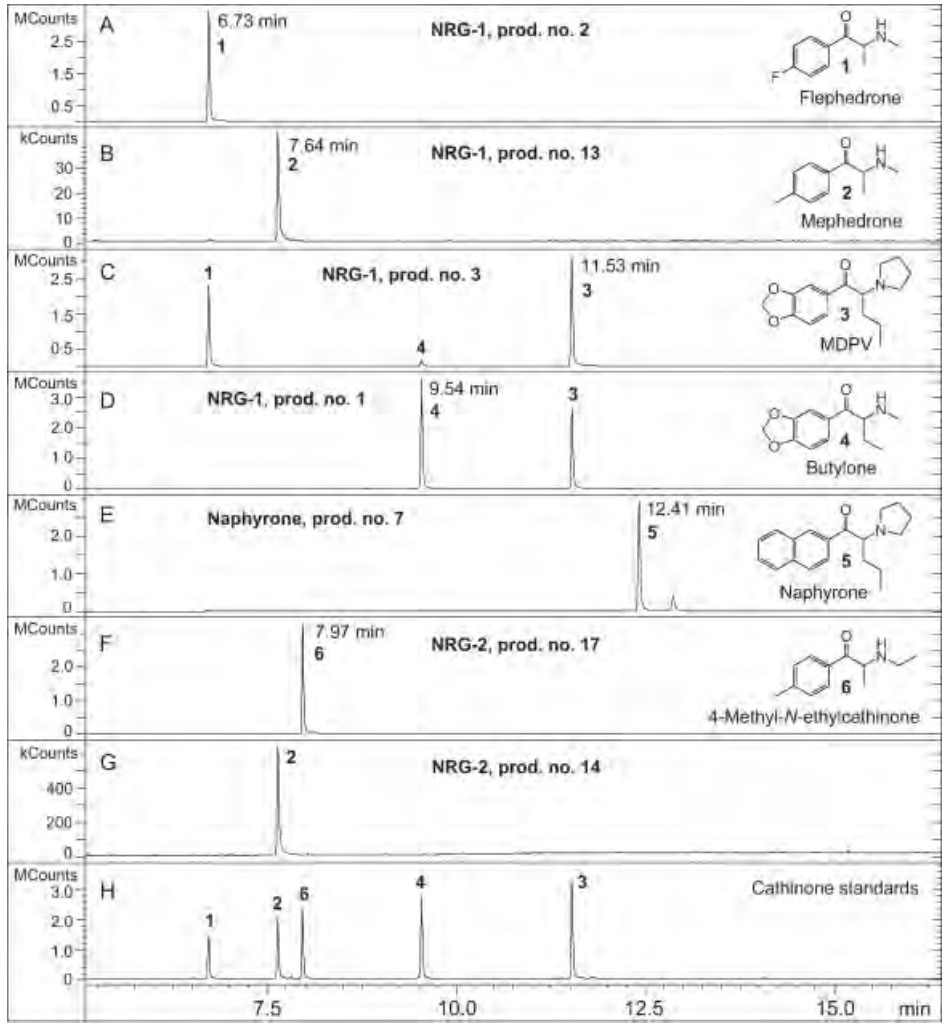

Figure 1. Representative GC-IT-MS traces of NRG-1 and NRG-2 products obtained from Internet websites. A variety of cathinone derivatives were detected (see Table 1 for summary).

related aromatic amine-like psychoactive drugs.[4] Flephedrone (4-fluoromethcathinone) **1** and 4-methyl-*N*-ethylcathinone **6** were synthesized as crude hydrochloride salts by adapting established procedures.[5–7] Mephedrone **2**, MDPV **3** and butylone **4** were available as single compounds obtained from Internet purchases prior to the introduction of legislation. NMR data of **3** were found to agree with data previously published.[8] Naphyrone **5** was not available as a standard but NMR data acquired from the purchased sample were found to be in agreement with literature values.[9] Remaining NMR and mass spectral data are reported below. Benzocaine (≥99%) **7**, caffeine (ReagentPlus) **8**, lidocaine (≥98%) **9** and procaine hydrochloride (≥99%) **10** were purchased from Aldrich (Dorset, UK).

Instrumentation

Samples were subjected to both electron ionization (EI) and chemical ionization (CI) modes. Both EI and CI mass spectra (scan range *m/z* 40–*m/z* 500) were obtained on a Varian 220-MS ion trap MS equipped with a Varian 450-GC gas chromatograph and a Varian 8400 autosampler. Data handling was carried out with the workstation, Version 6.91 software. The carrier gas was helium at a flow rate of 1 mL/min using the EFC constant flow mode. A CP-1177 injector (275 °C) was used in split mode (1 : 20). Transfer line, manifold and ion trap temperatures were set at 280, 80, and 220 °C, respectively. HPLC grade methanol was used as the liquid CI reagent. CI ionization parameters (0.5 s/scan): CI storage level 19.0 *m/z*; ejection amplitude 15.0 *m/z*; background mass 55 *m/z*; maximum ionization time 2000 µs; maximum reaction time 40 ms; target TIC 5000 counts. The number of ions in the trap was controlled by an automatic gain control function. Separations were carried out using 30 m × 0 25 mm (0.25 µm film thickness) Factor Four capillary column (VF-5 ms, Varian). The column temperature was programmed as follows: 100 °C held for 1 min, then heated at 20 °C/min to 280 °C and held constant for 10 min; total run time was 20 min.

A Micromass LCT orthogonal acceleration time-of-flight mass spectrometer (Micromass, Manchester, UK) equipped with an electrospray ionization source was operated in positive mode. Samples were introduced by flow injection using a Harvard Apparatus (Pump 11) (Kent, UK) syringe pump at 20 µL/min. The instrument was tuned and calibrated in the mass range of 100–1000 Da using a sodium formate solution (0.005 M in 50 : 50 acetonitrile-water). Exact mass measurements of cathinone products were based on the protonated molecules $[M+H]^+$. Leucine enkephalin (1 µg/mL) was used as lock mass standard after

instrument calibration. Operation settings were: capillary voltage: 3000 V; sample cone voltage: 30 V; RF lens: 250 V; desolvation temperature: 150 °C; source temperature: 100 °C; acceleration: 200 V; cone gas flow: 22 L/h; and desolvation gas flow: 602 L/h. Data acquisition was carried out using MassLynx Version 4.0 SP2.

NMR spectra were recorded using a Bruker Avance 300 spectrometer at 300.1 MHz (^{1}H NMR) or 75.5 MHz (^{13}C NMR). ^{1}H, ^{13}C and DEPT-135 NMR spectra were recorded in D_2O and chemical shifts are reported relative to TSP-d_4 at $\delta = 0$ ppm.

NMR data for 1, 2, 4 and 6

Flephedrone **1** *hydrochloride*

^{1}H-NMR (D_2O): 8.11 (2H, dd, ArH, J_{HH} 8.8 Hz, J_{HF} 5.25 Hz). 7.36 (2H, ArH, dd ~ t, $J_{HH} = J_{HF} \sim 8.7$ Hz), 5.10 (1H, q, α-CH, J 7.3 Hz), 2.83 (3H, s, *N*-CH_3), 1.63 (3H, d, α-CH_3, J 7.3 Hz,). ^{13}C-NMR (D_2O): 196.1 (CO), 132.1 (CH), 132.0 (CH), 128.9 (C), 116.6 (CH), 116.3 (CH), 60.0 (CH), 30.9 (*N*-CH_3), 15.2 (α-CH_3). HRESIMS theory $[M+H]^+$: 182.0981; observed: 182.0997 (+ 8.8 ppm).

Mephedrone **2** *hydrochloride*

^{1}H-NMR (D_2O): 7.95 (2H, d, ArH, J 8 3 Hz,), 7.47 (2H, d, ArH, J 8.1 Hz,), 5.11 (1H, q, α-CH, J 7.2 Hz), 2.84 (3H, s, *N*-CH_3), 2.47 (3H, s, 4-CH_3), 1.64 (3H, d, α-CH_3, J 7.2 Hz). ^{13}C-NMR (D_2O): 197.2 (CO), 147.4 (C), 129.9 (CH), 129.7 (C), 129.0 (CH), 59.3 (CH), 31.0 (*N*-CH_3), 21.0 (4-CH_3), 15 5 (α-CH_3). HRESIMS theory $[M+H]^+$: 178.1232; observed: 178.1244 (+ 6.7 ppm).

Butylone **4** *hydrochloride*

^{1}H-NMR (D_2O): 7.71 (1H, dd, ArH, J 8,2, 1.9 Hz,), 7.49 (1H, d, ArH, J 1.9 Hz), 7.05 (2H, d, ArH, J 8.3 Hz,), 6.154 (1H, d, OCH_2O, J_{gem} 0.9 Hz), 6.148 (1H, d, OCH_2O, J_{gem} 0.9 Hz), 5.06 (1H, t, α-CH, J 5.3 Hz), 2.79 (3H, s, *N*-CH_3), 2.17 (1H, ddq~ doublet of pentets, J_{gem} 5.3 Hz, J_{HH} 7.6 Hz), 2.07 (1H, ddq~ doublet of pentets, J_{gem} 5.3 Hz, J_{HH} 7.6 Hz), 0.90 (3H, t, α-$CH_2C\underline{H}_3$, J 7.6 Hz). ^{13}C-NMR (D_2O): 194.9 (CO), 153.6 (C), 148.4 (C), 127.6 (C), 108.6 (CH), 107.9 (CH), 102.7 (OCH_2O), 64.1 (α-CH), 31.7 (*N*-CH_3), 23.6 (α-CH_2), 7.5 (α-$CH_2C\underline{H}_3$). HRESIMS theory $[M+H]^+$: 222.1130; observed: 222.1118 (− 5.4 ppm).

4-Methyl-N-ethylcathinone **6** *hydrochloride*

^{1}H-NMR (D_2O): 7.95 (2H, d, ArH, J 8.3, 1.7 Hz,), 7.47 (2H, d, ArH, J 8.1 Hz,), 5.14 (1H, q, α-CH, J 7.2 Hz), 3.25 (1H, dq, *N*-CH_2, J_{gem} 12.4 Hz, ^{3}J 7.3 Hz), 3.15 (1H, dq, *N*-CH_2, J_{gem} 12.6 Hz, ^{3}J 7.2 Hz), 2.47 (3H, s, 4-CH_3), 1.62 (3H, d, α-CH_3, J 7.3 Hz), 1 38 (3H, t, *N*-$CH_2C\underline{H}_3$, J 7 3 Hz). ^{13}C-NMR (D_2O): 197.1 (CO), 147.5 (C), 129.9 (CH), 129.7 (C), 129.1 (CH), 57.9 (CH), 41.4 (*N*-CH_2), 21.0 (4-CH_3), 15.7 (α-CH_3), 10.7 (*N*-$CH_2\underline{C}H_3$). HRESIMS theory $[M+H]^+$: 192.1388; observed: 192.1400 (+ 6.2 ppm).

Results and Discussion

A total number of 24 legal high products were purchased from 18 UK-based websites over a period of 6 weeks following the ban on mephedrone in April 2010. Most products were delivered in transparent plastic or, occasionally, silver foil bags. The majority of products appeared as white or beige-coloured powders or crystals. Product No. 10 appeared as dark-brown oil whereas product No. 22 was delivered in the form of green-coloured granules. The majority of envelopes delivered by postal mail did not show any indication of the correlating website (e.g. via invoice, label, or address). All product envelopes showed UK-based postal stamps.

Table 1. 'Legal highs' purchased online on UK-based websites over a period of 6 weeks following the ban of mephedrone on 16th April 2010. Focus was placed on NRG-1 and NRG-2 products.[a] Website number;[b] Product number

WS[a]	Prod. no.[b]	Label	Compounds detected
1	1	NRG-1	Butylone + MDPV
2	2	NRG-1	Flephedrone (4-fluoromethcathinone)
3	3	NRG-1	Flephedrone + MDPV
4	4	NRG-2	4-Methyl-*N*-ethylcathinone
5	5	NRG-1	Flephedrone + MDPV
6	6	NRG-1	Caffeine (+ mephedrone traces)
7	7	NRG-1	Naphyrone
8	8	NRG-1	Butylone + MDPV
9	9	MDAI	Inorganic material
10	10	NRG-1	Mephedrone
11	11	NRG-1	Inorganic material
11	12	NRG-2	Mephedrone + benzocaine
12	13	NRG-1	Mephedrone
12	14	NRG-2	Mephedrone
12	15	DMC	Caffeine + lidocaine
12	16	MDAI	Mephedrone
13	17	NRG-2	4-Methyl-*N*-ethylcathinone
14	18	NRG-1	Caffeine
14	19	NRG-2	Benzocaine + caffeine
15	20	NRG-2	4-Methyl-*N*-ethylcathinone
16	21	NRG-2	4-Methyl-*N*-ethylcathinone
16	22	Granules	Mephedrone
17	23	NRG-1	Procaine (+ mephedrone traces)
18	24	NRG-1	Caffeine

The results of the qualitative determinations are summarized in Table 1. Analysis of the 13 NRG-1 samples revealed that only one sample appeared to be consistent with what is generally believed to be naphyrone. In fact, product compositions varied dramatically and 7 NRG-1 products (54%) consisted of 4 different cathinones including mephedrone. The remaining 5 NRG-1 representatives (38%) also varied in composition and included inorganic material, caffeine, and local anaesthetics. In addition, product No. 6 and No. 23 appeared to show the presence of mephedrone traces.

Analyses of 7 NRG-2 products revealed the presence of 4-methyl-*N*-ethylcathinone in 4 products (Table 1) which to the best of the authors' knowledge appears to be absent from the currently published scientific literature. Two of the NRG-2 products consisted of either mephedrone alone (No. 14) or a mephedrone/benzocaine mixture (No. 12). The remaining NRG-2 sample (No. 19) consisted of a benzocaine/caffeine mixture. The presence of dimethocaine was not detected in the DMC sample which consisted of a mixture of caffeine and lidocaine instead (No. 15). The two samples labelled as MDAI were not found to contain the expected 5,6-methylenedioxy-2-aminoindane but mephedrone (No. 16) and inorganic material (No. 9) instead.

Compound Identification

The characterization of the 24 purchased Internet products was based on the implementation of GC-IT-MS analyses. Mass spectra were obtained from both EI-IT-MS and CI-IT-MS using

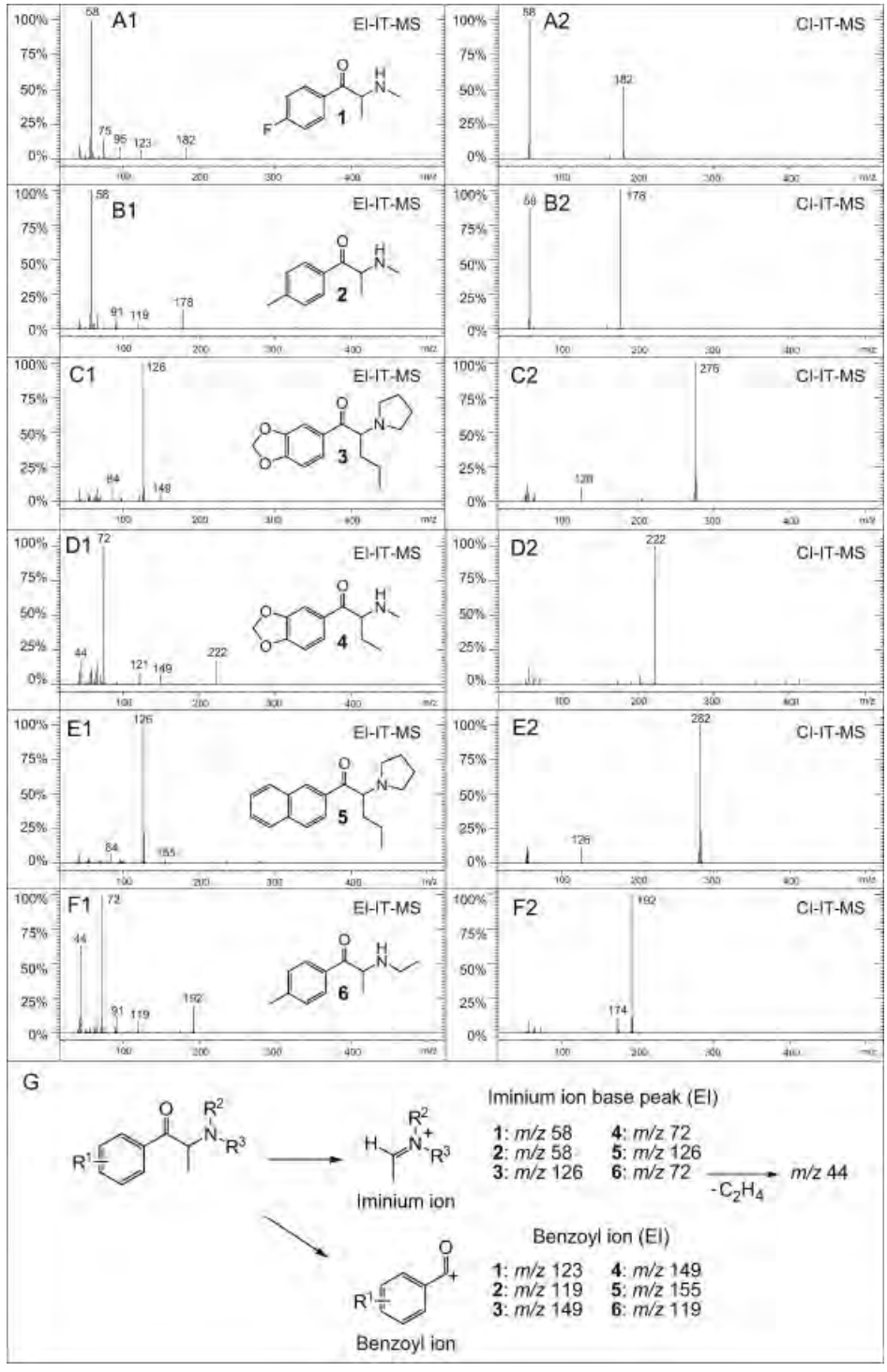

Figure 2. A – F: EI-IT-MS and CI-IT-MS spectra for derivatives **1** – **6**. G: Key fragmentation patterns observed under electron ionization conditions.

internal ionization with methanol as the liquid CI reagent. Compound identifications were also supported by comparison with standards and representative GC-IT-MS traces are shown in Figure 1. It can be seen that a number of NRG-1 products were represented by either individual cathinones or cathinone mixtures. For example, flephedrone (4-fluoromethcathinone) **1** and mephedrone **2** (Figures 1A and 1B) were present in sample numbered 2 and 13 whereas NRG-1 sample No. 1 consisted of a mixture of MDPV (3,4-methylenedioxypyrovalerone) **3** and butylone **4** (Figure 1D). A comparison with standards (Figure 1H) revealed identical retention times. Naphyrone **5** was not available as a standard and is therefore absent in the GC-IT-MS reference trace shown in Figure 1H.

Supporting evidence for compound identification came from mass spectral analyses under EI-IT-MS and CI-IT-MS conditions. All 12 mass spectra for cathinones **1** – **6** are summarized in Figures 2A – 2F and were consistent with their structural representation. The implementation of chemical ionization was particularly

helpful for the determination of the $[M+H]^+$ species in order to confirm the nominal masses of these derivatives. Molecular ion ($M^{\bullet+}$) information is often found to be absent due to extensive fragmentation under electron ionization conditions. Base peak formation reflected the presence of even-electron ions formed after α-cleavage. This typical fragmentation is a characteristic feature of derivatives carrying an ethylamine side chain, hence leading to formation of iminium ions $CH_2 = N^+ R^2R^3$ ($C_nH_{2n+2}N^+$) as summarized in Figure 2G.[10–12] Consequently, both MDPV **3**[8] and naphyrone **5** showed an identical iminium ion at *m/z* 126 under EI-IT-MS conditions (Figures 2C1 and 2E1) and CI-IT-MS analyses gave the corresponding protonated molecules at *m/z* 276 (Figure 2C2, **3**) and *m/z* 282 (Figure 2E2, **5**), respectively. The naphyrone sample also showed a second peak at 12.88 min (Figure 1E) and both EI- and CI-IT-MS spectra were identical to naphyrone, indicating the presence of an isomer. The most commonly employed synthetic route involves α-bromination of the appropriate ketone precursor. Whether this byproduct might represent the occurrence of β-bromination followed by nucleophilic substitution with pyrrolidine requires further investigation and availability of the appropriate standard.

In case of **3** and **5,** a corresponding $M^{\bullet+}$ was not observed but for the remaining derivatives **1, 2, 4,** and **6**, a protonated species was observed under EI-IT-MS conditions, presumably due to ion-molecule reactions occurring within the ion trap. Both butylone **4** and 4-methyl-*N*-ethylcathinone **6** gave an iminium ion at *m/z* 72 but the latter gave an additional *m/z* 44 ion (Figure 2F1) which was not observed for **4** (Figure 2D1) due to secondary fragmentation of the iminium ion after a neutral loss of C_2H_4 (Figures 2F1 and 2G). Another key fragmentation that provided an indication of potential substituents on the benzene ring involved the detection of benzoyl ions (Figure 2G), followed by a neutral loss of CO. Final confirmation was based on NMR where, for example, *para*-substitution was conveniently observed for derivatives **1, 2,** and **6**. Two proton resonances integrating for 2 protons indicated the presence of equivalent environments that can only be detected with substituents present at positions C1 and C4 of the benzene ring.

Interestingly, one of the NRG-1 samples (No. 10) differed from the 23 remaining products as it consisted of dark-brown oil. GC-IT-MS analysis confirmed the presence of mephedrone **2** (Table 1) but also showed an addition peak at 9.55 min. The $[M+H]^+$ was observed at *m/z* 220 but also showed both *m/z* 178 and 58 found for mephedrone (not shown). The corresponding EI-IT-MS spectrum was also similar to mephedrone **2** but also displayed the presence of *m/z* 44 and 100. The protonated molecule at *m/z* 220 and the *m/z* 100 species pointed towards the potential presence of *N*-acetylmephedrone that might indicate its involvement in the synthesis of mephedrone. Seven out of 24 Internet products (29%) showed the presence of benzocaine, caffeine, lidocaine, and procaine (Table 1), initially indicated by a NIST 2005 library search. Confirmation was obtained by chromatographic and mass spectral comparison with reference standards. Representative GC-IT-MS chromatograms are shown in Figure 3 and both EI- and CI-IT-MS spectra have also been inserted for completeness.

Several structurally diverse cathinone derivatives have been studied for their psychostimulant and antidepressant properties [6,13,14] and this might serve as a template to assess some of the pharmaco-toxicological properties of legal highs. One of the problems is that some of these so far unexplored compounds might not share the stimulant properties that are known from cathinone, methcathinone, or mephedrone which might lead to increased levels of consumption in an attempt to produce equivalent effects with unpredictable consequences.

The data reported here provide an initial snapshot of the post-ban situation and suggest that both consumers and online retailers (unlike manufacturers and wholesalers) are, most likely unaware that they are purchasing the recently controlled cathinones rather than 'new' psychoactive substances, and are therefore unaware of the criminal and health risks they may be taking. Furthermore, without a firm body of literature investigating the health effects of these drugs, users are likely to generate and disseminate an experientially derived and possibly flawed form of harm reduction.[15] Observation of user-orientated online discussion forums suggests that this is already occurring.

This situation is also reminiscent of earlier responses to ecstasy tablets which carried specific logos as an indicator of perceived content or 'quality'.[16] Increased popularity of certain 'brands' soon led to diversification of content and drug purity.[17] The difference now is that consumers may believe legal derivatives avoid the problems associated with the illegal purchase and possession of controlled drugs. Furthermore, both online retailers and high street 'head shops' may be unaware that some of the second-generation legal highs that they are selling are, in fact, first-generation and now illegal substituted cathinones. Anecdotal reports about psychoactive and pharmacological properties of NRG-1 might not provide any helpful information given the fact that the present analyses suggest that this product is likely to contain a variety of different drugs or drug mixtures other than the one claimed.

In summary, it was aimed to obtain a rapid insight into the content of 'new' products which emerged onto the legal highs market immediately after the introduction of the ban on mephedrone. The fact that 62.5% of the samples analyzed contained mephedrone and other cathinones requires continuing analysis of these Internet products. 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. Further characterizations of these products are necessary to assess the mid- and long-term development of alternative second-generation legal highs offered online. It appears conceivable that less commonly available analogues, such as 4-methyl-*N*-ethylcathinone, 4-methyl-α-pyrrolidinopropiophenone (MPPP) or 3,4-methylenedioxy-α-pyrrolidinobutiophenone (MDPBP) might appear on the streets as well as the current rebranding and misspelling of banned psychoactive substances. Availability of highly purified reference standards should allow for the implementation of quantitative procedures in the future. The implementation of derivatization procedures might also provide further information regarding the potential presence of non-volatile components.

Conclusion

The data presented here indicated that 70% of NRG-1 and NRG-2 products appeared to contain a mixture of cathinones banned in April 2010, rebranded as 'new' legal highs, rather than legal chemicals such as naphyrone as claimed by the retailers. Only one out of 13 NRG-1 samples appeared to show analytical data consistent with naphyrone. This misidentification has important health and criminal justice consequences that will require careful consideration. Regardless of the inherent problems with informal user-driven advice on usage, the fact that products sold as NRG-1 contain compounds other than those claimed by retailers and

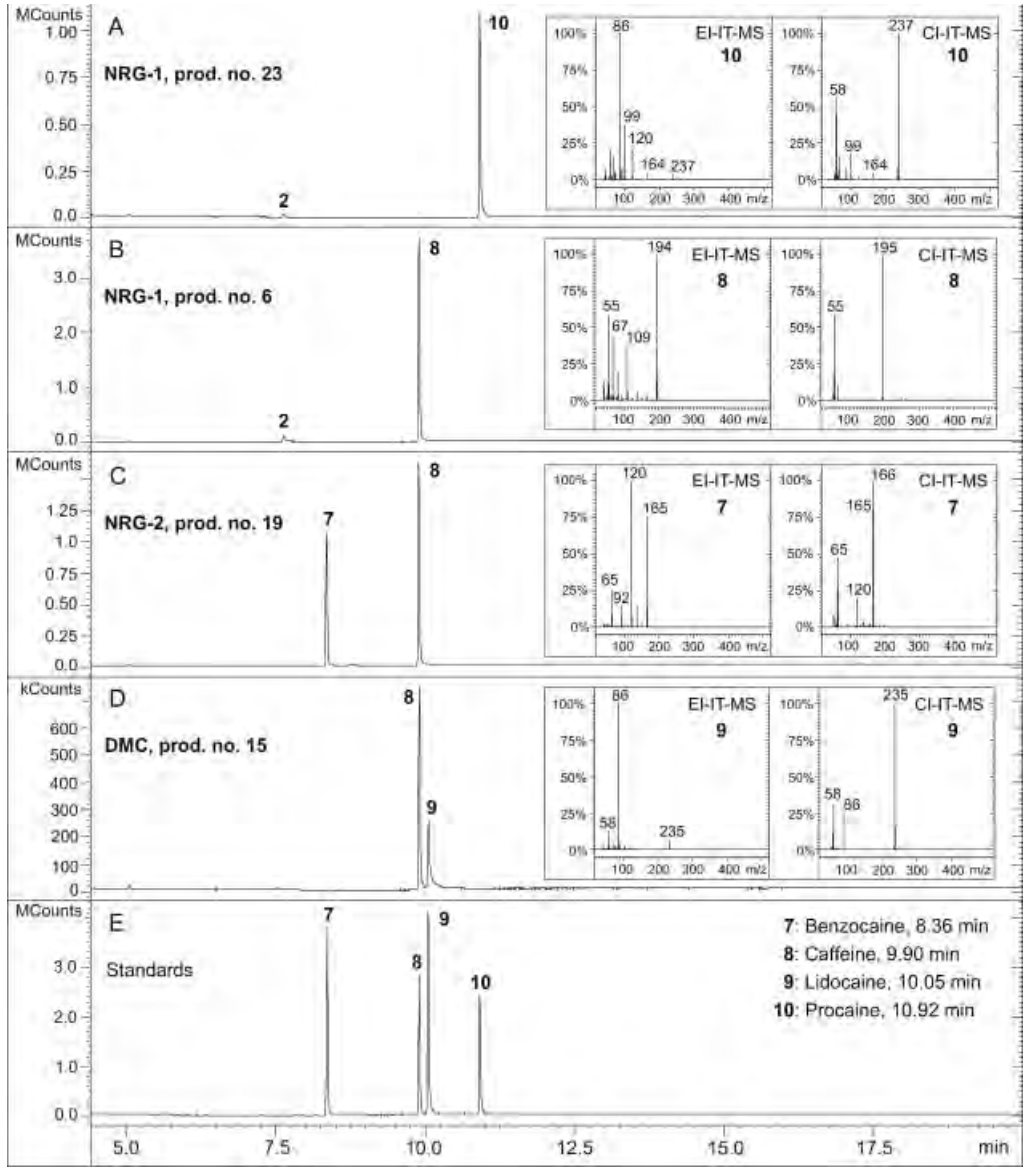

Figure 3. Representative GC-IT-MS traces of NRG-1, NRG-2 and DMC products. In these cases caffeine and three different local anaesthetics were detected.

other than those expected by users, means that this type of information is at best redundant, and at worst, harmful.

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