Drug Testing and Analysis

(www.drugtestinganalysis.com) DOI 10.1002/dta.319

A brief history of 'new psychoactive substances'

This special issue of DTA is devoted to what were once known as 'designer drugs', but in recent times have been described informally as 'legal highs'. The preferred term, as adopted by the European Community in 2005[1,2] is 'new psychoactive substances'. They are defined as 'Narcotic or psychotropic drugs that are not scheduled under the United Nations 1961 or 1971 Conventions, but which may pose a threat to public health comparable to scheduled substances'. Council Decision 2005/387/JHA superseded an earlier arrangement, known as the 'Joint Action on New Synthetic Drugs' that had been in operation since 1997. It provides a framework for the reporting of new substances (the 'Early Warning System'), a mechanism for formal risk-assessment of selected candidates and eventual EU-wide control where appropriate. The word 'new' means newly misused; in reality, nearly all of the substances encountered were first synthesized many years ago.

These compounds can be distinguished from what we might call the classical drugs of misuse (e.g. amphetamine, cocaine, heroin, cannabis) because the former have had little or no history of medicinal use. Following the appearance on the illicit drug market in the USA of a number of fentanyl derivatives, for example, α-methylfentanyl and 3-methylfentanyl, together with certain derivatives of α-prodine, the reverse ester of pethidine (meperidine), the term 'designer drugs' was created in 1984.[3,4] They were defined as 'analogues, or chemical cousins, of controlled substances that are designed to produce effects similar to the controlled substances they mimic'. These highly potent substitutes for heroin caused a number of accidental deaths. Furthermore, a synthetic contaminant (MPTP) in an α-prodine derivative[3] led to chemically induced Parkinson's disease in a number of injecting drug users. Not surprisingly, interest in designer narcotic analgesics soon disappeared.

Amphetamine derivatives, particularly ring-substituted examples, represented the next phase in the evolution of designer drugs. Whereas amphetamine and its side-chain derivatives are essentially central nervous system (CNS) stimulants, ring substitution, especially with alkoxy, alkyl and halogens leads to compounds with a novel pharmacology. Some may be hallucinogens, but many are better described as entactogens and empathogens. Isolated examples occurred in the 1960s with, for example, the appearance in the UK[5] of so-called STP (2,5,dimethoxy-4-methylamphetamine), the field receiving a major boost with the publication of the book *PIHKAL* in 1991.[6] The 'phenethylamine period' would last into the early years of the twenty-first century, with the scope for new substances having now largely been exhausted. In this time, around 50 illicit phenethylamine derivatives would be found in police and customs seizures in Europe and the USA. Almost all of these derivatives failed to find an established user-base, and many had a short lifespan. The hallucinogenic members were rarely regarded as superior to established indole alkaloids such as LSD and psilocybin (magic mushrooms), and the demand for such psychedelics was in any case limited. None of the other phenethylamines displaced MDMA (3,4-methylenedioxymethamphetamine) as the entactogen of choice. Originally developed by Merck as a pharmaceutical agent around 1914, MDMA was never formally marketed. In parallel with the phenethylamines, many tryptamine derivatives appeared throughout the 1990s. Their synthesis may have been inspired by the publication of the book *TIHKAL* in 1997,[7] though they never became widespread or were ever seen in large quantities. This limited interest may be partly due to them being hallucinogens rather than the more favoured entactogens and stimulants, and partly because many tryptamines are not active orally.

Throughout this period, illicit phenethylamines were manufactured in clandestine laboratories in the USA and Europe usually as tablets bearing characteristic logos. They were often marketed through criminal networks as 'Ecstasy', a term which initially meant MDMA or one of its homologues, but later became much broader. New substances rapidly followed the demise of the PIHKAL era, the next family being the piperazine derivatives. These represented a departure from the phenethylamines in that they could better be described as 'failed pharmaceuticals' rather than 'designer drugs', that is to say compounds that had been evaluated by the pharmaceutical industry as potential therapeutic agents, but which had never succeeded to market authorization. The prototypical member is 1-benzylpiperazine (BZP), with numerous ring-substituted phenylpiperazines eventually being seen. Even though there was some interest in the USA during the 1990s, BZP became firmly established in New Zealand in the early part of this century.[8,9] As a CNS stimulant, it was promoted as a safer alternative to methamphetamine. The piperazine derivatives arrived in Europe in around 2004, and their use was not checked until they came under EU-wide control after 2007. The current situation with BZP and its relatives is described by Elliott in this issue.[10]

The piperazines occupied a transition state in the marketing of 'new psychoactive substances'. Some were found as tablets bearing the usual markings that signalled Ecstasy, although later they would be in the form of loose powders. More importantly, the source was no longer a clandestine laboratory, but legitimate chemical supply companies, some of which were located in Asian countries. Since, by definition, the substances concerned were not initially controlled under drugs legislation, their production and distribution became far more overt. Alongside more traditional retail outlets (head shops), the growth of the internet opened up new channels for their sale or for online 'chat-rooms', where their properties could be openly discussed. It was at this time that the euphemism 'research chemical' appeared.

Gamma-hydroxybutyrate (GHB) is a drug that is also associated with the club or 'rave' scene, a commonly-used street name being 'liquid ecstasy.' Originally, GHB was reported to be misused by competitive body builders in the 1980s in the belief that it could increase muscle development because of its effect in acutely facilitating slow-wave sleep, a period when growth hormone is most consistently secreted. However, it was essentially a diverted active pharmaceutical agent that became part of the recreational

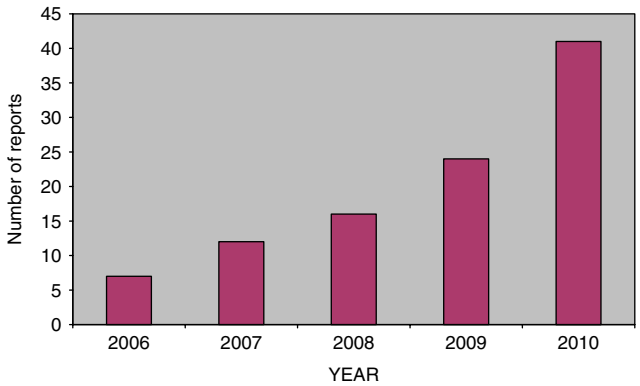

Figure 1. New psychoactive substances reported annually to EMCDDA since 2006.

drug scene from the late 1980s/early 1990s onwards. When GHB was listed in Schedule IV of the United Nations Convention on Psychotropic Substances around eight years ago, rapid substitution took place, and the metabolically active precursor chemical γ-butyrolactone (GBL) became prevalent. Both GHB and GBL, as well as the related substance 1,4-butanediol, are described by Wood *et al*.[11]

By around 2006, it became clear that manufacturers of new substances were now trawling the world's scientific and patent literature in search of failed pharmaceuticals or, as they also became known, 'designer medicines'. The piperazines were soon followed in around 2008 by cathinone derivatives, the most common of which in Europe was 4-methylmethcathinone (mephedrone). These β-keto analogues of phenethylamines are described in detail by Kelly,[12] and a specific and thorough review of the pharmacology and toxicology of mephedrone is provided by Dargan *et al*.[13] It is also important that healthcare professionals interacting with patients with type 1 diabetes mellitus are made aware and communicate that new psychoactive substances may cause particular problems, as many of these substances are presumed to have sympathomimetic activity that could antagonise the action of insulin, as exemplified in a case report by Wong and Holt.[14] To date, over 30 cathinone family members have been seen in law enforcement seizures and collected samples.

At the same time, the first synthetic cannabinoid agonists were identified in smoking mixtures, which are often known as 'Spice'. As before, they had been developed as potential pharmaceutical agents, particularly as analgesics, and their synthesis was well described in the accessible scientific literature. Some were naphthoylindoles, others were cyclohexylphenols and some were closer to traditional cannabinoids in their chemical structure (i.e. dibenzopyrans), but the ability to react with cannabinoid CB_1 receptors as cannabimimetics is a property shared by a diverse group of substances. The principal cannabinoid agonists, of which more than 20 have been identified in smoking mixtures or as white powders, are described by Hudson and Ramsey.[15]

In the last few years, there has been a rapid proliferation of new substances. Figure 1 shows the number of new compounds reported annually to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Of the approximately 170 substances reported since 1997, over half have appeared since 2006.

Although many of the latest substances continue to be CNS stimulants, their chemical structures are now quite diverse; they range from several derivatives of pipradrol, ketamine, and phencyclidine to arecoline, aminopropylbenzofuran, ring-substituted aminoindans, the thiophenyl bioisostere of methamphetamine, as well as compounds structurally related to cocaine. Aminoindane derivatives are described by Sainsbury *et al*.[16] This fast growth and fragmentation of form now creates further problems at both the analytical and legislative level. The absence of reference standards for both principal drugs and their metabolites has been a long-standing problem, and has led to increasing challenges to forensic and clinical laboratories in both the identification and quantification of new psychoactive substances. The traditional route and timescale of reference material production of 6–24 months is no longer appropriate in this rapidly changing environment and alternative approaches are required to produce materials of a suitable quality to satisfy the requirements of a robust quality system. Archer *et al*.[17] discuss the challenges facing producers of reference materials in meeting this demand.

Not only has there been an increase in the number of novel structures being encountered, but in the absence of those reference standards, further difficulties are caused by the complexity of some analytes particularly when mixtures or difficult matrices are present or when positional as well as stereoisomers may exist. Good examples here are the cannabinoid agonists, where the active constituents consist of a few milligrams among several grams of unknown vegetable matter. In this situation, recourse must be made to high resolution chromatography-mass spectrometry since NMR analysis is almost impossible due to its reliance on homogeneous, i.e. high purity, analytes. While the identification of solid samples may often be difficult, the analysis of new psychoactive substances in biological matrices is even more so. The risk to health of most of these substances is unknown, a major ethical consideration that makes it difficult to justify drug elimination studies that would help underpin interpretation of cases in analytical toxicology. In such circumstances, *in vitro* metabolic investigations, employing preparations containing human liver enzymes, are an indispensable aid to the identification and characterization of metabolites, as reviewed by Peters.[18] In forensic toxicology, emphasis is placed on low reporting thresholds, not least to improve retrospection of detection of drug administration, and sample extraction is therefore important to reduce matrix effects that can cause ion suppression and also to help concentrate the drugs targeted and also their metabolites. By contrast, in routine workplace drug testing programmes, the main aim is to deter drug misuse by focusing on detection of very recent drug administration and thus the reporting thresholds chosen are much higher, permitting direct analysis ('dilute and shoot') liquid chromatography-tandem mass spectrometry (LC-MS/MS) for rapid screening purposes, as presented by Bell *et al*.[19]

Sumnall *et al*.[20] describe how the social factors determining use of a new generation of psychoactive compounds differ from the major historical trends in recreational drug use of the twentieth century. They note how manufacture, distribution, and access to a range of psychoactive and so-called lifestyle/well-being drugs firmly embeds these substances into a new consumer culture. The synthetic methods and the precursor chemicals needed for the preparation of some of the major groups of new psychoactive substances are described in detail by Collins.[21]

In the UK, Ireland, and New Zealand some success in the past was achieved by using generic legislation for controlling new substances. This is based on a set of substances which can be defined in terms of a specific substitution pattern in a core molecule. In the UK, this has been applied to phenethylamines,

piperazines, cathinones, cannabinoid agonists, and many other groups.[22] Nevertheless, generic legislation has limited value when chemical structures do not conform to recognizable family groups. While it is not appropriate here to review the many legislative responses to the problem of 'legal highs', there is a general view that existing law is no longer adequate. The USA has used analogue legislation in this area for over 20 years, and similar approaches are being considered in several European countries. Analogue control relies on the questioned substance having a broad chemical and pharmacological similarity to existing controlled substances. Meanwhile, the UK government is about to introduce 'Temporary Class Orders' and has already activated import bans for specific substances. In Ireland, the Criminal Justice (Psychoactive Substances) Act came into force in 2010 specifically targeted at legal highs.

On the other hand, medicines legislation has had limited success in controlling new substances, a situation made worse when, as often happens, they are advertised as 'not for human consumption' or are described as 'bath salts' or 'plant fertilizer'. The frequent absence of scientifically valid published information on their pharmacology also vitiates part of the current EU-wide definition of a medicinal product. This, in turn, leads to perhaps the most important feature of new psychoactive substances: from a public health perspective, almost nothing is known about their harmful properties. What little we do know comes from occasional work in animal toxicology, fatal poisonings in humans, or clinical observations of intoxicated patients.

There is little doubt that some of the substances discovered so far are less harmful than the controlled drugs they seek to replace, but their acute, and particularly chronic, toxicological properties are difficult to predict. While there has been no repeat of the problems posed 30 years ago by MPTP, a major public health crisis in the future cannot be ruled out so long as there is uncontrolled experimentation with novel substances.

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