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J Psychopharmacol 2013 27: 817 originally published online 19 June 2013

DOI: 10.1177/0269881113487950

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4-Methyl-amphetamine: a health threat for recreational amphetamine users

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Journal of Psychopharmacology
27(9) 817–822

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DOI: 10.1177/0269881113487950

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Abstract

4-Methylamphetamine (4-MA) was originally developed as an appetite suppressant, but development was halted due to side effects. It has recently resurfaced as a new psychoactive substance in Europe, and is mostly found together with amphetamine. Around 11.5% of tested Dutch speed samples were positive for 4-MA. In Belgium, 4-MA was also found in speed samples. In 2011 and 2012, several fatal incidents after amphetamine use were observed in Belgium, the United Kingdom and The Netherlands. In all victims, toxicological analysis confirmed the presence of 4-MA, in addition to amphetamine. The observed blood amphetamine levels were too low to be fatal. Contrary to amphetamine, which displays noradrenergic and dopaminergic activity, 4-MA also shows serotonergic activity, which may contribute to the observed toxicity. Other mechanisms of toxicity are put forward in this paper as well. To conclude, the observed toxicity is most likely the result of the combined dopaminergic activity of amphetamine and the serotonergic activity of 4-MA. In addition, the presence of 4-MA may have dampened the psychoactive effects of amphetamine by attenuation of the amphetamine-induced dopamine release, potentially inclining users to ingest higher doses of contaminated speed. Also, slower metabolism of 4-MA and its MAO-inhibiting properties can also contribute to the unusual high toxicity of 4-MA.

Keywords

4-methylamphetamine, toxicology, amphetamines, neuropharmacology, new psychoactive substances

Introduction

Amphetamine, often referred to as ‘speed’, is one of the oldest synthetic psychostimulants and a widely abused recreational drug. Amphetamine acts as a monoamine releaser at the level of both vesicular and plasma membrane transporters (Fleckenstein et al., 2007). As a result, amphetamine increases the extracellular dopamine (DA) concentration in brain, which induces strong feelings of euphoria. In addition, amphetamine increases synaptic norepinephrine (NE) concentrations (Rothman et al., 2001), and causes dependence and neurotoxicity in the long run (Kita et al., 2009).

Fatalities involving amphetamine as the sole intoxicating substance are relatively rare (Carvalho et al., 2012), but more common in cases where amphetamine is combined with other drugs (polydrug use) (De Letter et al., 2006; Schifano et al., 2010; Vanthomme et al., 2011; Verschraagen et al., 2007). Recently, several casualties (fatal incidents) related to the use of amphetamine were observed in Belgium, the United Kingdom and The Netherlands. In all victims, toxicological analysis confirmed the presence of 4-methylamphetamine (4-MA) in addition to amphetamine (Figure 1).

This paper will therefore describe the recent fatal cases in Belgium and The Netherlands, where 4-MA was involved, as well as the appearance of 4-MA in speed samples on the Belgian and Dutch market. In addition, the combined occurrence of amphetamine and 4-MA in speed samples and the cause of the extreme toxicity of this combination is explained.

Recent developments on the drug market

4-Methylamphetamine (4-MA, 1-(4-methylphenyl)propan-2-amine, PAL-313, Aptrol©) is a phenethylamine derivative, originally developed in the 1960s as an appetite suppressant (Gelvin and McGavack, 1952). Aptrol is not licensed as a pharmaceutical drug. The pharmacological and toxicological data of 4-MA described in literature are limited, and sparse data on human toxicology are available.

In Belgium (and in most European member states), 4-MA is a non-controlled substance. Since 2009, 4-MA has been regularly detected in drug samples sold as speed in Belgium and The Netherlands. The introduction of 4-MA must be regarded in the

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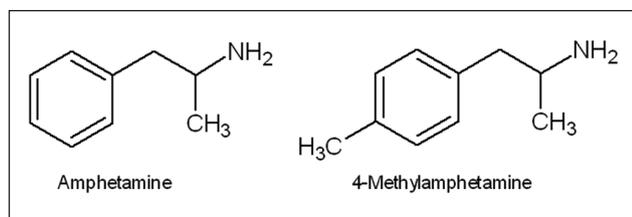


Figure 1. Chemical structure of amphetamine and 4-methylamphetamine.

context of the increasing consumption of new psychoactive substances (NPS), ('Legal Highs', designer drugs) in Europe. In virtually all cases, NPS are derivatives of known controlled substances, synthesized to circumvent current drug laws. Contrary to most NPS appearing on the European drug market, which are usually sold in pure form, 4-MA is almost always found in speed samples together with regular amphetamine. In fact, this novel distributed drug is mainly a combination of a legal NPS and an (controlled) illicit substance.

Epidemiology of amphetamine use in Belgium and The Netherlands

No epidemiological prevalence data concerning the use of 4-MA are available. However, since 4-MA has nearly always been found combined with amphetamine in powders sold as speed, the authors decided to estimate the prevalence of 4-MA use by looking at the prevalence of amphetamine use.

The lifetime prevalence of amphetamine use in the European Union is 5.0% for young adults (aged 15–34 years) (The Gallup Organisation, 2011). For Belgium and The Netherlands, these numbers are 4% and 5%, respectively. Amphetamines are mainly used as party drugs by younger people. Surveys indicate that the prevalence of regular amphetamine use in the party scene in Belgium and The Netherlands is considerable (10–11%) (VAD, 2009; Van Der Poel et al., 2010).

During 2011 and in the first half of 2012, six casualties were reported to the Belgian Early Warning System on Drugs, which were apparently related to the consumption of 4-MA, as traces of this drug were found in post-mortem blood. At the same time, in The Netherlands five casualties related to 4-MA were reported in 2011 and one in 2012. Finally, in the United Kingdom, three casualties were reported by ROAR Forensics from 2010 to 2012 which were related to 4-MA consumption.

Prevalence and case description of 4-MA in speed samples marketed in Belgium and The Netherlands

In contrast to Belgium, where the quality of street drugs is not monitored, the prevalence of speed samples contaminated with 4-MA in The Netherlands can be approximated using data of the Dutch DIMS-system (Drugs Information and Monitoring System) which performs chemical analysis of street drugs submitted voluntarily by users. In addition, information from the Netherlands Forensics Institute, which analyses drug samples seized by the Dutch police services is included (Figure 2 and Table 1).

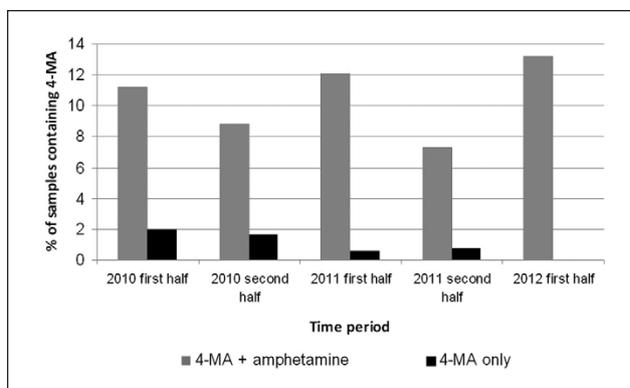


Figure 2. Prevalence (in %) of 4-MA in speed samples submitted by users through DIMS in The Netherlands. * 4-MA was the main psychoactive component in about 1% of contaminated samples; ** Content of 4-MA varied from 0.9–19.6% w/w; DIMS: Drug Information Monitoring System, The Netherlands.

Results from DIMS covering samples analysed in 2010 show that 11.5% of submitted speed samples are contaminated with 4-MA in varying concentrations (0.9–19.6% w/w) (Figure 2). Though the contaminated speed samples were found throughout The Netherlands, most of the contaminated samples originated from the southern part of the country (close to the Belgian border). Since the drug markets in Belgium and The Netherlands are quite similar, one may assume that the prevalence of speed samples contaminated with 4-MA is comparable for Belgium and The Netherlands (EMCDDA, 2012a, 2012b).

The results depicted in Table 1 refer to chemical analysis of samples by NFI, proven to be positive for either amphetamine or 4-MA, originating from seizures and crime-related cases, including traffic accidents, in The Netherlands. For comparison, the DIMS data are also included in Table 1. No major differences between the samples analysed by NFI and DIMS regarding the amount of contamination of the speed samples with 4-MA are observed.

In Belgium, federal police services reported in 2012 the seizure of 10 speed samples contaminated with 4-MA in varying amounts (Table 2). Average amphetamine concentration of these samples was 23.3%, whereas the average concentration of 4-MA was 15.2% (median value of 4-MA concentration was 2.3%). Of note is that one sample contained a very high amount of 4-MA (86.2%). DIMS data of analysed speed samples containing 4-MA revealed an average 4-MA content of 4.6%. Moreover, in the samples containing only 4-MA, average concentration was 20.6% (highest observed value was 42%).

Contrary to The Netherlands, in Belgium no powders have been seized containing only 4-MA.

Speed samples, containing a mixture of amphetamine and 4-MA, have also been found in other European countries, such as the United Kingdom, Spain, Austria and Switzerland (in these countries, 6–9% of analysed speed samples tested positive for 4-MA, with concentrations ranging from 0.6–32.7% (the mean concentration of 4-MA varied between 2.0% and 8.4%).

The combined epidemiological and laboratory data indicate that in Belgium and The Netherlands a significant proportion of drug users (notably in the party scene) have been exposed to the

Table 1. Prevalence of 4-MA in speed samples seized by Dutch authorities (NFI, Department Illicit Drugs, Netherlands Forensics Institute).

Data Source	Year	Total # of speed samples analysed	Amphetamine + 4-MA ^a	Only 4-MA
NFI	2011	1560	108 (6.9%)	27 (1.7%)
	2012 (until May)	461	41 (8.9%)	11 (2.4%)
DIMS	2010	1000	66 (6.6%)	9 (0.9%)
	2011	1169	108 (9.2%)	8 (0.7%)
	2012 ^b	1345	159 (11.8%)	0

^aSamples contained significant amounts of 4-MA. In addition, only traces of 4-MA were detected in an unknown number of samples. ^bMonitored until October 2012. NFI, unpublished data.

Table 2. Content of speed samples seized in Belgium.

Amphetamine (%)	4-MA (%)	Caffeine (%)
21	1	42
8.8	1	66
20	2	69
29	2.5	55.6
37	2.6	51
64	16	NQ
13	21	16
11	25	NQ
23	37	NQ
14	56	NQ
1.3	86	NQ

Data source: Belgian Early Warning System on Drugs; National Institute on Criminalistics and Criminology (NICC, federal police, Belgium). NQ: not quantified.

potentially lethal effects of 4-MA. Moreover, the user is unintentionally exposed to 4-MA, because they do not deliberately buy 4-MA; they were not aware of buying speed that was contaminated with 4-MA.

Table 3 provides an overview of the blood concentrations for amphetamine and 4-MA in the lethal cases observed throughout Europe, and where the cause of death may be attributed to the use of 4-MA. In the cases where a case history and detailed clinical symptoms were available, severe hyperthermia was observed.

The high toxicity of 4-MA contaminated speed

Fatal intoxications due to the use of amphetamine are rare (Carvalho et al., 2012). In those cases where fatal intoxications related to amphetamine use have occurred, other drugs were consumed as well (i.e. polydrug use), or death was attributed to other causes, such as physical trauma resulting from suicide or roadside accidents while under the influence (De Letter et al., 2006).

Amphetamine levels exceeding 5 mg/L (up to 17 mg/L) have been described in the blood of impaired drivers in Sweden. The median blood amphetamine level in a large sample of DUID (Driving Under the Influence of Drugs) offenders was 0.7 mg/L (mean level 0.9 mg/L) (Jones and Holmgren, 2005).

Of note is that these very high concentrations of amphetamine were tolerated without fatal consequences. Such concentrations are in the same range as those found after pharmacotherapy with

amphetamine (for example in the treatment of narcolepsy), which are usually about 0.2 mg/L.

Lethal amphetamine blood levels reported in literature vary from 0.5–41 mg/L with an average level of 8.6 mg/L (Baselt, 2011). However, most fatal amphetamine intoxications described in the literature involved polydrug use (MDMA or cocaine metabolites were found mostly). Also, a Dutch study regarding post-mortem cases related to amphetamine use confirmed that very few casualties directly resulted from intoxication with amphetamine (Verschraagen et al., 2007).

A missing piece of information is that no human toxic or lethal blood concentrations of 4-MA have been described in literature. However, data from Riva et al. (1969) and Marsh and Herring (1950) indicate that in mice, the LD₅₀-values for amphetamine and 4-MA are comparable. LD₅₀ values of 4-MA and amphetamine reported were respectively 160 and 205 mg/kg s.c. (Riva et al., 1969), and 101 and 136 mg/kg i.p. (Marsh and Herring, 1950). Limited human trials in the 1950s revealed that 1 mg/kg 4-MA (p.o.) neither changed blood pressure nor showed any evidence of central nervous stimulation. However, following a twofold dose (2 mg/kg) subjects showed substantial increase in both systolic and diastolic blood pressure which persisted 20–30 min before falling to a level about 20 mmHg above normal. Gastric distress was noted in most. The subjects apparently felt better after 3 or 4 h, but any motor activity produced exacerbations of the discomfort. All subjects became anorectic, that is, did not eat for 3 days after the experiment. Any central stimulatory effect was masked by the anorexia and gastric discomfort (Marsh and Herring, 1950). Apparently, 4-MA shows a steep dose-response curve.

The concentration of amphetamine in post-mortem bodily fluids observed in the casualties in Belgium and The Netherlands (Table 3) are not extraordinary high. Therefore, it is implausible that only the exposure to amphetamine was the cause of death in these cases. Apparently, the cause of death in these cases is related to the combined intake of 4-MA and amphetamine.

One of the most remarkable clinical signs reported in some of the fatal cases related to 4-MA use was hyperthermia. The neurobiology of drug-induced hyperthermia in humans is complex. For example, the mechanisms of thermogenesis induced by MDMA seem to result from an interaction between the hypothalamic–pituitary–thyroid axis and the sympathetic nervous system, wherein mechanisms leading to core and skeletal muscle hyperthermia after MDMA exposure seem to be differentially regulated by α 1- and β 3-adrenergic receptors (Sprague et al., 2003). Serotonergic activation can lead to the development of a serotonin toxidrome, of which increased hyperthermia is a hallmark. Activation of the sympathetic nervous system can lead to agitation with increased locomotor activity (as seen after the

Table 3. Concentrations of 4-methylamphetamine (4-MA) and amphetamine (AMP) in post-mortem blood in 11 fatal 4-MA related intoxications in Belgium and The Netherlands.

Case	Country	Year	(femoral) Blood concentration (mg/L)			Other drugs	Clinical symptoms
			4-MA	AMP	4-MA+AMP		
1	BE	2012	0.62	0.48	1.1	Cocaine Ketamine	Extreme hyperthermia Cardiac arrest. Powder found (11% AMP, 25% 4-MA)
2	BE	2012	+	+	unknown		Hyperthermia cardiac arrest Powder found (AMP + 4-MA, NQ)
3	BE	2012	+ (in urine, NQ)	+ in blood (NQ)		None found	No symptoms known
4	BE	2011	1.2	0.715	1.915		No symptoms known
5	BE	2011	1.45	0.75	2.2	Cocaine Olanzapine	Powder found (AMP and 4-MA, NQ)
6	BE	2011	1.98	1.07	3.05	MDMA (0.23 mg/L)	Powder found (14% AMP, 56% 4-MA)
7	NL	2012	0.5	0.6	1.1		
8	NL	2011	1.4	0.3	1.7		
9	NL	2011	0.98	1.7	2.68		
10	NL	2011	2.3	0.35	2.65		
11	NL	2011	2.2	0.04	2.24		

NQ: Not Quantified. Origin of data: Belgium: Belgian Early Warning System on Drugs; The Netherlands: Netherlands Forensics Institute, unpublished data. For cases 7–11, no data regarding clinical symptoms or other ingested drugs were available.

consumption of amphetamines and cocaine), resulting in potential hyperthermia.

In the hot and crowded conditions of club parties, mild versions of the serotonin toxidrome often develop, when hyperthermia, mental confusion and hyperkinesia predominate. This acute serotonergic overactivity is exacerbated by the high ambient temperatures, overcrowding (aggregate toxicity), overexertion, dehydration, and the use of other stimulant drugs (for example MDMA and amphetamine) (Parrott, 2002).

In the literature, no reports are available which describe the specific link between the use of 4-MA and hyperthermia. In rats, both amphetamine and 4-MA (5–40 mg/kg s.c.) dose-dependently produce hyperthermia (+1 to 3°C) with a comparable potency (Aldous et al., 1974; Riva et al., 1969). As MDMA produces a major acute release of 5-HT from nerve endings in the brain, it has been assumed that this amine is responsible for the hyperthermia elicited by MDMA (Shankaran and Gudelsky, 1999). We suggest that the pronounced serotonergic component of 4-MA (as compared with amphetamine; see pharmacological profile), together with the sympathomimetic and dopaminergic effects of amphetamine, are both responsible for the observed hyperthermia. The aetiology of hyperthermia is, however, complex and both dopamine and 5-HT receptors seem to be involved in modulating the hyperthermic response (Docherty and Green, 2010).

Since proper toxicity data of 4-MA are missing, one can only hypothesize why the contaminated speed showed such a high toxicity in the casualties in Belgium and The Netherlands. Possibly, the high blood levels of 4-MA compared with those of amphetamine observed could be due to a relatively rapid absorption or slow metabolism of 4-MA as compared with amphetamine, resulting in high peak or steady state 4-MA blood levels. Amphetamine is metabolized mainly through (1) N-deamination and oxidation into the corresponding benzoic acid derivatives that are further conjugated with glycine and excreted as the corresponding hippuric acids, and (2) hydroxylation in position 4 of the aromatic ring, generating 4-hydroxyamphetamine, followed by conjugation

of the phenol group with sulphate or glucuronic acid (Carvalho et al., 2012). The CYP2D6 mediated hydroxylation pathway is, however, unusable for 4-MA due to the presence of the methyl moiety at the aromatic 4-position. However, hydroxylation of the 4-methylgroup (and subsequent conjugation) is a possible pathway for biotransformation, much like the biotransformation that occurs with mephedrone (which also includes a 4-methylgroup in its structure) (Ciechomska et al., 2012; Meyer et al., 2010). Also, ring hydroxylation is a prominent pathway for amphetamine biotransformation in rodents, but is only a minor pathway in humans (Bach et al., 1999). This could potentially explain a slower metabolism of 4-MA compared with amphetamine, resulting in enduring elevated 4-MA levels, and the extraordinary high toxicity of the contaminated speed samples. Also, metabolism of 4-MA into amphetamine (by para-demethylation of 4-MA) has never been described in literature, and can thus be excluded as a potential explanation of the co-presence of 4-MA and amphetamine in post-mortem blood, especially since the powders, consumed by the victims, were analytically confirmed to contain both 4-MA and amphetamine.

Pharmacological profile of 4-MA

Another explanation of the high toxicity of the contaminated speed samples may be based on the different pharmacological profile of 4-MA as compared with amphetamine. A well-known side effect of stimulant drugs is their ability to induce hyperthermia (Kalant, 2001), although the incidence and severity of hyperthermia vary among stimulant drugs, such as cocaine, methamphetamine, 3,4-methylenedioxyamphetamine (MDMA), and para-methoxyamphetamine (PMA) (Jaehne et al., 2007). However, extreme hyperthermia following the use of amphetamine alone is rarely observed. Amphetamine is a potent and selective releaser of DA and NE. In contrast, 4-MA virtually non-selectively releases DA, NE and serotonin (5-HT) (Baumann et al., 2011). As such (unlike amphetamine), 4-MA retains a strong serotonergic action (Rothman

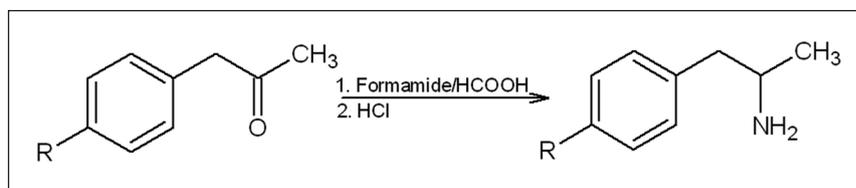


Figure 3. Synthesis of amphetamines according to the Leuckart route. R=H: amphetamine; R=CH₃: 4-methylamphetamine.

and Baumann, 2006; Wee et al., 2005). The relatively strong serotonergic action of 4-MA, alongside its dopaminergic action, may both be relevant in the complex regulation of body temperature, and the observed hyperthermia (Docherty and Green, 2010).

Indeed, severe hyperthermia was observed in part of the recent fatal cases in Belgium and The Netherlands. This substantiates the hypothesis that the fatality may be directly due to the specific serotonergic action of 4-MA. In addition, it cannot be excluded that the presence of amphetamine in the speed sample has contributed to the severe hyperthermia induced (core temperatures of 45°C were observed in cases in Belgium) knowing that the strong release of both 5-HT and DA seems to be chiefly responsible for severe hyperthermia, as is the case with MDMA (Green et al., 2003).

Furthermore, the serotonergic action of 4-MA could potentially attenuate or decrease the amphetamine-induced DA release (Baumann et al., 2011; Kimmel et al., 2009; Rothman et al., 2001; Rothman and Baumann, 2006). This in turn could lead to a blunted psychoactive effect ('kick') as desired by the user so that the user is prone to consume more of the contaminated speed, ultimately resulting in even more severe symptoms. Alternatively, (1) due to the delayed onset of the effect of 4-MA compared with amphetamine (Maickel and Johnson, 1973; Riva et al., 1969) or (2) the dilution of the amphetamine sample with a less active compound, a higher dose of the contaminated speed is taken. The inhibition of monoamine oxidase (MAO) by para-substituted amphetamines such as 4-MA can also contribute to the observed toxicity (Ross et al., 1977). As compared with amphetamine, 4-MA showed a very high degree of MAO inhibition (Fellows and Bernheim, 1950). Given the difficulty in untangling the exact mechanism of 4-MA's toxicity, a conclusive explanation for the high toxicity of the contaminated speed can as yet not be presented.

Origin of 4-MA in speed mixtures

Most amphetamine in Belgium and The Netherlands is produced following the Leuckart route (Figure 3).

The main precursor used for this route is benzylmethylketone (BMK), a controlled chemical in Europe (usually produced in China).

Currently, there are two hypotheses to explain the presence of 4-MA in speed in Belgium and The Netherlands. First, amphetamine manufacturers may not be aware that they use a contaminated precursor, that is, BMK contaminated with 4-methyl-BMK, or intentionally use 4-methyl-BMK to circumvent the use of the controlled precursor BMK (4-methyl-BMK is a non-controlled substance). Manufacturers may also include the uncontrolled precursor 4-methyl-BMK to increase their profit margins and elude law enforcement crackdown. As yet, it remains unclear whether illicit amphetamine manufacturers are aware that they

are using a contaminated precursor. Secondly, it is quite conceivable that illicit drug manufacturers are oblivious to the potentially lethal potency of 4-MA, and presume to have found a new designer drug.

Conclusion

Considering the relatively low amphetamine blood levels found in the fatal cases who have consumed the contaminated speed, it is unlikely that the cause of death can be solely attributed to the intake of amphetamine. The extreme hyperthermia observed in some cases implies additional serotonergic toxicity, which corresponds to the described profound serotonergic potency of 4-MA not shared by amphetamine.

We conclude that the toxicity observed in the fatal cases is most likely the result of the stimulant serotonergic and dopaminergic activity of amphetamine in combination with the serotonergic activity of 4-MA. In addition, the presence of 4-MA in the consumed speed may have dampened the psychoactive effects of amphetamine, inclining users to ingest higher doses of contaminated speed to achieve the desired effect, leading to increased toxicity and, ultimately in some cases, to a fatal incident. The slower metabolism of 4-MA (in comparison with that of amphetamine) and its MAO-inhibiting properties can also contribute to the unusual high toxicity of 4-MA in recreational speed users.

The governments in Belgium and The Netherlands have performed assessments of the presence of 4-MA on the drug market and its potentially lethal effect in recreational drug users. These have led to emergency scheduling of 4-MA in The Netherlands. In Belgium, 4-MA was added to the list of controlled substances in April 2013. Moreover, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) has launched an EU-wide risk assessment of the substance to assess the negative health impact of 4-MA on drug users throughout Europe.

Acknowledgements

The authors appreciate the supply of information about 4-MA by the members of the risk assessment committee of the CAM, Miren Ugarte Campomar (Asociación ai Laket), Constanze Nagy (Suchthilfe Wien) and Alexander Buecheli (Jugendberatung Streetwork, Zürich). We thank Raymond Niesink for the stimulatory discussions and Reinskje Talhout for her support in collecting the information. We would also like to thank Klaas Lusthof (Netherlands Forensic Institute) for providing data regarding the fatal cases in The Netherlands. We also would like to thank ROAR Forensics in the UK for analysing the UK cases.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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