New psychoactive substances legislation in Ireland – Perspectives from academia

Pierce V. Kavanagh* and John D. Power

The emergence of ‘legal highs’ or ‘new psychoactive substances’ (NPS) on the Irish market is reflective of their appearance in many countries, with some notable exceptions. The official response to the situation is examined here by looking at Irish controlled drugs legislation and drug enforcement policies as enacted in recent years and their effects on academic research on NPS. The philosophy and practice of outright bans of scheduled substances has not been effective in delivering the stated aims of illicit drug control, namely harm reduction. With these legislative changes, we have witnessed the removal of the ‘legitimate’ sale and open marketing of a number of NPS to the general public in commercial retail premises. However, as legislation was enacted, suppliers and vendors rapidly changed the contents of their legal high products from now controlled to non-controlled substances. We have found that it is administratively challenging to perform scientific research on controlled substances at academic institutions. It is desirable to gather analytical, pharmacological, and toxicological data on these substances as they emerge on the market but due to the restrictive nature of licensing requirements, once a substance or generic class of substances is controlled, this becomes more difficult. The facts that any quantity of substance, no matter how small, is controlled, the nomenclature used to describe compounds is not consistent within the enacted legislation and the use of catch-all classes of compounds with the intention of controlling many similar molecular structures, all create problematic issues for academic researchers. Copyright © 2014 John Wiley & Sons, Ltd.

Keywords: new psychoactive substance; NPS; Ireland; research; academia; legislation; forensic service provider; university

Background – the rise of the head shop and the government’s response

From 2005 onwards, legislators in Ireland were faced with the problem of what to do about the phenomenon of ‘legal highs’ (i.e., substances similar to controlled drugs but which were not covered by existing national drugs legislation) that were being sold in over 100 head shops around the country. The rapid rise in popularity of the products sold as legal highs, the marketing of these products, and concerns about their effects on users became an increasing political and societal concern in Ireland.1–3 Public concern peaked in 2010 when several head shops were attacked.4–6 Irish citizens and legislators are no strangers to the concept of ‘skirting around the law’ as evidenced from the legislative control on the sale of alcoholic beverages. From 1927 until the 1970s, public houses (bars) were closed on Saint Patrick’s Day but ‘dairy shops’ (convenience stores) were legally allowed to sell wine. Indeed, bars must still remain closed on Good Friday and Christmas Day but provisions in the law permit the sale of alcohol in other locations such as train stations (to bona fide travellers), hotels (to registered guests), and golf clubs (to members).7,8 With the emergence of the legal highs phenomenon, the problems and choices for Irish citizens and Irish lawmakers became more complex as we witnessed the arrival of the first generation of so-called new psychoactive substances (NPS).9 The initial NPS to take hold and gain rapid popularity in the Irish retail market were typically cathinone derivatives and indole-based cannabimimetics. Retailers complied with national laws and marketed their products as ‘legal’ and not for human consumption but their product names mimicked drug slang culture.2 The political system responded to a growing unease among the general public about the sale of legal highs by initially choosing the simplest route of confronting the problem with outright prohibition. The prohibition of named substances or classes of substances is an approach that reflected the existing model for drugs control and it has some merits, in particular, where fatalities or hospitalizations had been linked to known substances. In the midst of these changes in legislation, academics involved in NPS research had to ensure that they had the appropriate licenses for any substance under investigation in current or planned future research projects. Some researchers preferred to avoid projects involving, or that might involve controlled substances. With the increasing use of generic legislation covering many possible substituents to a stated molecular skeleton, an increasingly vast range of substances became controlled under the Misuse of Drugs Act (MDA).

The evolution of Irish NPS legislation

The Misuse of Drugs Act

The primary law for the control of drugs in Ireland is the MDA, which replaced the Dangerous Drugs Act (1934). It is comprised of the Misuse of Drugs Act 1977 (No. 12 of 1977) as amended by the Misuse of Drugs Act 1984 (No. 18 of 1984) and part 2 of the Irish Medicines Board (Miscellaneous Provisions) Act 2006 (No. 3 of 2006).10–13 The Misuse of Drugs Regulations 1988 and
Table 1. List of Statutory Instruments (*relevant to NPS)

<table>
<thead>
<tr>
<th>Statutory Instrument</th>
<th>Website</th>
</tr>
</thead>
</table>

Table 2. Individual compounds/compound classes controlled by S.I. 200/2010

<table>
<thead>
<tr>
<th>Individual compounds</th>
<th>Compound classes</th>
</tr>
</thead>
<tbody>
<tr>
<td>WIN 55,212-2</td>
<td>3–(1–Naphthoyl)indole, 3–(1–naphthylmethyl)indole, 3–(1–naphthyl)pyrrole, 1–(1–naphthylmethyl)indene, 3–phenylacetylindole and 2–(3–hydroxy cyclohexyl)phenol (CP47, 497 type compounds), benzylpiperazine and phenylpiperazine derivatives</td>
</tr>
<tr>
<td>HU-243</td>
<td></td>
</tr>
<tr>
<td>HU-210</td>
<td></td>
</tr>
<tr>
<td>Levonantradol (CP 50,556-1)</td>
<td></td>
</tr>
</tbody>
</table>

Ireland’s first broad spectrum NPS legislation – 2010

In May 2010, Ireland set about controlling a range of ‘first generation’ NPS, for example, mephedrone and JWH-018, by amending the MDA with a Statutory Instrument (S.I. No. 200/2010 – Misuse of Drugs (Amendment) Regulations 2010) (Table 2). The legislation contained a mixture of specifically named compounds and generic compound groups, especially for the indole and pyrrole genetic compound groups, especially for the indole and pyrrole and also appeared on the Irish market, rapidly replacing MDMA as the most popular drug found in illicit tablets, in same year.[15,16]

Further amendments, in the form of Statutory Instruments (Table 1), are also incorporated into the Act.[14] The Irish Department of Health and Children (DoHC) has the responsibility for preparing amendments to the MDA and proposing the scheduling of new compounds, a process which may be done through public consultation. The DoHC may also seek guidance from the National Advisory Committee on Drugs and Alcohol (NACDA), which is an expert group set up to advise the government on problem drug use. With the arrival of NPS, causing societal concern, amendments to the MDA were used as the means of regulating the supply of these substances on the Irish market. In 2009, the first NPS to be controlled, via a Statutory Instrument (S.I. No. 122/2009), was 1-benzylpiperazine which was banned in New Zealand in 2008 and also appeared on the Irish market, rapidly replacing MDMA as the most popular drug found in illicit tablets, in same year.[15,16]

The Psychoactive Substances Act 2010

Shortly after the introduction of S.I. 200/2010, the Criminal Justice (Psychoactive Substances) Act (PSA) was introduced (August 2010).[21] The Act took a novel and non-traditional approach to drug misuse and supply. The PSA was specifically directed at suppliers/vendors and it was an effort to force the closure of head shops. It states that ‘a person who sells a psychoactive substance knowing or being reckless as to whether that substance is being acquired or supplied for human consumption shall be guilty of an offence’ (with exceptions for the sale of medicines, alcohol and tobacco, which are covered by separate legislative controls). The law is quite straightforward and one interpretation of section (3)(a) of the PSA is that if the accused gives any indication (e.g. product labelling, website information, verbal communications) that the substance or product offered for sale is psychoactive, then no further proof of pharmacological activity is required. However, if this is not accepted, then the onus is placed on prosecutors to show that such compounds are psychoactive, beyond reasonable doubt, in a criminal prosecution. This can be a difficult and unworkable task, as little or no evidence is available regarding their pharmacological activities in vivo in humans and expert witnesses may be reluctant to extrapolate data from animal models, in silico or in vitro studies. However, the PSA did succeed in significantly reducing the number of head shops during its first year of operation (Figure 2) (Garda National Drugs Unit (GNDU), personal communication, August 2013).[22] This may have occurred for a number of reasons. There was considerable societal concern about head shops and the owners, being ‘business people’ who saw the potential to make a quick profit, in general, complied with retail and legitimate business rules, paid taxes, and preferred to operate in a licit rather than an illicit marketplace.[23,24] The introduction of the PSA and public protests at legal high retail units caused unease amongst these shop operators and, along with media pressure, many shops voluntarily closed and surrendered their products for destruction.[25]
derivatives were included in the previous Statutory Instrument (S.I. 200/2010), the definition was expanded to include $N$-haloalkyl compounds such as AM-694 which had been identified in a number of head shop products. With the introduction of S.I. 552/2011 and S.I. 200/2010, derivatives of the cannabimimetic molecular scaffolds shown in Figure 3 are now controlled in Ireland. However, indoles substituted at the 3-position with other groups such as adamantoyl or tetramethylcyclopropyl, as found in AB-001 and UR-144 respectively, are not controlled. The generic description (Figure 4) provided for substituted cathinones is quite broad and generally follows similar UK legislation.

**Proposed future legislation, 2013**

The most recent proposal for new drugs legislation in Ireland was part of a public consultation document (Draft Misuse of Drugs (Amendment) Regulations, 2013) to amend the Misuse of Drugs Regulations, 1988. This has relevance to NPS as 5-IT and phenazepam as compounds listed to be controlled. The decision to include 5-IT may have been prompted by the proposed plan for an E.U. wide ban resulting from an EMCDDA Risk Assessment of the compound. A number of phenylethylamine derivatives are also listed. The proposal specifically lists a range of benzodiazepines

<table>
<thead>
<tr>
<th>Cathinone derivative</th>
<th>Common name</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-(1,3-Benzodioxol-5-yl)-2-(1-pyrrolidinyl)-pentanone</td>
<td>MDPV</td>
<td><img src="image1" alt="Structure of MDPV" /></td>
</tr>
<tr>
<td>1-(2-Fluorophenyl)-2-methylaminopropan-1-one</td>
<td>Flephedrone, 2-isomer</td>
<td><img src="image2" alt="Structure of Flephedrone, 2-isomer" /></td>
</tr>
<tr>
<td>1-(3-Fluorophenyl)-2-methylaminopropan-1-one</td>
<td>Flephedrone, 3-isomer</td>
<td><img src="image3" alt="Structure of Flephedrone, 3-isomer" /></td>
</tr>
<tr>
<td>1-(4-Fluorophenyl)-2-methylaminopropan-1-one</td>
<td>Flephedrone, 4-isomer</td>
<td><img src="image4" alt="Structure of Flephedrone, 4-isomer" /></td>
</tr>
<tr>
<td>Methcathinone</td>
<td>–</td>
<td><img src="image5" alt="Structure of Methcathinone" /></td>
</tr>
<tr>
<td>1-(4-Methoxyphenyl)-2-(methylamino)propan-1-one</td>
<td>Methedrone</td>
<td><img src="image6" alt="Structure of Methedrone" /></td>
</tr>
<tr>
<td>2-Methylamino-1-(3,4-methylenedioxyphenyl)butan-1-one</td>
<td>Butylone</td>
<td><img src="image7" alt="Structure of Butylone" /></td>
</tr>
<tr>
<td>2-Methylamino-1-(3,4-methylenedioxyphenyl)propan-1-one</td>
<td>Methylone</td>
<td><img src="image8" alt="Structure of Methylone" /></td>
</tr>
<tr>
<td>1-(4-Methylphenyl)-2-methylaminopropan-1-one</td>
<td>Mephedrone, 4-isomer</td>
<td><img src="image9" alt="Structure of Mephedrone, 4-isomer" /></td>
</tr>
</tbody>
</table>

* Nomenclature as per the S.I.
but excludes more recent arrivals such as diclazepam, pyrazolam, and etizolam (a bioisosteric derivative).

**Effectiveness of NPS legislation**

The Irish State Laboratory, which performs toxicological analysis on biological fluids and tissue samples for the coroner’s service, reported a drop from 15 cases in 2010 to 5 cases in 2012 where post-mortem blood samples tested positive for cathinone derivatives.\(^{[29]}\) It should be pointed out that there is no suggestion that the cathinone derivatives were the cause of death or that all deaths, where drug misuse was suspected, were actually sent for analysis. The Drug Treatment Centre Board (DTCB) laboratory (Dublin), which screens methadone program patients, reported that 54% of stimulant screen patient urine samples tested positive for cathinone derivatives in 2010 and a 25% decrease was noted from January to August 2011 which it associates with the introduction of S.I. 200/2010.\(^{[30]}\)

**NPS legislation and academic research**

**NPS at the laboratory bench – the practicalities**

A potentially negative consequence of the legislative control of NPS was that, with little or nothing known about their actual harm potential, numerous compounds became controlled drugs, thus discouraging academia from pursuing research due to licensing requirements. At the time, little thought was given to this aspect and it may have been prudent, in hindsight, to allow researchers to study such compounds by allowing them to hold small amounts (i.e. quantities smaller than typical single doses as reported anecdotally) in their university based laboratories. Legislation can genuinely hinder research at the laboratory bench. Taking the case of a study involving the syntheses of cathinone derivatives, a researcher has to seek licenses for individual compounds, both to make them and then to possess them.\(^{[31]}\) Financially, this is not a problem as each license costs just over €30.00 and the researcher will know what they will initially be working with. However, an issue lies with diversity,
A phenyl ring modified to any extent with alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylethenedioxy, haloalkyl or halo substituents, whether or not further substituted in the phenyl ring by one or more other univalent substituents or any other monocyclic, or fused-poly cyclic ring system modified by substitution in the ring system to any extent with alkyl, alkenyl, alkynyl, alkoxy, alkylthio, haloalkyl or halo substituents, whether or not further substituted in the ring system by one or more other univalent substituents.

![Figure 4. Generic description for cathinone derivatives.](image)

Figure 4. Generic description for cathinone derivatives.

as research does not follow precise or predictable paths. Controlled by-products may be produced in reactions and, during the course of the work, new lines of investigation may be pursued, spurred on by initial findings, leading to even more controlled substances. Research stops if this happens and a new license has to be obtained for each compound, not because the compounds are necessarily pharmacologically active or even potentially harmful, but simply because they happen to fall into the catchment of legislation. All through this, the actual quantities being produced on the laboratory bench may be small and certainly not large enough for what could be regarded as supply or even personal use. The constant stop/starting possibilities that legislation creates are frustrating for students and it may jeopardize the successful completion of their postgraduate research studies in a timely manner. It is also disheartening for Principal Investigators and may actually deter future research pursuits in forensic drug chemistry, which in the long run is detrimental to our future understanding of these substances. One of the most upsetting things that we have had to do is destroy valuable compounds that have taken hundreds of hours to make and characterize simply because they have now fallen under the realms of control. The increased use of generic legislation based around a defined molecular scaffold also causes some concern, as researchers may not realize that they are working with or have synthesized a scheduled substance.

The above is illustrated by our work (unpublished), several years ago, on the syntheses and characterization of flephedrone isomers. The 2- isomer is difficult to synthesize as amination of the α-bromo ketone intermediate at room temperature produces highly chromophoric unworkable mixtures. This is presumably due to the initial formation of an indolinone derivative via an intramolecular aromatic nucleophilic substitution reaction. We also observed the indolinone derivative in GC chromatograms of 2-flephedrone when the injector port liner was contaminated after numerous analyses (Figure 5 and Supplemental 1). An attempted synthesis of the compound by the hydrolysis of 1,2-dimethylindol-3-yl acetate failed to yield the desired indolinone product, instead affording complex mixtures from which a dimer was isolated (Supplemental 2, 3, 4). Low temperature (acetone/dry ice) chemistry was found necessary for the synthesis of 2-flephedrone (Supplemental 5). We would like to revisit these studies from an academic, and not a forensic, point of view to explore the chemistry of the compounds but it is quite likely that controlled compounds would be synthesized during the course of the work. We cannot predict what we may encounter and thus it is impossible for us to apply for licenses for individual compounds if they are controlled. No administrative mechanism exists to apply for a generic type license reflective of the generic controls existing in the MDA.

Another interesting situation encountered during our research, is the case of dimethocaine which was controlled in November 2011. The compound was identified in several head shop products along with an impurity, des-ethyl dimethocaine. A decision was taken to control des-ethyl dimethocaine even though nothing was published about it or its effects, if any. Recently, nitracaine, the nitro analogue of dimethocaine, became available from Internet vendors. It is possible that dimethocaine and des-ethyl dimethocaine may be metabolites of nitracaine. Nitracaine is currently unregulated and researchers are free to work with it. However, if the situation arises with in vitro metabolism studies, that dimethocaine or des-ethyl dimethocaine are produced, even in infinitesimal amounts, the research scientist would require a license for their production and possession under the MDA regulations.

Currently we are investigating recent arrivals, such as mephedetamine and methoxypiperamide, on the NPS market. There is little or no chemical, pharmacological or toxicological data available on these compounds. What will we do if they become controlled during the course of our work? Research, especially pharmacological studies, will take some time and if we have to stop to apply for licenses following the introduction of any potential future legislation, it will further delay the project and dissemination of our results. It took one year from the start of research to peer-reviewed publication for our work on the discrimination of aminopropylbenzofuran APB isomers. Although this may appear to be a short timeframe within the realms of

![Figure 5. Indolinone formation from 2-flephedrone and related chemical reactions.](image)
academia, one year is enough to see the ‘rise and fall’ of a compound on the ‘research chemicals’ market; for example we identified fluorotropacocaine (3β isomer) in head shop products for a period of several months during 2010 and it did not appear again to our knowledge.[37] In fact, in the past, we have chosen to bypass the peer-review publication process, instead disseminating our findings using ‘easy to read’ pictorial poster formats which were made available to hospital emergency rooms, healthcare professionals, legislators, law enforcement authorities and the general public (Head Shop Legal Highs’ Active Constituents Identification Charts).[18,19,32] However, in a somewhat perverse twist, recent MDA legislation may be viewed as a stimulus for research as it directs scientists to attempt to predict future compounds that may emerge on the NPS market and thus study them prior to their control. The problem here is that with such a range of potential substances and the fact that only a small number of them may actually become controlled, subject to popular misuse, it is easier to study controlled compounds currently available ‘on the scene’.

We have also encountered difficulties possibly related to the poor understanding of and complexity of the nomenclature actually used in legislation. An Irish subsidiary of a leading supplier of laboratory chemicals was unaware that 2-aminoindane was controlled and they were willing to supply us with the compound (listed as 2-aminoindan on their website) without proof or inquiry as to whether we had the required license. This may have been due to a nomenclature misunderstanding, as S.I. 552/2011 refers to the compound as 2,3-dihydro-1H-inden-2-amine and not 2-aminoindane or 2-aminoindan. In fact, this is a general and growing problem with the MDA as there is difficulty in finding out if and where a particular substance is listed in the Act. This is especially true with generic legislation as numerous structures and variants may be controlled.

The relationship between academics involved in NPS research and forensic service providers

Legislation should recognize the potential for academics and academic institutions to be creditable partners working alongside forensic service providers, allowing a more relaxed carte blanche approach to facilitate this. In Ireland, this would require primary legislation rather than an amendment to an existing Act. Academia and forensic service providers could genuinely share a mutually beneficial existence if both communities were given more freedom and flexibility to work together. Over the past several years we have noted a number of areas of interaction that could be further enhanced by appropriate legislation.

An in-depth knowledge of synthetic organic chemistry now plays a pivotal role in forensic drug chemistry. Forensic drug chemists are primarily interested in uniquely identifying controlled substances in case samples rather than impurity or by-product profiling. However, the latter is an important intelligence-gathering tool, which can be used to link batches of drugs and provide a valuable insight into manufacturing and supply trends. As this type of work is more research orientated, it would be appropriate for academic institutions to be involved so that profiles and databases are generated if different seizures from a common source were to be linked forensically.

Forensic service providers have an untapped wealth of information in the actual case samples that they encounter. Most of these samples are destroyed after examination for the presence of controlled drugs only. Working in conjunction with academia, non-controlled NPS could be further and more fully characterized, synthesis by-products could be identified and impurity profiling performed. Technologies such as nuclear magnetic resonance (NMR) spectroscopy that are generally not available in the laboratories of most forensic service providers are required for the full analytical characterization of NPS. This means that samples may have to be taken outside the regulated confines of such establishments for analysis and future legislation should address and facilitate this, thereby recognizing academic institutions as viable providers of such analytical services. It makes no economic sense for forensic service providers to purchase such equipment.

Academic laboratories could supply synthesized reference standards long before they become commercially available, which would be of tremendous benefit to forensic service providers and wider drug testing community. The Irish National Advisory Committee on Drugs (NACD) highlighted the lack of availability of such NPS reference standards in a 2011 report.[38] In the wider European context, it would be desirable if the EMCDDA promoted and endorsed liaison between academic institutes and official forensic service providers (private or state funded) in the EU member states. In fact, a European depository to hold reference standards, made or verified by academic laboratories, for distribution to official forensic service providers should be also established. Actions 51 and 52 in the EU Drugs Action Plan 2013-2016, adopted by the Council of Ministers in June 2013, lay some foundations towards this type of liaison.[39] University laboratories are generally not accredited facilities but still meet very high performance standards as judged by the quality of peer-reviewed publications, etc. Ultimately, forensic service providers and law enforcement authorities should have to the power to decide if involvement of their academic colleagues is of benefit.

Generally, academics have more freedom and time to think outside the box and are not shackled by accreditation protocols or the seemingly ever-increasing workloads that forensic service providers continually face. We cannot predict the future but we can offer a vision of it, using our knowledge of synthetic organic chemistry and pharmacology. Admittedly, any relationship between academia and forensic service providers is made more challenging by the fact some of the work could involve case samples that are sub judice.

Conclusions

The rapid evolution of the NPS phenomenon, the offering of legal highs by retail suppliers who, in our experience, have tried to stay within national drugs laws and the emergence of international online suppliers have made existing approaches to drugs legislation somewhat impractical. The current legislative framework that we work within, in Ireland, needs to be reviewed and expanded to be more inclusive to accommodate an academic input and allow more targeted research. It would be beneficial to introduce primary legislation to allow registered postgraduate students and staff of academic institutions, who are performing research on the NPS, to possess controlled substances at their institutions, without the need for individual licenses for compounds. The amounts allowed could be typically less than one ‘dose’ as reported anecdotally or as sold by Internet vendors. Legislation should also provide better mechanisms for academia and forensic service providers to work together and share data so that more informed policy decisions can be made. We are also
Figure 6 shows the structures of the compounds discussed in the manuscript.

aware that when conducting online NPS test purchases, the compounds that are advertised may not be the ones shipped to us, thus it is possible that we could receive controlled substances for which we do not have licenses. In cases like this it would be appropriate to have a fast-track licensing system so that we could legally retain a portion of such samples for future reference. We also legitimately synthesize NPS, for which we have the relevant Irish licenses to make and possess, but often we have the need to share samples with other research groups around the world, which requires export licenses. This has caused problems in the past where a compound was not controlled in the destination country but the relevant authority there was unwilling to categorically state that. In the absence of such information, a license cannot be obtained to export. We feel that the rules for the inter-country movement of small ‘sub-dose’ amounts of NPS for bone fide academic research need to be more flexible. In some ways, legislation has also encouraged us to stay ‘one step ahead of the law’ and work with NPS that are not currently controlled, an example being the β-keto analogues of NBOMe’s which may potentially emerge as in the next wave of NPS. Figure 6 shows the structures of the compounds discussed in the manuscript.

References


Supporting information
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