New synthetic drugs in the European Union

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Introduction

In June 1997, the Council of the European Union (EU) adopted a so-called 'Joint Action' on new synthetic drugs (NSD). This was concerned with information exchange on new substances as well as procedures for risk assessment and legal control. The basis for this agreement was Article K.3 of the Treaty on the European Union, signed at Maastricht, concerning the approximation of the laws and practices of the Member States of the European Union to combat drug addiction and to prevent and combat illegal drug trafficking. The Joint Action was promoted by the Dutch Government and it took place against a political background whereby Europe had become a leading producer of these drugs. Difficulties were emerging in the EU because of the way in which certain drugs were treated differently in different Member States (MS).

The definition of a new synthetic drug

The Joint Action was concerned with those substances not already listed in the schedules of the United Nations Convention on Psychotropic Substances 1971. It was intended to focus attention on the plethora of 'designer drugs' which had appeared during the 1990s. Well-established drugs such as amphetamine, MDMA and MDEA were excluded since they were already controlled in international law. Table 1 shows those illicit substances which have been reported in the EU and are already listed in the 1971 Convention. The substances listed in Table 2 qualify as NSD under the terms of the EU Joint Action; nearly all have appeared in Europe since the mid-1990s, but the list also includes a few which have so far been reported only in the USA. The chemical properties of some of the drugs in Table 2 have been described in more detail elsewhere [1–8].

The first observation to be made about the drugs in Table 2 is that they are nearly all phenethylamines, most of which are ring-substituted. In other words, they can be seen as derivatives of amphetamine. This in turn is a reflection of the requirements of current youth culture. Depending on the substitution pattern, phenethylamines are either central nervous system stimulants or have entactogenic/empathogenic properties. By contrast, hallucinogens, as typified by the tryptamines, seem much less popular. The second feature of Table 2 is that the syntheses (and original acronyms) of most of the ring-substituted members can be found in a well-known book [9] published in 1991 and available on the Internet. The syntheses of three of the four tryptamines shown in Table 2 are set out in another book [10] by the same authors.

Risk assessment and legal controls

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) was set up in Lisbon following Council Regulation No. 302 of 1993. The EMCDDA had a broad remit and it was later tasked with developing risk assessment procedures for NSD under the terms of the above Joint Action [11]. A general perspective on synthetic drugs in the EU was also produced [12]. The main elements of the risk assessment criteria were a chemical and pharmacological description of the NSD, acute and chronic psychological risks, sociological and criminological evidence, and public health risks.

A procedure was established whereby notifications from MS would be channelled either via the 'Reitox' network of focal points to EMCDDA or via National Criminal Intelligence Services to the Europol Drugs Unit (EDU) in The Hague. Less formal information exchange networks were also set up amongst representatives of forensic science laboratories in the EU, some of which involved the

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European Network of Forensic Science Institutes (ENFSI). Inevitably, nearly all the information passed to EDU and EMCDDA has originated either in forensic science laboratories or from forensic or clinical toxicologists. Other epidemiological information was hindered by the fact that drug users were unlikely to know if they had consumed one of these drugs rather than MDMA or something else. A typical feature of NSD is that they are often presented in the form of white tablets bearing 'illicit' logos, which provide no clue to the chemical contents.

Despite the large number of NSD in Table 2, most have represented isolated seizures; few have been consistently seen in most MS. Since 1997, only two substances (MBDB and 4-MTA) have been sufficiently common or merited concern to be submitted formally to risk assessment by EMCDDA [13,14]. For MBDB, and to a lesser extent 4-MTA, risk assessments were made difficult because so little information was available in the published literature on their pharmacology and toxicology. Another problem with NSD is that they often have a limited lifetime on the illicit market. By the time risk assessment takes place they may no longer represent an immediate social problem. That is not a reason for taking a more relaxed attitude to their control, but it does mean that when a NSD disappears from the illicit market it is much more difficult to continue to collect epidemiological and other necessary information. In the case of MBDB, no final decision has been made by the EU on whether it should be controlled. However, the situation with 4-MTA was clearer. Firstly, there was evidence of large-scale production and the involvement of organised crime. Secondly, although there had been relatively few seizures, this drug had been directly associated with a number of fatal poisonings. Following a decision by the Council, MS are now required to implement controls on 4-MTA. For most purposes, this means 4-MTA will be treated similarly to

TABLE 1 Illicit 'Amphetamine-type' synthetic drugs reported in Europe since the mid-1990s and scheduled under the United Nations Convention on Psychotropic Substances 1971

Drug	*Acronym*
Amphetamine	-
Methylamphetamine	-
Methcathinone	-
3,4-Methylenedioxyamphetamine	MDA
3,4-Methylenedioxymethylamphetamine	MDMA
3,4-Methylenedioxyethylamphetamine	MDEA
4-Bromo-2,5-dimethoxyamphetamine	DOB
4-Methoxyamphetamine	PMA
N-Hydroxy-MDA	N-OH MDA

Note: As drugs which are already under international control, these substances do not qualify as 'new synthetic drugs' under the terms of the EU Joint Action.

TABLE 2 New synthetic drugs (as defined by the EU Joint Action) reported in Europe and the USA since the mid-1990s

Drug	*Acronym*
Ring-substituted phenethylamines	
3,4-Methylenedioxypropylamphetamine	MDPA
N-Methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine	MBDB
1-(1,3-Benzodioxol-5-yl)-2-butanamine	BDB
4-Bromo-2,5-dimethoxyphenethylamine	2C-B
3,4-Methylenedioxydimethylamphetamine	MDDM
2,5-Dimethoxy-4-(n)-propylthiophenethylamine	2C-T-7
4-Allyloxy-3,5-dimethoxyphenethylamine	AL
3,5-Dimethoxy-4-methylallyloxyphenethylamine	MAL
N-Hydroxy-MDMA	FLEA
2,5-Dimethoxy-4-chloroamphetamine	DOC
4-Methylthioamphetamine	4-MTA
2,5-Dimethoxy-4-ethylthiophenethylamine	2C-T-2
4-Methoxy-*N*-methylamphetamine	Me-MA
6-Chloro-MDMA	-
N-(4-ethylthio-2,5-dimethoxyphenethyl)-hydroxylamine	HOT-2
2,5-Dimethoxy-4-iodo-phenethylamine	2C-I
4-Methoxy-*N*-ethylamphetamine	-
***N*-Substituted amphetamines without ring-substitution**	
N-Hydroxyamphetamine	N-OHA
N,N-Dimethylamphetamine	
N-Acetylamphetamine-	
Di-(1-phenylisopropyl)amine	DIPA
Tryptamines	
N,N-Dimethyl-5-methoxytryptamine	5-MeO-DMT
N,N-Di-(n)-propyltryptamine	DPT
4-Acetoxy-*N,N*-di-isopropyltryptamine	-
α-Methyltryptamine	α-MT
Other phenylalkylamines and miscellaneous	
1-Phenylethylamine	1-PEA
N-Methyl-1-phenylethylamine	N-Me-PEA
4-Methyl-1-phenylethylamine	4-Me-PEA
1-Phenyl-3-butanamine	-
N-Benzylpiperazine	BZP

MDMA. The most likely chemical precursors to 4-MTA (i.e. 4-methylthiobenzaldehyde and 4-methylthiophenylacetic acid) have also been added to the EU monitoring list. This is a voluntary scheme for encouraging the chemical industry to notify authorities of suspicious purchases.

Analytical problems

From the perspective of the forensic scientist, recognising NSD is not straightforward. For most of the substances shown in Table 2, pure reference samples are not commercially available and, for many, analytical data are sparse. The situation becomes even more difficult when a totally new substance is suspected in a drugs exhibit or the body fluids of a poisoned patient. Both MBDB and 4-MTA were only identified following laboratory analysis using Nuclear Magnetic Resonance Spectroscopy (NMR). Interestingly, in both cases, NMR analysis was carried out almost simultaneously and independently in several countries. However, NMR is not appropriate for identifying small amounts of drugs in body fluids. Laboratories will sometimes need to use chromatography, mass-spectrometry and other techniques to suggest one or more candidate structures. These can then be synthesised and compared with the unknown. Since NSD will often appear in a number of countries, there is a clear need for collaboration at the analytical level. This should involve both exchange of information and reference samples. It is suggested that ENFSI could set up a central collection of new substances.

Specific problems occur in the analysis of *N*-hydroxyphenethylamines. For example, they often disproportionate during gas chromatography to give a mixture of the unchanged substance, the dehydroxylated (parent) compound and the ketoxime. But attempts to derivatise, using MBTFA for example, result in a derivative that is identical to the derivative of the parent drug. In the case of *N*-hydroxyMDA (*N*-hydroxytenamfetamine), a drug already listed in the UN 1971 Convention, acetylation provides a suitable method of identification [15]. In *N*-hydroxyamphetamine, the mass spectrum is found to be quite variable presumably because fragmentation is unusually sensitive to the precise electron impact energy.

Future developments

There is little doubt that the Joint Action has engaged the interest of other international bodies. Concern about 4-MTA led the World Health Organisation to recommend that it should be controlled under international law: a matter which was due to be debated at the United Nations Commission on Narcotic Drugs (UNCND) in March 2001.

Although the authors of the original Joint Action might have envisaged a rapid response system, a weakness of the present arrangements is that they have been seen as bureaucratic and slow moving. By contrast, the USA experienced similar problems with designer drugs in the 1980s. The Controlled Substances Analogue Enforcement Act of 1986 appears to have prevented the further proliferation of NSD. However, the concept of defining a controlled substance on a case by case basis and as a result of legal arguments is probably incompatible with the European Convention on Human Rights. The moderate success of the Joint Action has prompted calls within the EU for the setting up of a wider 'Early Warning System'. This would go well beyond NSD and include all new developments in drug abuse. In the meantime, the EMCDDA has carried out risk assessments on gamma-hydroxy butyrate (GHB) and ketamine. Neither of these can be considered to be NSD under the original definition, but both are abused and neither is under international control. Again, GHB is a candidate for discussion at the UNCND meeting mentioned above.

The concept of formal risk assessment of illicit drugs has also been a useful development in that it has inspired individual Governments to take a more structured approach to procedures for determining whether a substance (NSD or otherwise) should be brought under the control of the domestic criminal law.

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