



European Monitoring Centre  
for Drugs and Drug Addiction

**Risk Assessment Report  
of a new psychoactive substance:**

**1-(1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one  
(3,4-methylenedioxypropylone, MDPV)**

In accordance with Article 6 of Council Decision 2005/387/JHA on information exchange, risk assessment and control of new psychoactive substances

## 1. Introduction

This *Risk Assessment Report* presents the summary findings and the conclusions of the risk assessment carried out by the extended Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) on the new psychoactive substance 1-(1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one, commonly called 3,4-methylenedioxypropylvalerone (MDPV). The report has been prepared and drafted in accordance with the conceptual framework and the procedure set out in the *Risk assessment of new psychoactive substances: operating guidelines* <sup>(1)</sup>. It is written as a stand-alone document presenting a summary of the information considered during the detailed analysis of the scientific and law enforcement data available at this time. The conclusion section of the report summarises the main issues addressed and reflects the opinions held by the members of the Scientific Committee. A list of the information resources considered by the Scientific Committee, including a detailed *Technical Report* on MDPV, is provided below.

The risk assessment has been undertaken in compliance with Article 6 of Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances <sup>(2)</sup> (hereafter the 'Council Decision'). The Council Decision establishes a mechanism for the rapid exchange of information on new psychoactive substances (hereafter 'Early Warning System' <sup>(3)</sup>) that may pose public health and social threats, including the involvement of organised crime. Thus, it allows the institutions of the European Union and the Member States to act on all new narcotic and psychotropic substances <sup>(4)</sup> that appear on the European Union drug market. The Council Decision also provides for an assessment of the risks associated with these new psychoactive substances so that, if necessary, control measures can be applied in the Member States for narcotic and psychotropic substances <sup>(5)</sup>.

MDPV was first identified in a seizure made by Finnish Customs in November 2008 and formally notified to Early Warning System in December 2008 by Finland. Following an assessment of the available information on MDPV, and in accordance with Article 5 of the

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<sup>(1)</sup> EMCDDA (2009), *Risk assessment of new psychoactive substances: operating guidelines*, The Publications Office of the European Union, Luxembourg. Available at: <http://www.emcdda.europa.eu/html.cfm/index100978EN.html>

<sup>(2)</sup> OJ L 127, 20.5.2005, p. 32.

<sup>(3)</sup> The information exchange mechanism laid down by the Council Decision is operationalized as the *European Union Early Warning System on New psychoactive Substances ('Early Warning System')*. It is operated by the EMCDDA and Europol in partnership with the Retiox National Focal Points in the Member States, the European Commission and the European Medicines Agency.

<sup>(4)</sup> According to the definition provided by the Council Decision, a 'new psychoactive substance' means a new narcotic drug or a new psychotropic drug in pure form or in a preparation; 'new narcotic drug' means a substance in pure form or in a preparation that has not been scheduled under the 1961 United Nations Single Convention on Narcotic Drugs, and that may pose a threat to public health comparable to the substances listed in Schedule I, II or IV; 'new psychotropic drug' means a substance in pure form or in a preparation that has not been scheduled under the 1971 United Nations Convention on Psychotropic Substances, and that may pose a threat to public health comparable to the substances listed in Schedule I, II, III or IV.

<sup>(5)</sup> In compliance with the provisions of the 1961 United Nations Single Convention on Narcotic Drugs and the 1971 United Nations Convention on Psychotropic Substances.

Council Decision, on 16 December 2013 the EMCDDA and Europol submitted to the Council of the European Union, the European Commission and the European Medicines Agency (EMA) a *Joint Report* on MDPV <sup>(6)</sup>. Taking into account the conclusion of the *Joint Report*, and in accordance with Article 6 of the Council Decision, on 29 January 2014, the Council formally requested that ‘the risk assessment should be carried out by the extended Scientific Committee of the EMCDDA and be submitted to the Commission and the Council within twelve weeks from the date of this notification’.

In accordance with Article 6.2, the meeting to assess the risks of MDPV was convened under the auspices of the Scientific Committee of the EMCDDA with the participation of five additional experts designated by the Director of the EMCDDA, acting on the advice of the Chairperson of the Scientific Committee, chosen from a panel proposed by Member States and approved by the Management Board of the EMCDDA. The additional experts were from scientific fields that were either not represented, or not sufficiently represented on the Scientific Committee, and whose contribution was necessary for a balanced and adequate assessment of the possible risks of MDPV, including health and social risks. Furthermore, two experts from the Commission, one expert from Europol and one expert from the EMA participated in the risk assessment. The meeting took place on 1 and 2 April 2014 at the EMCDDA in Lisbon. The risk assessment was carried out on the basis of information provided to the Scientific Committee by the Member States, the EMCDDA, Europol and the EMA. A list of the extended Scientific Committee, as well as the other participants attending the risk assessment meeting is annexed to this report (Annex 1).

For the risk assessment, the extended Scientific Committee considered the following information resources:

- (i) *Technical Report on 1-(1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one (MDPV)* (Annex 2);
- (ii) *EMCDDA–Europol Joint Report on a new psychoactive substance: MDPV (3,4-methylenedioxypropylvalerone)*;
- (iii) Scientific articles, official reports, grey literature, Internet drug discussion forums and related websites (hereafter, ‘user websites’);
- (iv) Data from EMCDDA Internet monitoring of suppliers (that typically appear to be manufacturers and/or wholesalers) and retailers selling MDPV;
- (v) *Risk assessment of new psychoactive substances: Operating guidelines*; and,
- (vi) *Council Decision 2005/387/JHA of 10 May 2005 on the information exchange, risk assessment and control of new psychoactive substances*.

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<sup>(6)</sup> EMCDDA and Europol (2014), *EMCDDA–Europol Joint Report on a new psychoactive substance: EMCDDA–Europol Joint Report on a new psychoactive substance: MDPV (3,4-methylenedioxypropylvalerone)*, EMCDDA, Lisbon. Available at: <http://www.emcdda.europa.eu/publications/joint-report/MDPV>

Finally, it is important to note that this *Risk Assessment Report* contains a discussion of the available information on non-fatal intoxications and deaths associated with MDPV. Such information is critical to the identification of emerging toxicological problems associated with new psychoactive substances within the European Union. In this context, it is important to recognise that the capacity to detect, identify and report these events differs both within and between the Member States. In the past few years, programmes have been introduced in some Member States to strengthen these capacities. As a result, more information is available; however, it is likely that serious adverse events remain under-detected.

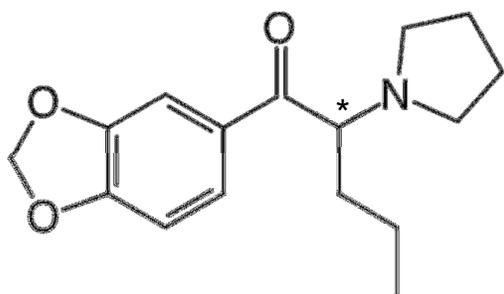
## 2. Physical, chemical and pharmacological description

MDPV is a ring-substituted methylenedioxy analogue of the synthetic stimulant pyrovalerone which is in turn an analogue of the naturally occurring chemical cathinone <sup>(7)</sup>. The systematic (International Union of Pure and Applied Chemistry, IUPAC) name for MDPV is (*RS*)-1-(1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one. Both pyrovalerone and cathinone are controlled under the 1971 United Nations Convention on Psychotropic Substances. MDPV contains one asymmetric carbon atom and is thus a chiral molecule (Figure 1). So far, only the racemic mixture of the 1:1 ratio of the two possible enantiomers has been characterised.

MDPV is one of over fifty synthetic cathinones that have been notified by the Member States to the Early Warning System; other examples include mephedrone <sup>(8)</sup> (4-MMC) and methylone (bk-MDMA).

The Chemical Abstract Service (CAS) Registry Number for MDPV (base) is 687603-66-3 and the molecular formula is C<sub>16</sub>H<sub>21</sub>NO<sub>3</sub>, equating to a molecular weight of 275.343 g/mol.

**Figure 1.** The molecular structure, formula, weight and monoisotopic mass of MDPV.



**Molecular formula:** C<sub>16</sub>H<sub>21</sub>NO<sub>3</sub>

**Molecular weight:** 275.3429

**Monoisotopic mass:** 275.152

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<sup>(7)</sup> Cathinone is the principle active stimulant found in the khat plant (*Catha edulis*).

<sup>(8)</sup> Mephedrone was subject to risk assessment at the European Union-level in 2010 and subsequently subject to control measures within the Member States.

The free base form of MDPV has been described as being a brown or yellow-green amorphous powder whilst the hydrochloride salt form is white but also described as white-tan coloured powder.

MDPV is typically supplied as a powder; there are also reports of its supply in tablet, capsule and liquid form. MDPV is soluble in water and the powder can be dissolved for oral use or intravenous and subcutaneous injection.

The detection of MDPV is straightforward using a range of analytical techniques. Methods have been developed for MDPV and some of its metabolites using gas chromatography coupled with ion trap mass-spectrometry (GC-IT-MS), ultra high-pressure liquid chromatography-tandem mass spectrometry (LC-MS/MS), ultra performance liquid-chromatography coupled with quadrupole time of flight mass-spectrometry (UPLC-QTOF-MS) and Raman spectroscopy coupled with high-performance liquid chromatography (HPLC). MDPV has been reported to cause false-positive phencyclidine immunoassay results in urine samples.

The tentative 'common doses' of MDPV reported by users by route of administration are: 5–11 mg (insufflation); 8–15 mg (oral); and, 6–12 mg (rectal). The onset of desired effects is typically seen within 5–30 minutes with desired effects lasting up to 2–7 hours for the common routes of administration (oral and nasal). In addition, there is evidence from non-fatal intoxications and deaths reported by the Member States to the Early Warning System, studies published in the literature, as well as from self-reported experiences on user websites and needle exchange programmes that MDPV is injected by some users, including problem drug users.

MDPV selectively inhibits catecholamine uptake (dopamine transporter (DAT) and norepinephrine transporter (NET)) while serotonin uptake is significantly less affected. The effects of MDPV appear to be longer lasting than cocaine in animal models; information provided in clinical case reports<sup>(9)</sup> appear to be consistent with these findings. The subcutaneous LD<sub>50</sub> value for MDPV in the mouse is 175 mg/kg.

The main phase I metabolic steps identified in both the rat *in vivo* and human *in vitro* studies included demethylation followed by methylation, aromatic and side chain hydroxylation and oxidation of the pyrrolidine ring to the corresponding lactam and ring opening to the corresponding carboxylic acid. No data are available on the biological activity of these metabolites.

MDPV was patented as a central nervous system stimulant in the mid-1960s. Currently, MDPV is available as an analytical reference material and is used in scientific research investigating its chemistry, pharmacology and toxicology as a result of its emergence on the drug market. There are currently no known uses of MDPV as an industrial, agricultural or cosmetic compound. According to information provided by the EMA, there is no known

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<sup>(9)</sup> The term 'clinical case reports' is used to denote both clinical case reports and case series published in the scientific literature.

human or veterinary medical use of MDPV in the European Union. There is no marketing authorisation (existing, on-going or suspended) for MDPV at European Union-level nor in the Member States that responded to the information request by the EMA that was launched under Article 5 of the Council Decision. There is no information to suggest that MDPV is used in the manufacture of a medicinal product in the European Union. However, it should be noted that there is no European Union database on the synthetic routes of all registered medicinal products.

### **3. Chemical precursors used within the manufacturing process**

The synthesis of MDPV is described in (now expired) patents granted in France, Germany, the United Kingdom and the United States all from the 1960s which describe the precursor 1-(1,3-benzodioxol-5-yl)pentan-1-one being  $\alpha$ -brominated to form a 2-bromopentan-1-one intermediate. Reaction of the intermediate with pyrrolidine yields MDPV which is then converted into the hydrochloride salt. The ketone precursor may be obtained from a number of starting materials including 1,3-benzodioxole, although several alternative routes can be used.

There is currently no information regarding manufacturing sites, the chemical precursors or the synthetic routes used for MDPV that has been detected on the drug market.

Analysis of seized products has found both MDPV on its own and in combination with active pharmaceutical ingredients (e.g. lidocaine, procaine, piracetam, trimethoprim and diltiazem) and/or other psychoactive substances (e.g. cocaine, ketamine, methamphetamine, TFMPP, BZP, mephedrone, methylone, 4-MEC, MDPBP, alpha-PVP and synthetic cannabinoid receptor agonists).

### **4. Health risks**

#### ***Individual health risks***

The assessment of individual health risks includes a consideration of the acute and chronic toxicity of MDPV, as well as its dependence potential, and its similarities to and differences from other chemically-related substances.

As noted, information on the acute toxicity associated with MDPV is not collected uniformly across the European Union. It is important to note that when interpreting the information from non-fatal intoxications and deaths reported by the Member States as well as from clinical case reports and user websites, individuals may have used other pharmacologically active substances in addition to MDPV. The presence of other substances may account for some the reported effects.

Information obtained from a series of studies carried out *in vitro* and in *in vivo animal models* suggests that the psychopharmacological (behavioural) profile observed for MDPV is similar to cocaine and methamphetamine. However, it appears that MDPV is more potent and longer lasting. Clinical case reports appear to be consistent with these findings. A key pharmacological mechanism of MDPV includes catecholamine-selective transporter blockage. Compared to cocaine, MDPV was shown to be 50-fold more potent at DAT, 10-

fold more potent at NET, and 10-fold less potent at SERT (serotonin transporter). In addition, it is clear that MDPV does not act as a substrate. Consistent with the *in vitro* data, *in vivo* microdialysis studies in rats found that MDPV increased extracellular concentrations of dopamine in the nucleus accumbens and that it was 10-fold more potent than cocaine. Furthermore, MDPV was also found to be 10-time more potent in its ability to induce locomotor activation, tachycardia and hypertension. The observation of hyperpyrexia in animals varies with ambient temperature which warrants further studies.

There are no data on the interactions between MDPV and other drugs and medicinal products (including oral contraceptives). Investigations with recombinant human cytochrome P450 isoenzymes (CYPs) revealed that CYP 2C19, CYP 2D6 and CYP 1A2 were important isoforms involved in metabolism which may be relevant when considering polymorphisms and the potential for drug-drug interactions that involve the same subtypes (e.g. CYP 2C19/10/9: fluoxetine, carbamazepine, moclobemide; CYP 2D6: tramadol, fluoxetine, haloperidol, diltiazem, citalopram; CYP1A2: caffeine, diazepam, cannabis, olanzapine).

A total of 525 non-fatal intoxications associated with MDPV have been reported to the Early Warning System by eight Member States: Belgium (2 cases), France (19), Germany (6), Greece (2), Ireland (1), Italy (3), Slovakia (5) and Sweden (487). Of these cases, 110 have been analytically confirmed, with MDPV being confirmed in biological samples in all but one case. These cases are from: Belgium (2 cases), France (4), Greece (1), Ireland (1 involving analysis of the substance taken), Italy (3) and Sweden (99). In 13 of the cases, no other substances were reported. In addition, there are 77 European <sup>(10)</sup> and 89 non-European clinical case reports associated with MDPV use that include analytical confirmation of the substance in biological samples.

Data from these reports, along with information from self-reported experiences on user websites, suggest that individuals typically present with features similar to those seen with other stimulant drugs such as cocaine, amphetamines and mephedrone. These features include tachycardia, hypertension, convulsions, insomnia, nausea, stomach cramps, sweating, headache, reduced appetite, dilated pupils, dizziness, breathing problems, depression, confusion, agitation, aggression, severe and prolonged anxiety attacks, auditory and visual hallucinations, violent outbursts, and paranoid psychosis. In addition, there are reports of more severe toxicity including hyperpyrexia, rhabdomyolysis, acute kidney injury and stroke.

Since experience on the toxicological profile of MDPV is limited, it is difficult to be sure that rare, but clinically significant, severe effects are not associated with its use.

There have been a total of 108 deaths associated with MDPV (September 2009 to August 2013) reported to the Early Warning System by 8 Member States and Norway in which MDPV has been detected in post-mortem biological samples and/or implicated in the cause

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<sup>(10)</sup> There is a possibility that some of the non-fatal intoxications published in the scientific literature that have occurred within the European Union might be the same as some of the non-fatal intoxications reported to the Early Warning System by the Member States.

of death: Austria (1 death), Finland (40), France (1), Hungary (1), Ireland (8), Poland (3), Sweden (21), United Kingdom (32) and Norway (1). In addition there have been deaths published in the scientific literature that have occurred within the European Union (17 deaths) <sup>(11)</sup> and elsewhere, including the United States (33) and Japan (1). It should be noted that in some of these deaths it is likely that other drugs and/or other medical conditions or trauma may have contributed to and/or been responsible for death.

There are no published animal or human studies that have investigated the potential for neurotoxicity, reproductive toxicity, genotoxicity and carcinogenic potential of MDPV use. There are three clinical case reports of individuals who developed medium to long-term consequences (renal failure requiring haemodialysis (2) and stroke (1)), secondary to complications of the acute adverse health effects of MDPV.

A number of animal studies have investigated the abuse potential of MDPV using models involving self-administration, intracranial self-stimulation, discrimination, substitution and conditioned taste-aversion. These studies suggest that MDPV has rewarding and hedonic properties similar to methamphetamine; it is also self-administered including dose escalation. There have been no studies investigating the abuse liability and dependence potential of MDPV in humans. There are published reports in the scientific literature of individuals with suspected dependency on MDPV.

There is no information on the psychosocial consequences of chronic MDPV use such as the effects on psychological development and the interaction with the social environment.

### ***Public health risks***

The public health risks associated with MDPV may be categorised in terms of patterns of use (extent, frequency, route of administration, etc.); availability and quality of the drug; information, availability and levels of knowledge amongst users; and, negative health consequences.

There are reports to the Early Warning System of detections of MDPV in 27 Member states, Norway and Turkey since 2008. There is limited information available on the quality and purity of MDPV available to users.

In some cases, MDPV is being sold and used as a substance in its own right and has also been detected in combination with other psychoactive substances. Similar to other drugs, users may combine MDPV with other substances (stimulants, hallucinogens and/or depressants including alcohol). However, some users have taken MDPV unknowingly along with or instead of other substances, particularly when they may have intended to use other stimulant drugs. Therefore it is likely that information related to the use of MDPV is under-reported.

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<sup>(11)</sup> There is a possibility that some of the deaths published in the scientific literature that have occurred within the European Union might be the same as some of the deaths reported to the Early Warning System by the Member States.

There appears to be no co-ordinated national or European population surveys examining MDPV use. The only European data is available from non-representative studies. One non-representative Internet survey in 2010/11 of clubbers in the United Kingdom reported lifetime and last year use of 4.4 % and 3.0 %, respectively. The total number of respondents was not reported.

MDPV is available to users from Internet suppliers and retailers, bricks and mortar head shops and street level drug dealers. EMCDDA monitoring of Internet suppliers and retailers selling MDPV (conducted in the month prior to the risk assessment) identified more than twenty companies, which may be based within the European Union and China, offering up to multi-kilogram quantities of the substance.

There are limited data available on the characteristics and behaviour of users; however, it is likely that these will be similar to those using other stimulant drugs. There is no data available on context-related risks for MDPV users.

The injection of MDPV by problem drug users has been reported in a number of countries, including Hungary, Finland and Romania. In the study from Hungary, 183 clients of a needle exchange programme agreed to report their drug using habits. This study found that during 2011 changes occurred in the nature of primary injected substances: amphetamine was cited as the primary injected substance by 45.9 % of the respondents and MDPV by 48.1 %. Almost half of the former amphetamine injectors had switched to MDPV (64 persons, 45.1 %) as had 10 (41.7 %) of the former heroin injectors and 11 (78.6 %) of those using other substances (cocaine and mephedrone). Injecting MDPV carries public health risks of bacterial infections and transmission of blood borne viruses such as human immunodeficiency virus, hepatitis C and hepatitis B.

## **5. Social risks**

There is limited information on the social risks associated with MDPV. There is no information on whether the use of MDPV affects education or career, family or other personal or social relationships, including marginalisation. However, in some countries, MDPV has been used by marginalised problem drug users.

Although there are no relevant studies, it may be assumed that the acute behavioural effects of MDPV on operating machinery and driving are similar to those caused by other stimulant substances.

The detection of MDPV has been reported in biological samples other than non-fatal intoxications and deaths from 2009 onwards. These cases relate to fatal and non-fatal road traffic accidents, driving under the influence of drugs (DUID) and/or other petty crimes in Finland (519 cases), Germany (2), Sweden (14) and the United Kingdom (1). In addition, studies have demonstrated that MDPV was detected in 0.2 % and approximately 5 % of DUID samples analysed in Denmark and Finland, respectively. In the majority of these cases, other substances, such as amphetamines or benzodiazepines were also detected. The available information does not permit comment on the extent of driving impairment.

There are healthcare costs associated with the treatment of acute MDPV toxicity presenting to hospitals. Most of these cases involve short assessments within the emergency department; however there are a minority that have had more prolonged clinical features over a few days and/or have required admission to critical care. In addition, some individuals have also required admission to psychiatric facilities due to on-going symptoms.

Severe agitation, aggression and violence are not uncommon in MDPV users which appeared to be a more pronounced feature than normally observed with other classical stimulant drugs.

## **6. Involvement of organised crime**

There is no evidence available regarding the involvement of organised crime in the production and wholesale trafficking of MDPV. Bulk quantities of MDPV are being offered for sale from companies trading on the Internet. However, in the context of its widespread control, MDPV continues to be sold on the illicit market and multi-kilogram seizures continue to be reported. There have been reports of tablets with markings that would normally be associated with other recreational drugs (e.g. 'ecstasy'). There are some indications that suggest a degree of organisation in the tableting and distribution of this substance in the European Union.

MDPV has been found in combination with a range of new psychoactive substances and/or classical recreational drugs. It is not possible to determine whether this adulteration was intentional or not.

## **7. Assessment of the new psychoactive substance in the United Nations system**

The World Health Organization is the specialised agency of the United Nations designated for the evaluation of the medical, scientific and public health aspects of psychoactive substances under the 1961 United Nations Single Convention on Narcotic Drugs, and the 1971 United Nations Convention on Psychotropic Substances.

The World Health Organization informed the EMCDDA that MDPV will be subject to evaluation at the thirty-sixth meeting of the Expert Committee on Drug Dependence, which will be held in June 2014.

Article 7.1 of Council Decision states:

*'No risk assessment shall be carried out in the absence of a Europol/EMCDDA Joint Report. Nor shall a risk assessment be carried out where the new psychoactive substance concerned is at an advanced stage of assessment within the United Nations system, namely once the WHO expert committee on drug dependence has published its critical review together with a written recommendation, except where there is significant new information that is relevant in the framework of this Decision'.*

The risk assessment has been carried out on the understanding that MDPV is not at an advanced stage of assessment within the United Nations system.

## **8. Current control measures within the Member States**

MDPV is not listed for control in the 1961 United Nations Single Convention on Narcotic Drugs nor in the 1971 United Nations Convention on Psychotropic Substances (together 'UN drug conventions').

Twenty-one Member States (Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, France, Germany, Hungary, Ireland, Finland, Italy, Latvia, Lithuania, Luxembourg, Poland, Slovakia, Slovenia, Sweden, and the United Kingdom) as well as Turkey and Norway control MDPV under legislation by virtue of their obligations under the UN drug conventions.

Seven Member States (Austria, Greece, Malta, Netherlands, Portugal, Romania, and Spain) do not control MDPV by virtue of their obligations under the UN drug conventions.

Of these seven Member States, four of them (Austria, Netherlands, Portugal, and Romania) use other legislative measures to control MDPV. In Austria it is controlled under the generic definition within the New Psychoactive Substances Act. The Netherlands uses its medicines legislation to control MDPV. In Portugal it is listed as controlled under Decree-Law 54/2013. In Romania the Law 194/2011 subjects to control any psychoactive substance that qualifies by conforming to certain criteria (all substances with psychoactive potential are subject to control until proven harmless by a special designated commission).

## **9. Options for control and possible consequences of the control measures**

Under Article 9.1 of the Council Decision, the option for control that is available is for the Member States to submit the new psychoactive substance MDPV to control measures and criminal penalties, as provided for under their legislation, by virtue of their obligations under the UN drug conventions. There are no studies on the possible consequences of such control measures on MDPV. If this option of control is pursued, the Committee considers that the following consequences are possible. Some of these may apply to any new psychoactive substance.

- MDPV is controlled in 21 Member States under legislation by virtue of their obligations under the UN drug conventions. Should a decision be made to submit MDPV to control measures it would be expected to further facilitate the detection, seizure and monitoring of MDPV related to its unlawful manufacture, distribution and use by facilitating cooperation between the judicial authorities and law enforcement agencies across the European Union. However, this may have little impact on the manufacturers and suppliers based outside of the European Union.
- A positive health consequence that may result from this control is the benefit brought about by the presumed reduction of availability and use.
- This control option would imply additional costs to some countries. Such costs may include the criminal justice system, including forensic services, law enforcement and the courts.

- In some countries, this control option could lead to replacement with other (established or new) psychoactive substances, which may in themselves have public health consequences.
- It is not possible to gauge to what extent this control is likely to impact on current and future research by research/academic institutes, pharmaceutical or chemical industries.
- In some countries, this control option could create an illicit drug market in MDPV with increased risk of associated criminal activity, including organised crime.

In order to examine the consequences of control, the Committee wishes to note that should this option be pursued it will be important to monitor for the presence of MDPV on the market post-control.

Aside from the option for control under those stipulated in Article 9.1 of the Council Decision, other options for control may be available to Member States. These may include medicines legislation or restricting the importation and supply of the substance using other legislative options.

## **10. Conclusions**

MDPV is a ring-substituted synthetic derivative of cathinone chemically related to pyrovalerone, both of which are subject to control under the 1971 United Nations Convention on Psychotropic Substances. MDPV has potent cocaine-like stimulant properties. It was first identified in a seizure made by Finnish Customs November 2008 and formally notified to the Early Warning System in December 2008 by Finland. MDPV is found mostly as a powder but tablets and liquid forms have also been encountered. MDPV has been sold by Internet suppliers and retailers, in bricks and mortar head shops, as well as by street-level drug dealers. Analysis of seized products has found both MDPV on its own and in combination with other pharmacologically active substances including psychoactive drugs.

MDPV has been reported in seizures in 27 Member states, Norway and Turkey. EMCDDA monitoring of Internet suppliers and retailers selling MDPV has identified more than twenty companies that may be based within the European Union and China, offering up to multi-kilogram quantities of the substance.

There are no systematic data at national level in Europe on the prevalence of use of MDPV. The only European data are available from non-representative studies. There are limited data available on the characteristics and behaviour of users; however, it is likely that these will be similar to those using other stimulant drugs. Routes of administration include nasal insufflation, inhalation, oral and rectal administration and injection.

MDPV selectively inhibits the uptake of dopamine and norepinephrine, while it does not act as a substrate. In addition, serotonin uptake is significantly less affected. The effects of MDPV appear to be more potent and longer lasting than cocaine in animal models in addition clinical case reports appear to be consistent with laboratory findings.

A total of 525 non-fatal intoxications associated with MDPV have been reported by eight Member States. Key adverse effects associated with MDPV intoxication frequently reported in clinical case reports include: paranoid psychosis, hypertension, tachycardia, diaphoresis, severe agitation, auditory and visual hallucinations, profound anxiety, hyperthermia, violent outbursts and multiple organ dysfunction.

Data from animal studies and clinical case reports indicate that MDPV shows reinforcing effects with high abuse liability.

There have been a total of 108 deaths associated with MDPV reported by eight Member states and Norway in which MDPV has been detected in biological samples and/or implicated in the cause of death. In many of these cases it is not possible to determine the role of MDPV in the death. There are no data on the potential for reproductive toxicity, genotoxicity and carcinogenic potential associated with use of MDPV.

There is very limited information available on the social consequences of MDPV use. However, some countries have reported the use of MDPV by marginalised groups, such as injecting drug users.

Although MDPV has been seized on a multi-kilogram scale in Member States, detailed information on the involvement of organised crime with MDPV is not available. There are indications that suggest some degree of organisation in the tableting and distribution of MDPV within the European Union. There is no information to suggest that MDPV is currently manufactured in any of the Member States. The chemical precursors and the synthetic routes used to manufacture the MDPV detected in the Member States are unknown.

MDPV has no established or acknowledged medical value or use (human or veterinary) in the European Union. There are no indications that MDPV may be used for any legitimate purpose other than in analytical reference materials and in scientific research.

MDPV is not listed for control in the 1961 United Nations Single Convention on Narcotic Drugs or in the 1971 United Nations Convention on Psychotropic Substances. MDPV is currently undergoing assessment by the United Nations system. Twenty-one Member States, Turkey and Norway control MDPV under legislation by virtue of their obligations under the UN drug conventions; four Member States use other legislative measures to control MDPV.

Many of the questions posed by the lack of evidence on the health and social risks of MDPV, as for any new psychoactive substance, could be answered through further research. Areas where additional information would be important include: receptor binding and functional activity studies; metabolic pathway studies; behavioural studies; clinical patterns of acute and chronic toxicity in humans; the potential interaction between MDPV and other substances (in particular those that affect the monoaminergic system); prevalence and patterns of use (including targeted studies that examine user groups and risk behaviours); market studies; chemical profiling studies; studies on the abuse liability and dependence potential; and, studies on the social risks associated with its use.

The Committee notes that many Member States have measures in place to control MDPV. Should a decision be made to submit MDPV to control measures this would be expected to further facilitate the detection, seizure and monitoring of MDPV related to its unlawful manufacture, distribution and use by facilitating cooperation between the judicial authorities and law enforcement agencies within the European Union. This has a potential positive consequence in terms of reducing availability and therefore the adverse health and social consequences arising from the use of MDPV. It is important, however, to anticipate and minimise where possible any potential negative consequences of control. Control measures could extend an illegal market in MDPV with the associated risk of criminal activity. The implementation of control measures may also lead to the criminalisation of those who continue to use this substance with the possible attendant risks of socio-economic stigmatisation and marginalisation. Finally, control should not inhibit the gathering and dissemination of accurate information on MDPV to users and to relevant professionals.

## **11. List of annexes**

**Annex 1:** List of participants attending the risk assessment meeting.

**Annex 2:** *Technical Report on 1-(1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one (MDPV).*



## Annex 1. List of participants at the Risk Assessment meeting on MDPV, 2 April 2014

### A. Extended Scientific Committee

#### Scientific Committee Members

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LINC, Leuven Institute of Criminology, University of Leuven Faculty of Law, Leuven

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### **EMCDDA**

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## **B. Invited Experts**

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European Monitoring Centre  
for Drugs and Drug Addiction

## Annex 2. Technical Report on 1-(1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one (3,4-methylenedioxypropylamphetamine, MDPV)

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*This Technical Report was prepared under EMCDDA contract. Given the time frame stipulated in the Council Decision, it has not been formally edited by the EMCDDA. As a result, while the scientific data presented has been verified to the extent possible, minor changes may be introduced at a later date when the report is officially published. The EMCDDA may not be held responsible for the use of the information contained herein without prior consultation. The Risk Assessment Report on 1-(1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one (3,4-methylenedioxypropylamphetamine, MDPV), to which this report is annexed was produced by the Scientific Committee of the EMCDDA and shall be regarded as the authoritative document.*

*Suggested citation: Technical Report on 1-(1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one (3,4-methylenedioxypropylamphetamine, MDPV). EMCDDA, Lisbon, April 2014.*

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## SUMMARY

MDPV (3,4-methylenedioxypropylone) is a synthetic derivative of the naturally occurring chemical cathinone, and it is the methylenedioxy derivative of propylone. It was patented, along with other related substances, as a central nervous system stimulant in the mid-1960s; however it would appear that there has been no further development of these patented products. Apart from its use as an analytical standard and as research chemical in experiments investigating the pharmacology and toxicology of MDPV, it has no known legitimate uses as an industrial, cosmetic or medicinal product.

MDPV was first detected in Europe in 2008 with formal notification to the EMCDDA in December 2008 by the Finnish National Focal Point. There are reports to the EMCDDA or Europol of detections <sup>(1)</sup> of MDPV in 27 Member States, Norway and Turkey. The size and number of MDPV detections has increased year on year, particularly since 2010.

There have been over fifty other synthetic cathinone derivatives reported to the European Union Early Warning System, including mephedrone (4-MMC), which was subject to a risk assessment at EU-level and subsequent control measures in 2010, methylone (bk-MDMA) and 3,4-methylenedioxy- $\alpha$ -PPP (MDPPP).

There are currently no co-ordinated national or European population surveys on the prevalence of MDPV use. There are reports from targeted surveys in the United Kingdom and the US. The targeted surveys from the United Kingdom are from 2009-11 and suggested life-time use of MDPV of less than 5% amongst the group surveyed.

MDPV is typically supplied as a powder; there are also reports of its supply in tablet, capsule and liquid form. It is used nasally, orally, and by intravenous injection; other reported routes of use include rectal insertion, smoking and subcutaneous injection. Tentative 'common doses' of MDPV reported by users range from 5 to 11 mg (insufflation); and from 8 to 15 mg (oral). Single use doses of MDPV are typically reported to be 5 – 20mg, users have reported taking repeated doses per session with doses typically of 200mg per session.

MDPV has been and/or is available from bricks and mortar head shops, street-level drug dealers and Internet suppliers. In the 2011 and 2012 EMCDDA Internet Snapshot surveys

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(1) 'Detections' is an all-encompassing term and may include seizures and/or collected and/or biological samples. Seizure means a substance available (seized) through law enforcement activities (police, customs, border guards, etc.). Collected samples are those that are actively collected by drug monitoring systems (such as test purchases) for monitoring and research purposes. Biological samples are those from human body fluids (urine, blood, etc.) and/or specimens (tissues, hair, etc.)

MDPV was found to be available in 5-8% of Internet sites that were selling new psychoactive substances.

There have been no reports of anti-social behaviour related to the use of MDPV. There have been only a small number of cases of detection of MDPV in cases of other crimes. MDPV has been detected in a number of cases of driving under the influence of drugs in Denmark, Finland, Germany, Sweden and the United Kingdom.

There have been numerous *in vitro* and *in vivo* studies investigating the pharmacodynamics of MDPV, these show that MDPV has selectivity for inhibition of catecholamine uptake with greater activity at the dopamine and norepinephrine transporters (DAT and NET) than the serotonin transporter (SERT). MDPV predominantly acts as a transport blocker rather than altering substrate release. The effects of MDPV on DAT and NET are more potent and longer lasting than cocaine. Data on the pharmacokinetics of MDPV is limited to three studies with data on the likely metabolites of MDPV and one study on the blood-brain permeability of MDPV. Information from user self-reports and clinical data on individuals presenting to hospital with acute MDPV toxicity suggest that the desired effects of MDPV are similar to those seen with other stimulants such as cocaine and amphetamine type stimulants.

A number of animal models have investigated the acute adverse effects and the potential for toxicity associated with MDPV. These have shown that it has both dose- and time-dependent locomotor and psychomotor stimulant effects, causes cardiovascular stimulation and hyperpyrexia (particularly at increased ambient temperature). The stimulant effects of MDPV appear to be intermediate between the stimulant effects of cocaine and methamphetamine.

A total of 525 non-fatal intoxications associated with MDPV have been reported by eight Member states (Belgium (2), France (19), Germany (6), Greece (2), Ireland (1), Italy (3), Slovakia (5) and Sweden (487)). 110 of these cases have been analytically confirmed, with MDPV being confirmed in biological samples in all but one case. These cases are from: Belgium (2), France (4), Greece (1), Ireland (1 – analysis of substance taken), Italy (3) and Sweden (99). In addition, there are other European and non-European case reports and case series related to analytical confirmation of MDPV in biological samples. Data from these cases, along with information from user self-reports, suggest that individuals typically present with stimulant features including agitation/aggression, psychosis, delirium,

tachycardia, hypertension and convulsions; there are also reports of more severe toxicity including hyperpyrexia, rhabdomyolysis, acute kidney injury and stroke.

A number of animal studies have investigated the dependence and abuse potential of MDPV using models involving self-administration, intracranial self-stimulation, discrimination, substitution and taste-aversion. These studies suggest that MDPV has dependence potential that is dose-dependent. Some studies suggest that the dependence potential for MDPV is greater than that for methamphetamine, but this is not seen in all studies. A number of studies suggest that the dependence potential for MDPV is greater than that observed for other cathinones such as mephedrone and methylone but similar to MDMA. There have been no formal studies investigating the dependence and abuse potential of MDPV in humans. There has been one user report on Erowid.com and one report to the French National Focal Point, both of a single individual with self-reported "addiction" to MDPV. There is a report from Hungary of "more than 30%" of 15 individuals who developed "withdrawal" related to MDPV; however, there is insufficient detail in this report to be able to determine the nature of this withdrawal syndrome and whether it was related to MDPV.

There have been a total of 108 deaths associated with MDPV reported to the EU Early Warning System by 8 Member States and Norway in which MDPV has been detected in post-mortem biological samples and/or implicated in the cause of death: Austria (1), Finland (40), France (1), Hungary (1), Ireland (8), Poland (3), Sweden (21), United Kingdom (32) and Norway (1). In addition there have been other reports in the scientific literature of deaths from EU countries and from the US (33) and Japan (1). It should be noted that in some of these deaths it is likely that other drugs and/or other medical conditions or trauma may have contributed to and/or been responsible for death.

There are no animal or human studies that have investigated the potential for chronic toxicity associated with the use of MDPV. There are 3 reports of individuals who have developed medium to long-term consequences (haemodialysis (2), stroke (1)) secondary to complications of the acute health effects of MDPV.

In conclusion, MDPV is a synthetic cathinone which is used for its stimulant effects and there is increasing evidence of its use and availability in Europe. A number of animal studies have shown that MDPV has significant acute harm effects and dependence potential. In addition there are numerous reports of non-fatal intoxication and deaths related to MDPV use. There is therefore a significant risk of increasing non-fatal intoxications, chronic morbidity,

dependence and mortality related to MDPV use in Europe, with associated health care utilisation and social costs.

## SECTION A. PHYSICAL, CHEMICAL, PHARMACEUTICAL AND PHARMACOLOGICAL INFORMATION

### A1. Physical, chemical and pharmaceutical information

#### A1.1. Physical and chemical description (including methods of synthesis, precursors, impurities if known – type and level)

The systematic chemical (International Union of Pure and Applied Chemistry, IUPAC) name for MDPV is 1-(1,3-benzodioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one. MDPV is the common name for 3,4-methylenedioxypropylone. It is also known as MDPK or MP4 (in Hungary) and additional chemical synonyms reported are:

1-(3,4-Methylenedioxyphenyl)-2-pyrrolidinyl-pentan-1-one;

1-(3,4-Methylenedioxy-phenyl)-2-pyrrolidin-1-yl-pentan-1-one;

1-(Benzo[d][1,3]dioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one;

1-(1,3-Benzodioxol-5-yl)-2-(pyrrolidin-1-yl)-1-pentan-1-one;

1-(1,3-Benzodioxol-5-yl)-2-(1-pyrrolidinyl)-1-pentanone.

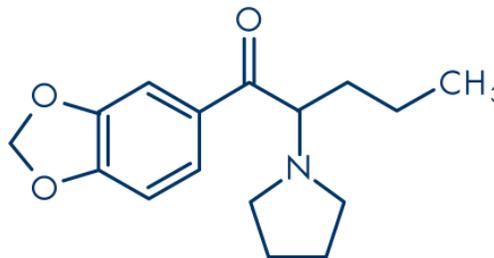
The pentan-1-one ending may also be replaced with 1-pentanone.

There are no non-proprietary names or trademark names for MDPV.

The Chemical Abstract Service (CAS) Registry Number for MDPV (base) is 687603-66-3 and the molecular formula is  $C_{16}H_{21}NO_3$ , equating to a molecular weight of 275.343. The CAS number for MDPV (hydrochloride salt) is 24622-62-6 and the molecular formula is  $C_{16}H_{22}ClNO_3$  equating to a molecular weight of 311.81. The CAS number for the MDPV *R*-enantiomer (form not specified) is 1388142-27-5, for the MDPV *S*-enantiomer (form not specified) is 1388142-28-6, for the MDPV deuterated  $D_8$  hydrochloride salt is 1246820-09-6 and for the MDPV deuterated  $D_8$  base is 1246912-12-8.

The chemical structure of MDPV is shown below in Figure 1:

Figure 1: Chemical Structure of MDPV



MDPV is a synthetic derivative of the naturally occurring chemical cathinone, and is the methylenedioxy derivative of pyrovalerone. Pyrovalerone is a Schedule IV substance under the 1971 UN Convention, Schedule IV. The synthesis of MDPV is described in patents from the France, Germany, the United Kingdom and USA all from the 1960s (Boehringer Ingelheim, 1967; Boehringer Ingelheim, 1969; Köppe, 1969a, Köppe, 1969b). Briefly, the precursor 1-(1,3-benzodioxol-5-yl)pentan-1-one is  $\alpha$ -brominated to form a 2-bromopentan-1-one intermediate. Reaction of the intermediate with pyrrolidine yields MDPV which would then typically be converted into the hydrochloride salt. The ketone precursor may be obtained from a number of starting materials including 1,3-benzodioxole, although several alternative routes can be used.

MDPV contains one asymmetric carbon atom, thus it is a chiral molecule. So far only the racemic mixture of the 1:1 ratio of the two possible enantiomers has been characterised. MDPV is one of over fifty synthetic cathinones that have been reported to the EU Early Warning System - others include mephedrone (4-MMC), methylene (bk-MDMA) and 3,4-methylenedioxy- $\alpha$ -PPP (MDPPP).

The following street names for MDPV have been reported: MDPK, Magic, Super Coke, PeeVee, New Ivory Wave, Kannibaldrogen, Apdamm, Aakkoset (meaning alphabet in Finnish), Bath Salt, MP, MP4 and MP3. The following 'legal high'/new psychoactive substance product names have been associated with MDPV: Mojo, Yellow Submarine, Ivory Wave, Vanilla Sky, NRG-3, Flower Magic, Gumi Cucuriedka, Kamikadze, Xtacy, Extreme Star Dust, Hurricane Charlie, Dogs Bollix, Doves Red, Doves Ultra, Sextasy, Orange Orbits, Stardust, Blow, Recharge, Charge+, Lucky, Generation 2012, El Padrino (meaning the Godfather in Spanish), Coco Jumbo, Cherry Coco Jumbo, Sunrise, Techno, Greenway Speedway, Dana, Olga, Lena, Eva, Clara, Marketa and Jana. It is important to note that in the US, MDPV is one of a number of synthetic cathinones found in products often called "bath salts" or "plant food"; MDPV was detected in five out of 14 "bath salt" products bought at a "head shop" in Pennsylvania, USA in 2011 (Leffler, 2014).

The nuclear magnetic resonance (NMR) and mass spectroscopic characterization of MDPV was first published in 2008 (Uchiyama, 2008) and confirmed in further publication in 2009 (Westphal, 2009; Takahashi, 2009). Gas chromatography with ion trap mass-spectrometry (GC-IT-MS) and NMR were used to analyse MDPV and other 'legal highs' in Internet purchased products (Brandt, 2010a; Brandt, 2010b) and a number of publications have described the use of ultra high-pressure liquid chromatography-tandem mass spectrometry (LC-MS/MS) for the analysis of MDPV in urine (Bell, 2011), bulk powder (Jankovics, 2011),

oral fluids (Strano-Rossi, 2012) and wastewater (van Nuijs, 2013). Other analytical techniques that have been developed for MDPV include ultra-performance liquid-chromatography with quadrupole time of flight mass-spectrometry (UPLC-QTOF-MS) (Reitzel, 2012), solid phase Fourier transform infrared (FT-IR) spectroscopy (Yohannan, 2010), ultraviolet spectrophotometry (Yohannan, 2010), Immunoassay (Swortwood, 2013), and Raman spectroscopy with high-performance liquid chromatography (HPLC) (Christie, 2013). One study has shown that MDPV can be detected using colour spot tests such with testing kits that use reagents including the Marquis reagent and Liebermann's reagent (Toole, 2012). MDPV has been reported to cause false-positive phencyclidine immunoassay results in urine samples (Macher, 2013).

**A1.2. Physical/pharmaceutical form (i.e. powder, capsules, tablets, liquids, injectables, cigarettes. Any distinctive markings, logos, etc., to be noted)**

The free base form of MDPV has been described as being a brown or yellow-green amorphous powder whilst the hydrochloride salt form is described as a white-tan crystalline powder. The melting point of the hydrochloride salt of MDPV is 229–231 °C (Boehringer Ingelheim, 1967; Boehringer Ingelheim, 1969; Köppe, 1969a, Köppe, 1969b). In the reports of seizures of MDPV to the EU early Warning System it is most commonly found as a powder but capsules and tablets been found, see the table in Section C for more details.

**A1.3. Route of administration and dosage (e.g. oral, inhalation, intravenous etc)**

MDPV is used by the oral route either as capsules or tablets, 'bombing' (wrapping the powder in cigarette papers and swallowing), dabbing (dipping a moistened finger into the powder) or ingestion of the powder dissolved in water; it is also commonly taken by nasal insufflation; other routes of use include smoking, intravenous injection and rectal insertion.

The tentative 'common doses' of MDPV reported by users by route of administration are: 5-11 mg (insufflation); 8-15 mg (oral); 6-12 mg (rectal) (Erowid, 2013a) (Table X). Users have reported taking repeated doses per session with doses typically of 200mg per session (Ross et al., 2012).

Table X. MDPV tentative 'common doses' reported by users.

Dose	Insufflated	Oral	Rectal
Threshold	1 - 3 mg	2 - 6 mg	1 - 5 mg
Light	2 - 5 mg	4 - 10 mg	3 - 8 mg
Common	5 - 11 mg	8 - 15 mg	6 - 12 mg
Strong	10 - 20 mg	12 - 25 mg	10 - 25 mg

There is some limited information in the Boehringer Ingelheim patents (registered in France, Germany, the United Kingdom and USA) from the 1960s on doses of a number of pyrovalerone-type compounds with a 3,4-(methylenedioxyphenyl) nucleus (Boehringer Ingelheim, 1969, Köppe, et al., 1969b). The doses proposed for “peroral” and “injectable” use are “2 – 40 mg but preferably between 10 – 20 mg”.

## A2. Pharmacology, including pharmacodynamics and pharmacokinetics

### *Pharmacodynamics*

There have been a number of studies that have investigated the mechanisms of action of MDPV, many but not all of these were summarised in a recent review (Iversen, 2014).

One comprehensive paper reports a series of experiments carried out both *in vitro* and *in vivo* in rats and mice investigating the mechanisms of action of MDPV in comparison to other stimulants including cocaine, amphetamine, mephedrone and methylone (Baumann, 2013). The first studies reported in this paper were *in vitro* studies using rat brain synaptosomes. Transport activity at dopamine transporters (DAT), norepinephrine transporters (NET) and serotonin transporters (SERT) was assessed and MDPV was compared to cocaine, amphetamine, methylone and mephedrone. As shown in Table 1 and Figure 3 (2a,c,e in Figure 3), these studies demonstrated that MDPV is a potent blocker at DAT (DAT uptake  $IC_{50}$  4.1nM  $\pm$  SEM 0.5) and NET (NET uptake  $IC_{50}$  26nM  $\pm$  SEM 8), with weaker effects at SERT (SERT uptake  $IC_{50}$  43349nM  $\pm$  SEM 305). MDPV, like amphetamine, has selectivity for inhibition of catecholamine uptake with greater activity at DAT and NET than SERT; cocaine, mephedrone and methylone are non-selective inhibitors with similar activity at DAT, NET and SERT. Compared to cocaine, MDPV is 50-times more potent as a blocker at DAT, 10-times more potent at NET and 10-time less potent at SERT. Release experiments (Table 1 and 2b, d, f in Figure 2) showed this predominantly relates to MDPV acting as a transport blocker rather than it acting as a substrate; MDPV results in less than 30% maximal release from DAT and NET, but no release from SERT in rat synaptosomes pre-loaded with substrate. As shown in Table 1 this contrasts with amphetamine, methylone and mephedrone all of which significantly increase release at all three transporters.

Figure 2: Data from Bauman et al comparing inhibition of uptake/stimulation of release at DAT, NET, SERT in rat brain synaptosomes.

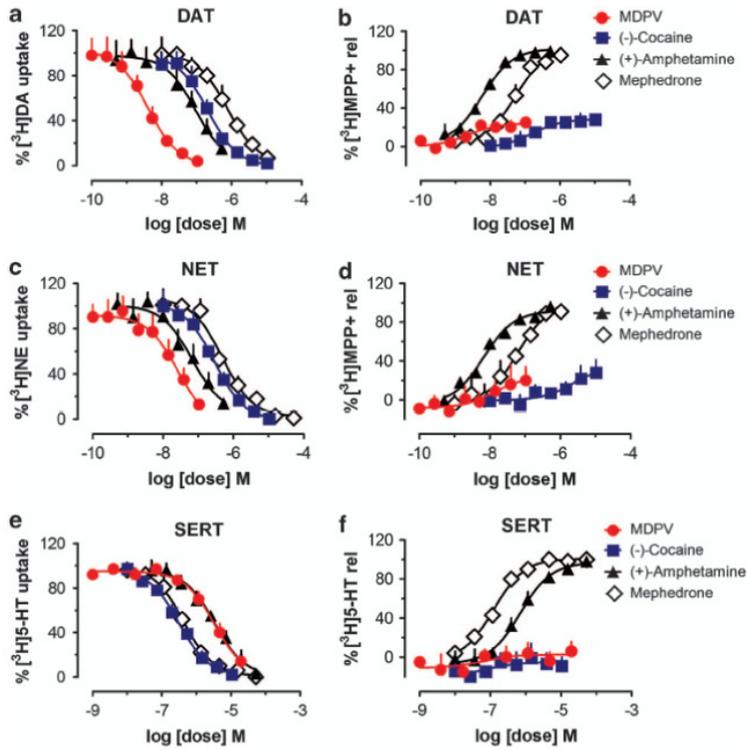


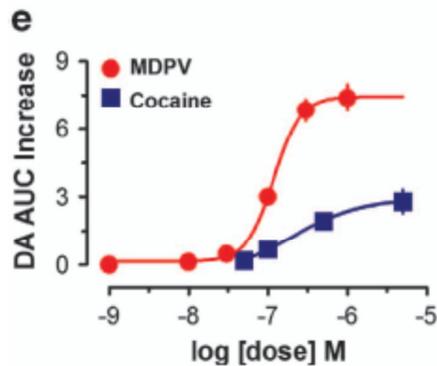
Table 1. Effects of MDPV, cocaine, amphetamine, mephedrone and methylone on transporter-mediated uptake and release in rat brain synaptosomes

	MDPV	Cocaine	Amphetamine	Mephedrone	Methylone
DAT uptake IC <sub>50</sub> (nM ± SEM)	4.1 ± 0.5	211 ± 19	93 ± 17	762 ± 79	1232 ± 133
NET uptake IC <sub>50</sub> (nM ± SEM)	28 ± 8	292 ± 34	67 ± 16	487 ± 66	1031 ± 162
SERT uptake IC <sub>50</sub> (nM ± SEM)	3349 ± 305	313 ± 17	3418 ± 314	422 ± 26	1017 ± 59
DAT release IC <sub>50</sub> (nM ± SEM) (E <sub>max</sub> %)	2.3 ± 0.8 (24 ± 1)	151 ± 35 (29 ± 1)	5.8 ± 0.4 (102 ± 1)	51 ± 5 (102 ± 2)	117 ± 12 (96 ± 1)

NET release (nM ± SEM) (E <sub>max</sub> %)	13 ± 16 (24 ± 6)	2190 ± 883 (34 ± 6)	6.6 ± 07 (92 ± 1)	58 ± 11 (99 ± 4)	104 ± 17 (94 ± 2)
SERT release (nM ± SEM) (E <sub>max</sub> %)	Inactive	Inactive	698 ± 71 (97 ± 2)	122 ± 10 (101 ± 1)	234 ± 35 (98 ± 2)

In the same paper, dopamine clearance was studied using fast scan cyclic voltammetry in striatal slices from male CB57/BL6 mice, thus, confirming that MDPV was an uptake blocker. As shown in Figure 3, MDPV (EC<sub>50</sub> 115 ± 17 nM) was significantly more potent than cocaine (EC<sub>50</sub> 308 ± 75 nM) at inhibiting dopamine clearance, p<0.001. In addition, it was suggested that high affinity to DAT might have contributed to slow dissociation from the target, potentially accounting for the longer-lasting action of MDPV compared to cocaine.

Figure 3: Dose-response curve for dopamine (DA) area under the curve (AUC) for MDPV and cocaine in mouse striatal slices.



The final studies reported in this paper were *in vivo* microdialysis studies in conscious male Sprague-Dawley rats implanted with an intracranial cannula in the nucleus accumbens at least a week prior to the studies (Baumann, 2013). Both MDPV and cocaine increased extracellular dopamine in the nucleus accumbens, but MDPV was ten-times more potent and the lowest effective intravenous MDPV dose was 0.1mg/kg compared to 1.0 mg/kg for cocaine. Furthermore, these studies suggested that the effects of MDPV lasted longer than the effects of cocaine: the increase in extracellular dopamine related to 0.3 mg/kg MDPV remained above saline control for 60 minutes after injection; however, the effects of 3.0 mg/kg cocaine only remained above saline control for 40 minutes after injection.

Similar results were described in a study using HEK 293 cells stably expressing human SERT, NET and DAT to assess the *in vitro* pharmacology of a number of cathinones including MDPV together with cocaine and a number of amphetamines (Simmler, 2013a). This study also showed that MDPV has high transporter and receptor binding affinity for DAT and NET, but low affinity for SERT (mean  $\pm$  SD  $K_i$  for DAT, NET and SERT:  $0.08 \pm 0.02 \mu\text{M}$ ,  $0.01 \pm 0.002 \mu\text{M}$ ,  $2.86 \pm 0.1 \mu\text{M}$  respectively); and is a potent DAT and NET transport inhibitor, but with limited SERT inhibition (Mean (95%CI)  $\text{IC}_{50}$ : DAT  $0.031 (0.031 - 0.04) \mu\text{M}$ , NET:  $0.044 (0.03 - 0.07) \mu\text{M}$ , SERT:  $9.30 (6.8 - 12.8) \mu\text{M}$ ). MDPV (together with pyrovalerone) were the most potent DAT inhibitors. The DAT:SERT ratio (95% CI) for MDPV and pyrovalerone were both  $> 100$  compared to  $> 10$ ,  $3.1 (2.0 - 4.8)$ ,  $1.4 (0.9 - 2.4)$  and  $0.08 (0.04 - 0.16)$  for amphetamine, cocaine, mephedrone and MDMA respectively. These studies confirmed the findings of Bauman et al, that MDPV produces no DA or 5-HT efflux and therefore that the effects on DAT and SERT relate to potent transporter inhibition rather than substrate release. Finally, this study also assessed receptor binding affinity and showed that MDPV had limited binding to 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>,  $\alpha_{1A}$ ,  $\alpha_{2A}$ , D<sub>1</sub>, D<sub>2</sub> and D<sub>3</sub> receptors.

Overall, the authors of this study classified the cathinones into three groups based on the variation in their selectivity for DAT, NET and SERT and potency to act as monoamine transport inhibitors / substrate releasers.

- Group one: “Cocaine-MDMA-Mixed Cathinones”:
  - Mephedrone, methylone, ethylone, butylone and naphyrone
- Group two: “Methamphetamine-like Cathinones”:
  - Cathinone, methcathinone, flephedrone
- Group three: “Pyrovalerone-cathinones”
  - Pyrovalerone and MDPV.

This group reported another *in vitro* study in HEK-293 cells expressing the human DA transporter (Simmler, 2013b). This study demonstrated that MDPV inhibited DA uptake and methamphetamine-induced DA release, and that these effects were more potent than the effect of bupropion and methylphenidate (Table 2).

Table 2: Effects of MDPV and reference compounds on dopamine (DA) uptake and methamphetamine-induced DA release in HEK-293 cells expressing the human DA transporter

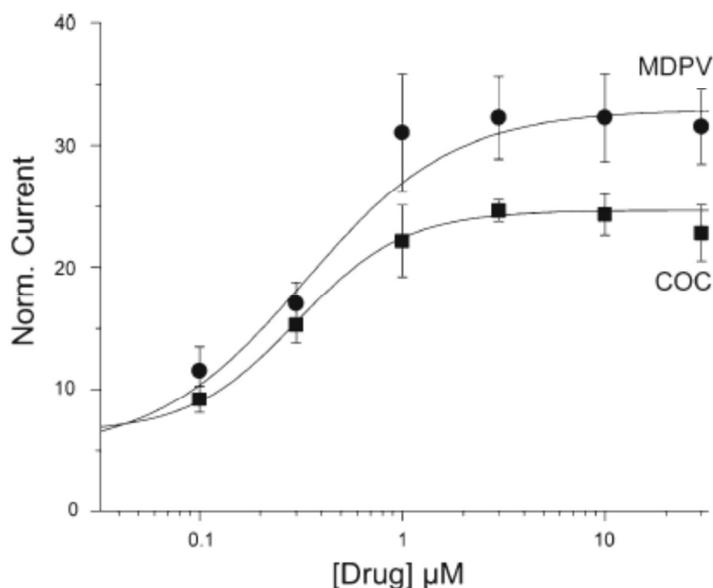
	DA Uptake Mean (95%) $\text{IC}_{50}$ ( $\mu\text{M}$ )	Methamphetamine-induced DA release

		Mean (95%) IC <sub>50</sub> ( μM)
Methamphetamine	1.05 (0.7 – 1.5)	
Bupropion	1.76 (1.1. – 2.8)	14.2 (9.7 – 2)
Methyphenidate	0.14 (0.1. – 0.2)	1.67 (0.7 – 4.0)
MDPV	0.0031 (0.03 – 0.04)	0.28 (0.1 – 0.6)

The potent DAT and NET transporter inhibitor, but limited SERT transporter inhibition of MDPV has been confirmed in another *in vitro* study using a variety of cell culture and binding assays (Eshleman, 2013). This study also confirmed that MDPV has very limited binding affinity for 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors. Detailed uptake, release and affinity data was reported in this paper. The inhibition of [3H]DHTB binding to hVMAT2: MDPV,  $K_i = 990 \mu\text{M}$ ; MDMA,  $K_i = 661 \mu\text{M}$ ; methamphetamine,  $K_i = 920 \mu\text{M}$ . The inhibition of hVMAT2 [<sup>3</sup>H]5-HT uptake: MDPV,  $\text{IC}_{50} > 100 \mu\text{M}$ ; MDMA,  $\text{IC}_{50} = 5.8 \mu\text{M}$ ; methamphetamine,  $\text{IC}_{50} = 4.72 \mu\text{M}$ . hVMAT2 [<sup>3</sup>H]NE release assay: MDPV,  $\text{EC}_{50} = 148 \mu\text{M}$  with efficacy (E) of 35.8%; MDMA,  $\text{EC}_{50} = 114 \mu\text{M}$ , E = 63%; methamphetamine,  $\text{EC}_{50} = 79 \mu\text{M}$ , E = 95%. The inhibition of binding to 5-HT receptors: MDPV:  $K_i$  h5-HT<sub>1A</sub> = 14.8  $\mu\text{M}$ ,  $K_i$  h5-HT<sub>2A</sub> = 207  $\mu\text{M}$ ,  $K_i$  h5-HT<sub>2C</sub> = 107  $\mu\text{M}$ ; LSD:  $K_i$  h5-HT<sub>1A</sub> = 1.32 nM,  $K_i$  h5-HT<sub>2A</sub> = 0.15 nM,  $K_i$  h5-HT<sub>2C</sub> = 1.29 nM. The potency and efficacy at 5-HT receptors: MDPV: h5-HT<sub>1A</sub>  $\text{EC}_{50} = 60.8 \mu\text{M}$ , E = 69%; h5-HT<sub>2A</sub>  $\text{IC}_{50} = 270 \mu\text{M}$ , E = 67.7%; h5-HT<sub>2C</sub>  $\text{IC}_{50} > 1 \text{ mM}$ , E = 24.5%; LSD h5-HT<sub>1A</sub>  $\text{EC}_{50} = 5.8 \text{ nM}$ , E = 107.8%; ketanserin h5-HT<sub>2A</sub>  $\text{IC}_{50} = 2.98 \text{ nM}$ , E = 95.9%; SB-242084 h5-HT<sub>2C</sub>  $\text{IC}_{50} = 0.28 \text{ nM}$ , E = 86.5%. The inhibition of [<sup>3</sup>H](+)-pentazocine binding to hSigma1, MDPV  $K_i = 4.4 \mu\text{M}$ ; haloperidol  $K_i = 0.94 \text{ nM}$ ; MDMA  $K_i = 19.4 \mu\text{M}$ ; methamphetamine  $K_i = 3.18 \mu\text{M}$ . MDPV did not show any measureable affinity for dopamine receptor subtypes up to 10  $\mu\text{M}$ .

Another study used human DAT expressed in *Xenopus laevis* oocytes to investigate the mechanisms of action of MDPV compared to mephedrone, methamphetamine, methcathinone and cocaine (Cameron, 2013a). The oocytes were voltage clamped at -60 mV, near the resting potential of the cells, and the drugs were applied for 60 seconds at a concentration of 10  $\mu\text{M}$ . MDPV generated a cocaine-like outward hyperpolarising current compared with baseline; this contrasted to the inward depolarising current seen with mephedrone, methamphetamine and methcathinone. This hyperpolarisation relates to inhibition of DAT. As shown in Figure 4, the effects of both MDPV and cocaine were dose-related. Overall, the inhibitory effects of MDPV on DAT were greater than the effects of cocaine (remaining %dopamine pre-pulse  $24.6 \pm 0.5\%$  and  $32.9 \pm 1.9\%$  respectively,  $p < 0.01$ ) but were of similar potency ( $\text{EC}_{50}$   $0.30 \pm 0.04 \mu\text{M}$  and  $0.33 \pm 0.07 \mu\text{M}$  respectively,  $p > 0.05$ ).

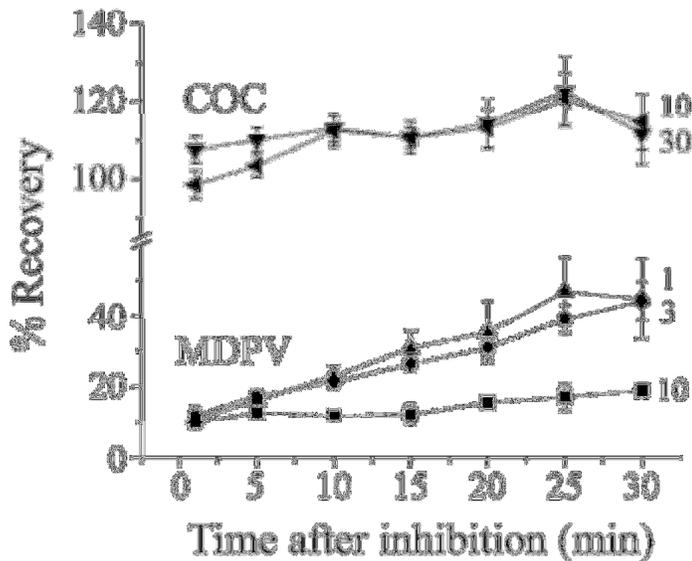
Figure 4: Dose-dependent effects of MDPV and cocaine (COC) on human DAT expressing *Xenopus* oocytes voltage clamped at -60mV. Data expressed as percentage of dopamine (DA) pre-pulse peak current cocaine (Cameron, 2013a).



These findings demonstrating that MDPV is a more potent DAT inhibitor have been confirmed in two other studies using voltage-clamped *Xenopus laevis* oocytes expressing human DAT (Cameron, 2013b; Kolanos, 2013). As shown in Figure 5, in addition to the DAT inhibitory effects of MDPV being more potent to those of cocaine, they are also longer lasting (Cameron, 2013b). One minute after cocaine (10 and 30μM) administration, DA induced current recovered to baseline; however, one minute after MDPV administration (1, 3 and 10μM), DA induced current recovered to 10% of baseline for all three doses and at 30 minutes, recovery from MDPV was 50%, 40% and 20% for the 1, 3 and 10 μM doses respectively.

Figure 5: Recovery of dopamine (DA) induced current after treatment with cocaine (COC) and MDPV.

D



The results of a microdialysis study (available in Japanese only) made similar conclusions (Fuwa, 2007; Satoh, 2009). Extracellular levels of dopamine (DA) and serotonin (5-HT) were determined in the striatum of freely-moving mice, using microdialysis and high performance liquid chromatography with electrochemical detection (HPLC-EC). Dialysates were collected at 10 minute intervals for 2.5 hours after oral administration of MDPV. Sixty minutes after MDPV administration, the experimental group showed increased extracellular DA levels 2.1 times higher than those of the control group. The effect of MDPV on the increase in DA was less marked than for MDMA and methamphetamine. Similar to other studies, MDPV showed no significant influence on 5-HT.

#### Pharmacokinetics

There have been three studies that have investigated pharmacokinetic parameters of MDPV; one has investigated blood-brain barrier permeability (Simmler, 2013a) and two have investigated MDPV metabolism (Strano-Rossi, 2010; Meyer, 2010). No studies have assessed other pharmacokinetic parameters such as absorption, distribution or excretion.

The high blood brain barrier permeability of MDPV has been demonstrated using an *in vitro* human blood brain barrier permeability model (Simmler, 2013a). In this study, using conditionally immortalised human brain endothelial cells (TY09) the permeability coefficient ( $P_e$ ) for MDPV was  $>10$ . Previous studies have shown that a  $P_e \geq 3$  indicates high blood

brain barrier permeability (Abe, 2012). Further analyses in the MDPV blood-brain barrier study showed that apical to basolateral transport of MDPV was greater than basolateral to apical transport ( $p < 0.05$ ), these results suggest active transport of MDPV by one of the blood-to-brain influx carriers (Simmler, 2013a).

The first study investigating the metabolism of MDPV was an *in vitro* study using human liver microsomes and S9 cellular fractions (Strano-Rossi, 2010). Phase I, Phase II (uridine 5'-diphosphoglucuronosyltransferase (UGT)) and Phase II (sulfotransferase (SULT)) metabolism were investigated. 1 mL of 1 mg/mL MDPV was incubated with 6.5 mL of human liver microsomes or S9 cellular fraction. Metabolites were analysed by gas chromatography mass spectrometry (GC-MS) and structures were confirmed by accurate mass measurement using a liquid chromatography quadrupole time-of-flight (LC/QTOF) mass spectrometer. Approximately 80% of the MDPV remained unchanged, the authors felt that this may have related to the dose of MDPV used saturating their model; only a single dose was studied. Approximately 7% of the MDPV was metabolised to catechol pyrovalerone and 10% to methylcatechol pyrovalerone. The metabolic pathway that was postulated by the authors is the opening of the methylenedioxy ring, followed by demethylation giving rise to a catechol group which is then methylated by catecholmethyltransferase in position 3.

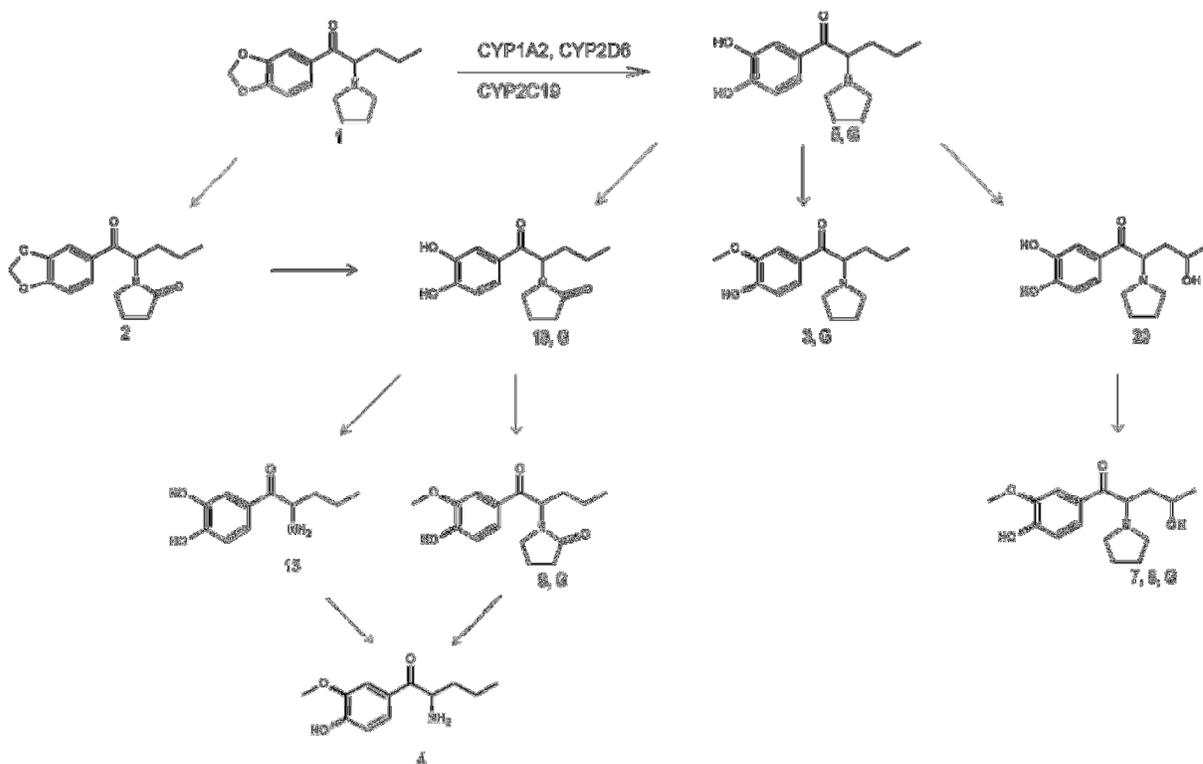
The Phase II studies suggested that these metabolites are conjugated with sulphate (approximately 50%) and glucuronide (approximately 40%); no hydroxylated or oxidatively deaminated metabolites were detected.

The second study to investigate the metabolism of MDPV involved a combination of an *in vitro* human liver microsomal model, *in vivo* experiments in rats administered MDPV and analysis of human urine samples from drug users (Meyer, 2010). The *in vitro* experiments were carried out in pooled human liver microsomes and baculovirus-infected insect cell microsomes with human cDNA expressed cytochrome-P450 isoenzymes. The animal drug administration study involved administration of a single 20 mg/kg dose of MDPV by gastric intubation to male Wistar rats; urine was collected for 24 hours after administration. The human urine samples were samples that were submitted to the authors' laboratory for toxicological analysis. Analysis was performed using gas-chromatography mass-spectrometry (GC-MS) and liquid chromatography high-resolution mass spectrometry (LC-HR-MS). Many more metabolites were elucidated in this study than in the study discussed above. The main Phase I metabolic steps identified in both the rat *in vivo* and human *in vitro* studies were: demethylenation followed by methylation, aromatic and side chain hydroxylation and oxidation of the pyrrolidine ring to the corresponding lactam and ring

opening to the corresponding carboxylic acid. The metabolites elucidated included: demethylenyl-MDPV, demethylenyl-methyl-MDPV, demethylenyl-methyl-oxo-MDPV, oxo-MDPV, demethylenyl-methyl-alkyl-hydroxy-MDPV, carboxy-oxo-MDPV, demethylenyl-methyl-carboxy-oxo-MDPV, demethylenyl-methyl-N,N-bisdealkyl-MDPV, demethylenyl-oxo-MDPV, demethylenyl-N,N-bis-dealkyl-MDPV, demethylenyl-alkyl-hydroxy-MDPV and demethylenyl-methyl-phenyl-hydroxy-MDPV. Using recombinant human cytochrome P450 isoenzymes (CYPs), the CYPs that were found to be responsible for the initial metabolism of MDPV were CYP 2C19, CYP 2D6 and CYP 1A2.

The scheme proposed by the authors for the metabolism of MDPV in humans is shown in Figure 6 below.

Figure 6: Human metabolic pathways for MDPV proposed by Meyer et al (G = glucuronic acid conjugates)



In addition to the unchanged parent MDPV, the following metabolites were found in human urine at an unknown time after use of an unknown dose of MDPV: demethylenyl-MDPV, demethylenyl-methyl-MDPV, demethylenyl-oxo-MDPV, demethylenyl-methyl-oxo-MDPV, oxo-MDPV, demethylenyl-methyl-hydroxy-alkyl-MDPV, demethylenyl-hydroxy-alkyl-MDPV

and demethyl-methyl-N,N-bisdealkyl-MDPV. The most abundant metabolite in the human urine samples was demethylenyl-methyl-MDPV.

A number of the MDPV metabolites elucidated in the above study were also detected in urine samples obtained from an individual who presented to an Emergency Department in Italy with MDPV toxicity. The Phase I and Phase II metabolites identified were demethylenyl-MDPV, demethylenyl-methyl-MDPV, demethylenyl-methyl-oxo-MDPV, demethylenylhydroxy-alkyl-MDPV, demethylenyl-methyl-hydroxy alkyl-MDPV, demethylenyl-oxo-MDPV and the corresponding glucuronides (Favretto, 2012).

In the absence of formal pharmacokinetic data, the only information available on the likely onset and duration of effects of MDPV comes from user reports on Internet discussion forums and data from clinical case reports. Table 3 provides an overview of self-reported duration of effects when MDPV is taken by the oral and insufflated routes as reported by Erowid (2013c). This information was collated from users, research, and other resources. No further details were provided on the methodology used to collate this information.

**Table 3.** Examples of self-reported duration of effects of MDPV per route of administration (tentative) as reported by Erowid (2013c). No information on the doses that were used was provided.

<b>Duration of effects for MDPV</b>	<b>Oral</b>	<b>Insufflated</b>
<b>Total Duration</b>	2.0–7.0 hrs	2.0–3.5 hrs
<b>Onset</b>	15–30 mins	5–20 mins
<b>Coming Up</b>	30–60 mins	15–30 mins
<b>Plateau</b>	30–180 mins	30–100 mins
<b>Coming Down</b>	30–120 mins	30–60 mins
<b>After effects</b>	2–48 hours	1–7 days
<b>Hangover / Day After</b>	?	?

*Interactions with other drugs, medicinal products (including oral contraceptives) and other forms of interaction*

There is no data on the potential for interactions between MDPV and other drugs and medicinal products.

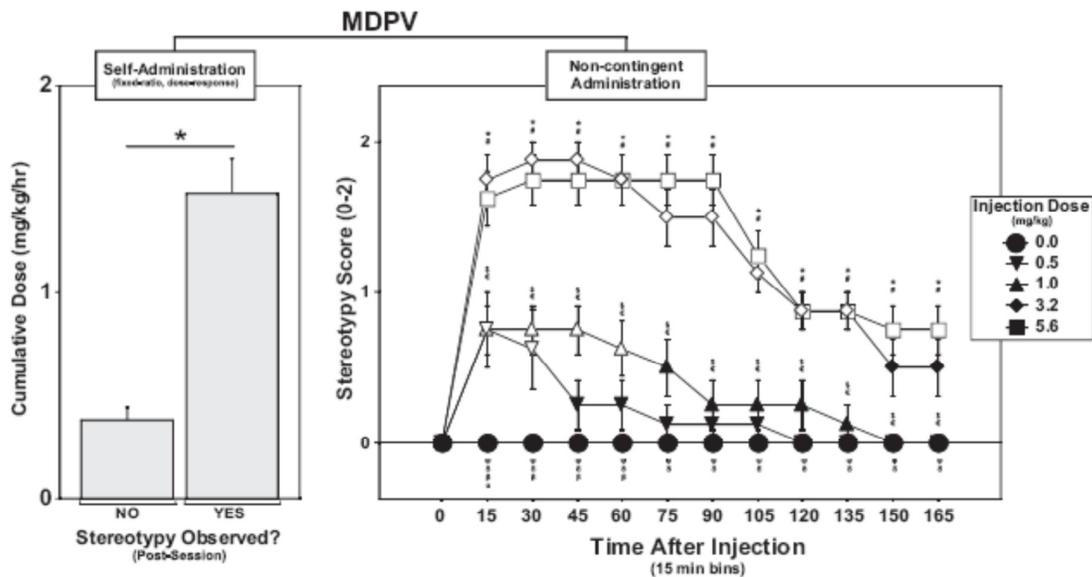
### A3. Psychological and behavioural effects

#### A3.1. Animal Studies

There is limited animal data on the psychological and behavioural effects of MDPV - three animal studies (two in rats and one in mice) have assessed stereotypy after MDPV administration and one study in mice used a functional observational battery.

A series of behavioural observations were undertaken to assess stereotypy in male Wistar rats (Aarde, 2013). Stereotypy was defined by the observation of: repetitive licking, biting or sniffing of the walls/bars of the cage. These observations were undertaken both during single dose non-contingent and intravenous self-administration studies. MDPV was associated with significant stereotypical behaviour. As shown in Figure 7, the cumulative dose of intravenous MDPV (mg/kg/hour) during fixed-dose self-administration was larger when post-session stereotypy was observed (mean  $\pm$ SD:  $1.4 \pm 0.5$  mg/kg) than when stereotypy was not observed ( $0.6 \pm 0.4$  mg/kg). After non-contingent dosing with MDPV, stereotypy scores increased in a dose-dependent manner. When compared to saline vehicle (where stereotypy was never observed), stereotypy scores were higher after subcutaneous MDPV at doses of 5.6 mg/kg and 3.2 mg/kg for the whole of the 165 minute sessions studied; after subcutaneous doses of 1.0 mg/kg and 0.5 mg/kg MDPV stereotypy scores were higher for the first 60 and 15 minutes respectively.

Figure 7: Mean  $\pm$ SEM stereotypy scores after MDPV or saline vehicle administration.



Stereotypy was also assessed in six male Sprague-Dawley rats (Baumann, 2013). Stereotypic movements were measured for one hour after subcutaneous doses of MDPV (0.1-3.0mg/kg), cocaine (3-17mg/kg) or saline control. Stereotypy was significantly increased by both MDPV ( $F [4,25] = 26.31, p < 0.0001$ ) and cocaine ( $F [3,20] = 7.68, p < 0.001$ ). The threshold dose of MDPV associated with significant stereotypy was 0.3 mg/kg ( $p < 0.05$ ), compared to the threshold dose of cocaine for stereotypy of 3 mg/kg ( $p < 0.05$ ). Additionally, MDPV induced significantly greater peak effects than cocaine for stereotypy (3.0 mg/kg MDPV vs 10 mg/kg cocaine,  $p < 0.001$ ).

In a study in male Harlan Sprague-Dawley mice which was investigating the locomotor and thermoregulatory effects of MDPV, abnormal behavioural effects were seen at higher doses of MDPV (Fantegrossi, 2013). At the highest dose of MDPV (30 mg/kg), significant focused stereotypy was observed at an ambient temperature of 28°C but not at an ambient temperature of 20°C. Four (of six) mice treated with 30 mg/kg MDPV at an ambient temperature of 28°C engaged in skin-picking and self-biting necessitating that the animals were removed from the study and euthanised. Stereotypy and self-injury were not seen at lower doses of MDPV, or at 30mg/kg MDPV at an ambient temperature of 28°C.

In a study in male ICR Harlan mice used a functional observational battery to classify behavioural effects of MDPV (Marusich, 2012). MDPV was given by intra-peritoneal injection at doses of 1-30 mg/kg and compared to saline vehicle. Self-injury or stereotyped biting or licking were not seen with MDPV. However, MDPV was associated with increases in exploration, increases in circling, stereotyped head weaving, stereotyped head circling, stereotyped compulsive movements. These effects occurred at all MDPV doses with the exception of stereotyped compulsive movements which were not seen at an MDPV dose of 1 mg/kg, but were seen  $> 3$  mg/kg.

### **A3.2. Human Studies**

There are no published formal studies assessing the psychological and/or behavioural effects of MDPV humans.

#### **A3.2.1 User Reports**

The section below includes a discussion of the characteristics of users which includes information from self-reported use from Internet drug discussion forums and related websites (hereafter 'user websites'). As such it is important to note that it is not possible to confirm the specific substance(s) used, nor the purity, dose, etc. Analysis of products containing new psychoactive substances that are sold on the drug market have shown that the composition

can differ between that claimed by the retailer, as well as differ over different geographical areas and time. Similar caveats apply to these types of information that have been provided in case reports/series unless biological and collected samples were taken and subjected to toxicological and forensic analysis. In addition, the information provided by patients in case reports/series as well as that provided on user websites should be regarded as illustrative only and not taken as representative of users of MDPV in general. Finally, information from seizures, collected samples and user websites suggest that MDPV has been commonly sold as a ‘legal’ replacement for cocaine, amphetamine or ‘ecstasy’ (MDMA). There is also information to suggest that MDPV has been sold directly on the illicit drug market as cocaine, amphetamine and MDMA, as well as mephedrone. In these cases, users may be unaware that they are consuming MDPV. Additional research is required in order to examine to what extent the characteristics of MDPV users reflect those who use other stimulant drugs.

No studies were identified that have examined the subjective effects of MDPV in humans; information is largely limited to that provided in case reports/series (see ‘non-fatal intoxications’ in Section D1.2) and self-reported experiences from user websites. Table 4 provides an overview of subjective effects of MDPV as reported by Erowid (2013c). This information was collated from users, research, and other resources. No further details were provided on the methodology used to collate this information. Information provided in case reports and case series of non-fatal intoxications associated with MDPV appear to support some of these effects. Section D1.2 provides an overview of the other adverse effects reported to be associated with MDPV.

**Table 4.** Examples of subjective effects of MDPV as reported by Erowid (2013a). No information on the doses that were used was provided.

<b>Subjective effects of MDPV</b>	
<b>Positive</b>	Stimulation (mental and physical) Euphoria, mood lift Increased sociability / talkativeness Increased productivity and motivation Increased mental clarity Enhanced creativity Feelings of empathy Sexual arousal
<b>Neutral</b>	Stimulation (mental and physical) Mild elevation in heart rate
<b>Negative</b>	(Likelihood of negative side effects increases with higher doses) Tightened jaw muscles, grinding teeth (trismus and bruxia) Reduced enjoyment of eating / loss of appetite Disturbed sleep patterns Involuntary body movements (twitching, lip-smacking, etc.) Confusion and/or scrambled thoughts Gastrointestinal disturbance Muscle tension Residual depressed mood

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Nystagmus / eye spasm  
Anxiousness / nervousness / paranoia  
Harsh comedown effects  
Fiending (redosing repeatedly without planning to do so)  
Excessive excitation / hyperactivity  
Headache  
Very elevated heart rate  
Hallucinations / psychotic behavior (at high doses or with repeated use)

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#### **A4. Legitimate uses of the product**

MDPV is available as an analytical reference standard and is used in scientific research in studies investigating the pharmacology and toxicology of MDPV. There are currently no other indications that MDPV is used for other legitimate purposes. There are no known uses of MDPV as a component in industrial, cosmetic or agricultural products. There is no information that MDPV is currently used in the manufacture of a medicinal product in the European Union. However, in the absence of a European Union database on the synthetic routes of all medicinal products this information cannot be verified. There is no marketing authorisation (existing, ongoing or suspended) for MDPV in the European Union nor in the Member States.

## SECTION B. DEPENDENCE AND ABUSE POTENTIAL

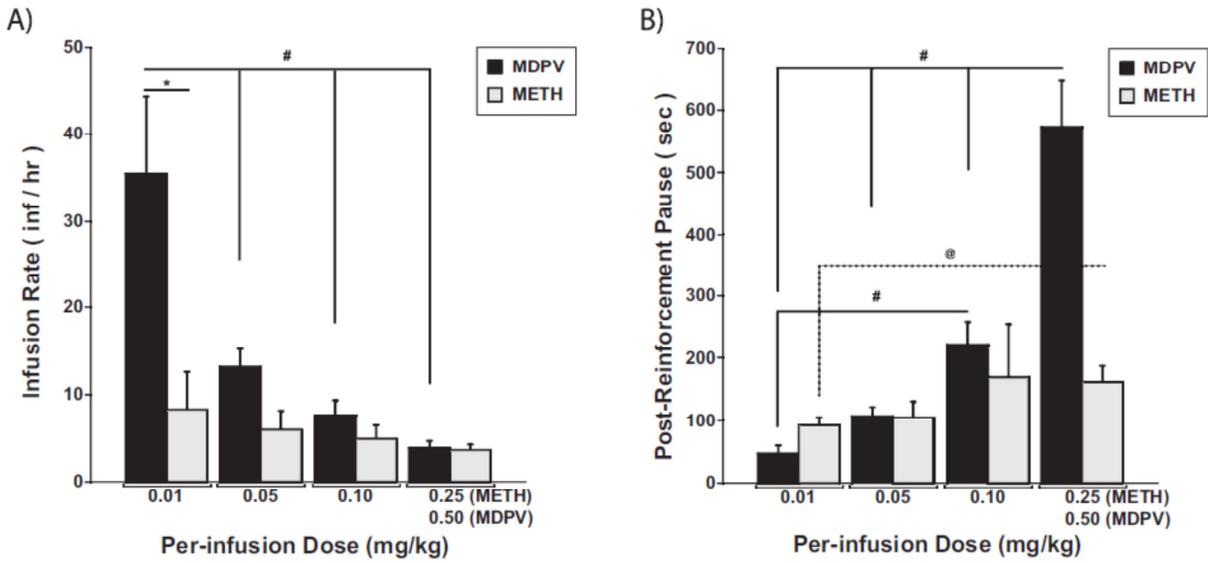
### B1. Animal data

A number of *in vivo* animal studies have investigated the abuse potential of MDPV using models involving self-administration, intracranial self-stimulation, discrimination, substitution and taste-aversion.

In a self-administration study in twenty four male Wistar rats, MDPV was compared to methamphetamine (Aarde, 2013). The rats went through four sequential phases: lever-press training, drug self-administration acquisition (once daily one hour self-administration sessions for ten days, with a drug infusion of 0.05 mg/kg over the one hour session), fixed-ratio dose response testing and progressive-ratio dose-response testing.

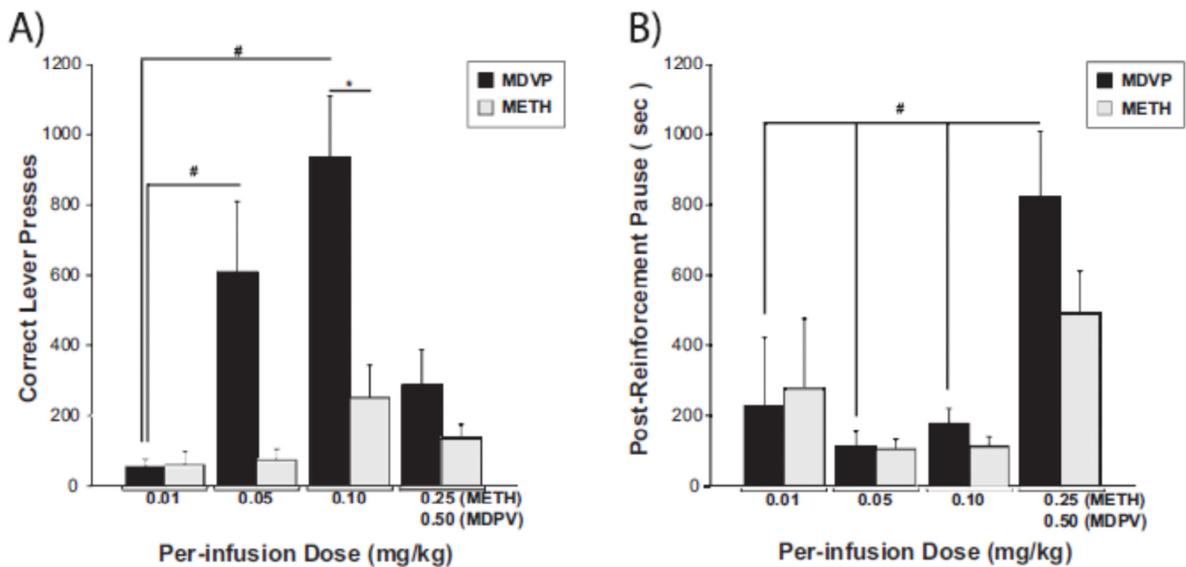
MDPV and methamphetamine were consistently self-administered during the self-administrations phase; during non-food restricted sessions the infusion rate of MDPV was higher than that of methamphetamine but there was no difference in lever discrimination between MDPV and methamphetamine. As shown in Figure 8, in the fixed-ratio schedule there was a dose-dependent effect of dose for MDPV ( $p < 0.001$ ), but only a trend towards dose effect for methamphetamine ( $p = 0.055$ ) for both the infusion rate and the average post-reinforcement pause.

Figure 8: Fixed-ratio, dose-response testing. Mean $\pm$ SEM of infusion rate (infusions/hour; Graph A) and post-reinforcement pause length (average time in seconds between an infusion and the next correct response; Graph B) for MDPV (n=10) and methamphetamine (MEPH, n=10). \*, # and @ indicate significant differences ( $p < 0.05$ ).



As shown in Figure 9, under the progressive-dose ratio schedule, as the per-infusion dose increased both the number of correct lever presses and length of the average post-reinforcement pause increased.

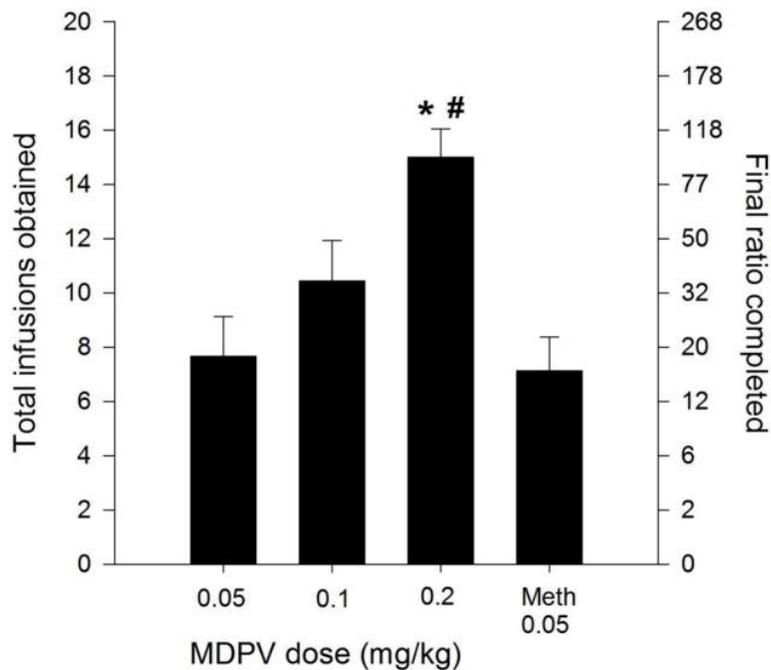
Figure 9: Progressive-ratio, dose-response testing. Mean±SEM of total correct lever presses (1st 3 hours of the session only; includes lever presses during post-reinforcement time out; Graph A) and post-reinforcement pause length (average time in seconds between an infusion and the next correct response; 1st 3 hours of the session only; Graph B). MDPV (n=8) and metamphetamaine (METH, n=8). \* and # indicate significant differences.



Overall, this study suggests significant dependence potential for MDPV that is potentially greater than the dependence potential for methamphetamine.

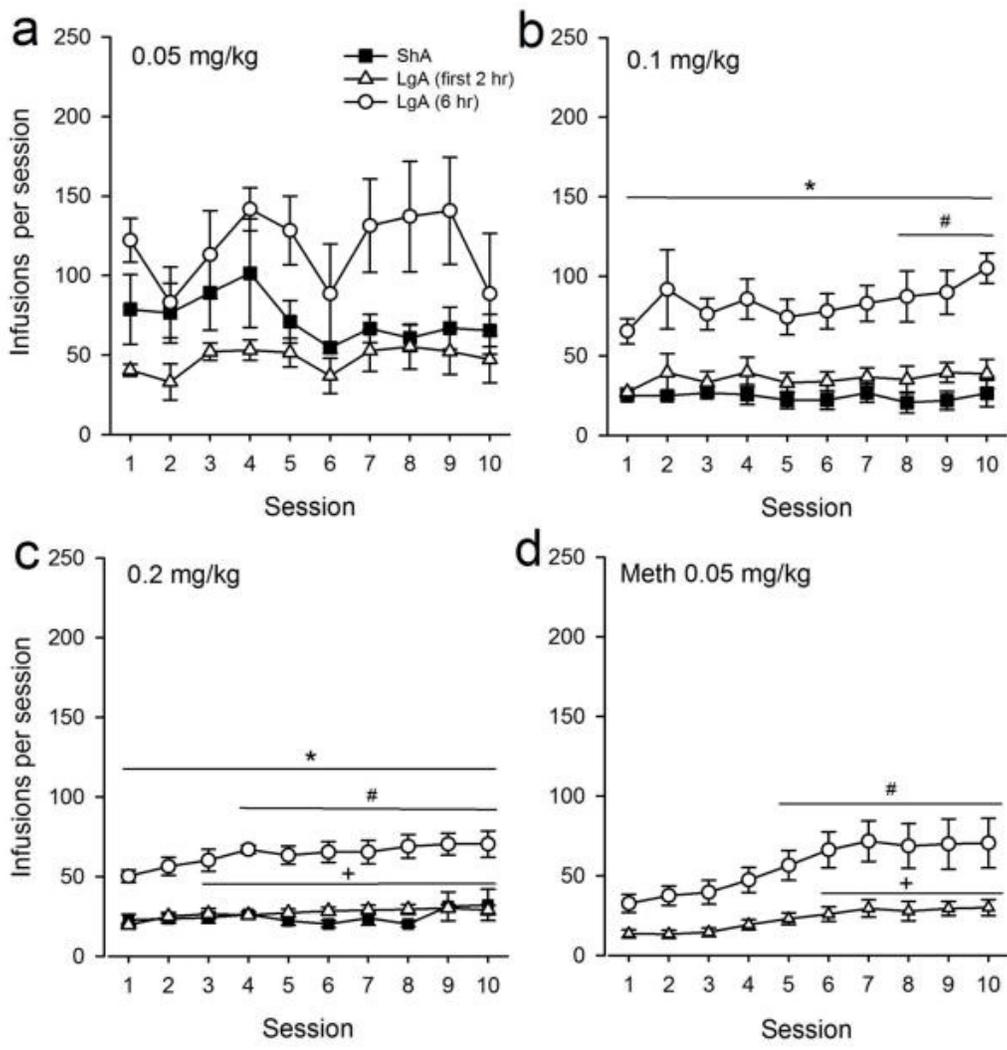
In a study in 48 Sprague-Dawley rats, the abuse potential of MDPV was studied by assessing its ability to support intravenous self-administration and decrease thresholds for intracranial self-stimulation (ICCS) (Watterson, 2012). Rats were trained to intravenously self-administer drugs every day for ten days and were divided into four groups which self-administered two hour infusions of MDPV 0.05, 0.1 or 0.2 mg/kg or methamphetamine 0.05mg/kg as a positive control. The rats were then allowed to self-administer MDPV/methamphetamine using a 16 hour overnight progressive ratio (PR) reinforcement schedule. Each MDPV dose group of rats was then divided into two groups with one group continuing with two hourly daily self-administration for 10 days (short access, ShA) and the other group progressing to six hourly daily self-administration sessions for 10 days (long access, LgA); all of the methamphetamine control rats were assigned to an LgA group. Self-administration of MDPV was maintained at all three doses. As shown in Figure 10, in the PR reinforcement studies, there was a dose dependent MDPV effect with a greater number of infusions in the 0.2mg/kg group than the 0.05mg/kg ( $p<0.001$ ) and 0.1mg/kg ( $p<0.05$ ) groups. There was no significant difference between the methamphetamine control group and the 0.05mg/kg MDPV group ( $p>0.05$ ).

Figure 10: Total number of infusions during PR responding for the 0.05, 0.1, and 0.2 mg/kg/infusion doses of MDPV ( $n = 9$  for each group) and 0.05 mg/kg/infusion methamphetamine ( $n=9$ ). The left y-axis shows the total number of infusions during the PR session and the right y-axis shows the total number of active lever presses completed [ $*p<0.05$  vs. the 0.05 mg/kg dose of MDPV.  $\#p <0.05$  vs. the 0.1 mg/kg dose of MDPV].



As shown in Figure 11, in the SgA and LgA studies there were no significant differences seen in the 0.05mg/kg MDPV group. In the 0.1 mg/kg and 0.2 mg/kg rats, LgA was associated with escalation of drug intake of similar pattern to the methamphetamine group. In summary, the reinforcing and rewarding properties of MDPV were similar to methamphetamine and cocaine with features including escalation under extended access conditions. Escalation of MDPV intake occurred at higher rather than lower doses and the MDPV amounts administered after 10 sessions were higher than for methamphetamine.

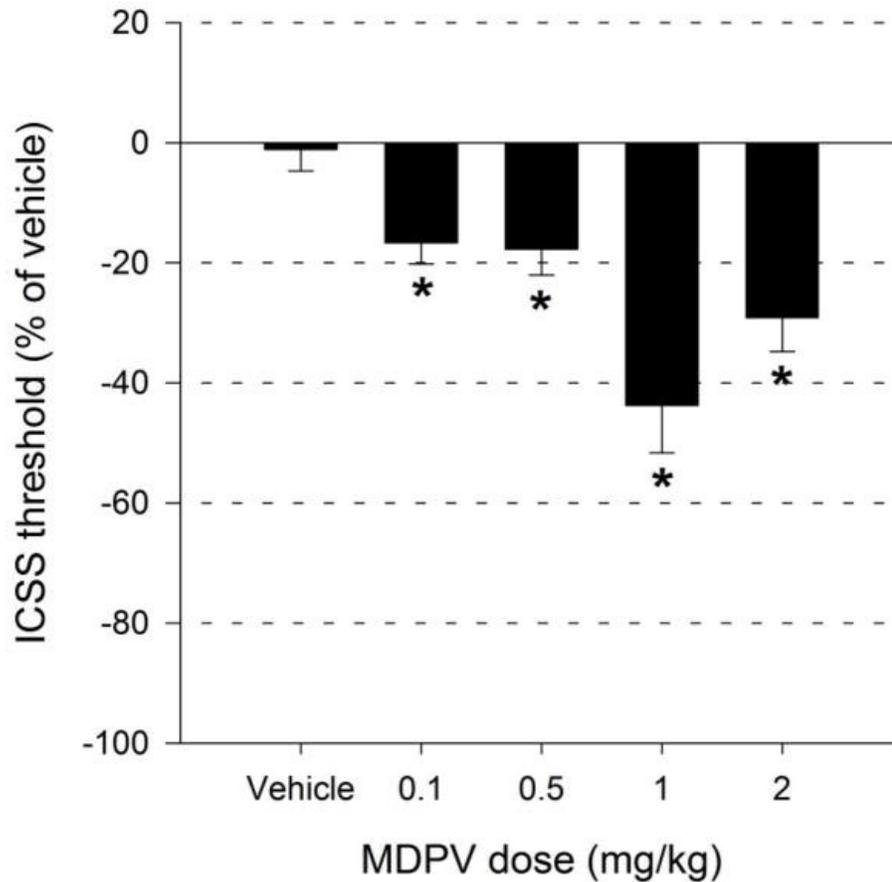
Figure 11: Total number of infusions during ShA, LgA, and the first 2 hours of LgA across the final ten days for (a) 0.05, (b) 0.1, and (c) 0.2 mg/kg/infusion MDPV groups (n = 5 for each LgA group) and (d) 0.05mg/kg methamphetamine (n=9).



In summary, these experiments demonstrated that MDPV has reinforcing and rewarding properties with similarities to methamphetamine and cocaine including escalation under extended access conditions. Escalation of MDPV intake occurred at higher rather than lower doses and MDPV amounts administered after 10 sessions were higher than for methamphetamine. The reward value for MDPV when compared to methamphetamine was similar in this study.

In the second group of experiments in this study, the effects of MDPV on intracranial self-stimulation (ICCS) using a bipolar electrode implanted into the medial forebrain bundle was assessed after administration of 0.1, 0.5, 1.0 and 2.0 mg/kg intra-peritoneal (i.p.) doses of MDPV (Watterson, 2012). As shown in Figure 12, MDPV significantly lowered ICCS thresholds at all of these doses ( $p < 0.05$ ) which suggested hedonic and rewarding effects.

Figure 12: Effects of control vehicle and MDPV (0.1, 0.5, 1 and 2 mg/kg i.p.) on thresholds for ICSS (n = 5). \*p < 0.05 vs. vehicle.



Another study in eighteen male Sprague-Dawley rats looked at intracranial self-stimulation (ICSS) with electrodes in the medial forebrain bundle at the level of the lateral hypothalamus and compared MDPV, methylone, mephedrone and methcathinone (Bonano, 2014). After electrode implantation, the rats were trained in lever press responding until they reliably responded to frequency trials under a fixed regime with the intensity being kept constant. Doses of 0.32– 3.2 mg/kg MDPV were studied and compared to methcathinone (0.1 – 1.0 mg/kg), methylone (1.0 – 10 mg/kg) and mephedrone (1.0 – 10 mg/kg); these drugs were given intra-peritoneally. All drugs tested facilitated ICSS; MDPV, similar to methylone and mephedrone, produced dose-dependent and time-dependent increases in low-rates of ICSS and also produced depression of high ICSS rates maintained by high brain stimulation frequencies. Methcathinone was most potent with significant effects at doses  $\geq 0.1$  mg/kg, this was followed by MDPV (effects at doses  $\geq 0.32$  mg/kg), then methylone and mephedrone ( $\geq 1$  mg/kg). All drugs had a rapid onset of action but MDPV and methylone had longer durations of action; in particular, MDPV maintained significant facilitation of ICSS beyond

300 minutes, with some facilitation still present at 24 hours after drug administration; whereas for mephedrone ICSS peaked at 10 minutes and was no longer significant at 300 minutes.

In a drug discrimination and substitution study in male NIH Swiss Harlan Sprague-Dawley mice, six mice were trained to discriminate MDPV (0.3mg/kg) from saline and interoceptive effect of substitution doses of MDPV, MDMA and methamphetamine (METH) were assessed (Fantegrossi, 2013). All mice reliably discriminated MDPV from saline. Cumulative doses of MDPV, MDMA and METH fully substituted for MDPV. There was no significant difference in the interpolated ED<sub>50</sub> for cumulative MDPV, MDMA or METH (0.03±0.01mg/kg, 0.03±0.01mg/kg, and 0.08±0.03mg/kg respectively). The ED<sub>50</sub> for cumulative MDPV was 0.03 mg/kg; cumulative doses of MDMA (ED<sub>50</sub> 0.03 mg/kg) and methamphetamine (ED<sub>50</sub> 0.08 mg/kg) elicited full substitution. The interoceptive effects of MDPV were both dose- and time- dependent; potency differences were observed when it was administered cumulatively compared to single bolus administration.

Another study used male Sprague-Dawley rats to assess drug discrimination and substitution comparing MDPV with a number of drugs including cocaine and methamphetamine (Gatch, 2013). Rats were trained to discriminate either methamphetamine (1mg/kg) or cocaine (10mg/kg) from saline; all doses were given intra-peritoneally. In the substitution studies a number of drugs were investigated including MDPV (0.05 – 2.5mg/kg). MDPV fully substituted for the discriminative stimulus effects of cocaine and of methamphetamine; the ED<sub>50</sub> for MDPV for cocaine discrimination was 0.68±0.06 and for methamphetamine discrimination was 0.67±0.11 with a potency ratio for cocaine and/or methamphetamine of 1.105. Compared to the other cathinones studied (mephedrone, methylone, naphyrone, flephedrone, butylone), MDPV was the most potent for discrimination in cocaine-trained rats; MDPV was of equal potency to mephedrone, and greater potency to the other cathinones in methamphetamine-trained rats. MDPV was associated with full substitution in both cocaine-trained rats (ED<sub>50</sub> MDPV 0.68 mg/kg; ED<sub>50</sub> cocaine 3.09 mg/kg) and methamphetamine-trained rats (ED<sub>50</sub> MDPV 0.67 mg/kg; ED<sub>50</sub> methamphetamine 0.37 mg/kg).

The final study assessing the dependence abuse potential of MDPV assessed taste aversion in adolescent (postnatal day 32) and adult (postnatal day 84) Sprague-Dawley rats (Merluzzi, 2013). Taste aversion was seen in both adolescent and adult rats at intra-peritoneal doses of MDPV of 1.0, 1.8 and 3.2 mg/kg, however the aversions were weaker and developed more slowly in adolescent than in adult rats. This suggests the potential for a

greater dependence potential in adolescent rats; however further studies are required to confirm the significance of these findings.

## **B2. Human data**

There have been no formal studies investigating the dependence and abuse potential of MDPV in humans.

In a case reported to the EU Early Warning System, a 28-year-old male injected 50 mg of MDPV four or five times a day (length of time not specified) and also used buprenorphine. He developed fatigue and sleep disorder with pain at the injection site. He also became anxious with intellectual stimulation, “an obsession to consume MDPV and psychic withdrawal symptoms”. The patient became withdrawn from others and was absent from work; no further case details were specified.

In a study from Hungary of 15 cases (13 male, 2 female; age 21 – 50 years) of self-reported MDPV use, it is reported that “withdrawal” developed in “>30% cases” (Kalapos, 2011). No further detail is provided on the frequency or duration of MDPV use, or on the nature of the “withdrawal”.

There is a study from Ohio, USA of a newborn child with neonatal withdrawal syndrome (Jolliff, 2013). A 24 year old female who was 34 weeks pregnant and had a history of use of cannabis, opioids and "bath salts" was found unconscious on the street after use of "bath salts". She was transferred to the ED and intubated and stabilised (no further clinical details are available). Fetal heart sounds were absent and so an urgent caesarean section was carried out. Meconium stained fluid was present and the infant had Apgar scores of 2 at 1 minute and 5 at 5 minutes. Opiates and THC were present in the infant's urine and infant blood, urine and cord blood were positive for MDPV (100 ng/mL, 270 ng/mL and 41 ng/mL respectively). The child was admitted to the neonatal intensive care unit and was noted to be jittery, vigorous and hypertonic. The infant became more agitated and developed tremor and myoclonic jerks. The child was started on IV morphine to control the withdrawal symptoms. Morphine was weaned on day 13, there was no rebound withdrawal and the infant was discharged on day 24. It is not possible to determine from this report whether the features seen were due to opioid or MDPV withdrawal, or a combination of both of these drugs.

There is a user-report on Erowid.com from 2011 of *potential* MDPV dependence (Erowid Dependence). A 39- year-old male who used MDPV daily for nine months described MDPV as “...extremely habit forming. When I would stop, I did have what I felt were mild

withdrawals...muscle aches all over but not debilitating. More like if I had been at the gym the previous day. I also felt depressed for about two weeks. It took about 3 months for my head to get back together though. Lingering paranoia and depression stayed with me for about 45 days, and the feeling of being scatterbrained only cleared after 90 days. I still get heart palpitations every so often, but I feel much better about my heart now that I no longer use 'PV.'"

## SECTION C. PREVALENCE OF USE

MDPV was first detected in Europe in 2008 with formal notification to the EMCDDA in December 2008 by the Finnish National Focal Point. There are reports to the EMCDDA of detections <sup>(2)</sup> of MDPV from in 27 Member States, Norway and Turkey which are summarised in Table 5.

**Table 5.** Reports to the EMCDDA of detections <sup>(3)</sup> of MDPV from in 27 Member States, Norway and Turkey.

Country	Amount and Details of the MDPV Seizure
Austria	2009: First half of year, first identification in Austria seizure by police. Weight not specified 2012: Four samples of powder from Checkit!, collected from a venue. Weight not specified 2013: Five samples of powder from Checkit!, collected from a venue. Weight not specified. "Some of which" contained caffeine and amphetamine. 13 police seizures. Weight and form not specified
Belgium	2010: Police seizure of 40g powder 2011: Four police seizures in total 110g beige/white powder 2012: Two customs seizures in total 100g powder 2013: Nine customs seizures in total 5850g powder
Bulgaria	2010: One police seizure of 16247g white powder 2011: Two police seizures in total 224.69g powder (range 68.69g – 156g some of which also contained mephedrone, methylone and lidocaine) 2012: One customs seizure of 22g (form not specified, also contained caffeine and benzocaine) One police seizure of 15.99g powder (form not specified, also contained caffeine)
Croatia	2010: One police seizure of 1.69g (form not specified, also contained JWH-018)

<sup>2</sup>The term 'detection' from an EMCDDA perspective refers to seizures, collected samples and/or biological samples.

<sup>3</sup>The term 'detection' from an EMCDDA perspective refers to seizures, collected samples and/or biological samples.

	<p>2011: Four police seizures in total 5.38g powder (range 0.04g – 4.65g)</p> <p>No dates given: Six police seizures in total 4.19g powder (range 0.51g – 3.31g some of which was light yellow), 1.03g tablets and 3.31g other form</p>
Cyprus	<p>2012: One police seizure of 1g white powder</p> <p>2013: Three police seizures in total 3.5g white powder</p>
Czech Republic	<p>2010: Two custom seizures in total 9120g powder</p> <p>2011: One custom seizures of 505g powder</p> <p>Eight police seizures in total 215.46g powder (some of which also contained MDPBP, 4-MEC, lidocaine, bk-MDMA, ethylphenidate, 2-DPMP)</p> <p>2012: Two police seizures in total 7.746 powder (some of which also contained “sacharosa”)</p>
Denmark	<p>2010: One police seizure in total 3.5g beige powder and 1.7g milky solution/suspension marked ‘DMPV 100mg/ml’</p> <p>2011: Three customs seizures in total 104.9g white powder</p> <p>One police seizure of 0.26g beige powder</p> <p>2012: One police seizure of 1.7g white powder (also contained 2C-C)</p> <p>2013: Three customs seizures, two of 62.5g white powder (some of which also contained pentedrone, MDPBP and caffeine) and one of 49.8g beige powder</p> <p>One police seizure of 0.25g light beige powder</p>
Estonia	<p>2013: One customs seizure of 1.68g white powder (also contained PVP and pentedrone)</p>
Finland	<p>2008: Three customs seizures in total 12g powder (range 1 – 10g)</p> <p>2009: 17 customs seizures in total 24.9g powder (range 0.2 – 10g) and one seizure of one unit, form other</p> <p>Police seizure of 246 powder samples total weight 3967g (no range given) and biological (blood) samples from 80 driving under the influence of drugs(DUID) cases</p> <p>2010: 74 custom seizures in total 6364.1g powder (range 0.1 - 2005g); one custom seizure of 0.1mL liquid and three custom seizures in other form in total 13 units (range 1-11 units)</p> <p>Police seizures (i) 278 powder samples total weight 2802g; (ii)</p>

	<p>one sample of one tablet; (iii) four samples of liquid total volume 9.7mL; (iv) 21 trace samples and biological (blood) samples from 219 DUID cases</p> <p>2011: 102 custom seizures in total 476.5g powder (range 0.2 – 51.5g); seven custom seizures in total 40 tablets (range 2 – 10); one custom seizure of 10 capsules containing powder and one custom seizure of one blotter</p> <p>Police seizures (i) 117 powder samples total weight 1511g; (ii) 19 liquid samples total volume 19ml; (iii) 8 trace samples and biological (blood) samples from 111 DUID cases</p> <p>2012: 188 custom seizures in total 4768.5g powder (range 0.1 – 1001.5g); two custom seizures in total 56 capsules containing powder (range 5 – 51) and one custom seizure other form 1 unit</p> <p>Police seizures (i) 106 powder samples total weight 350g; (ii) 10 liquid samples total volume 25mL; (iii) 18 trace samples and biological (blood) samples from 84 DUID cases</p> <p>2013: 89 custom seizures in total 785.7g (range 0.1 – 199.1g) and two custom seizures in total 200 capsules containing powder (each 100 capsules)</p> <p>Police seizures: 16 powder samples total weight 76.5g and biological (blood) samples from 24 DUID cases.</p>
France	<p>2012: One police seizure of powder which also contained 4-MEC; three seizures of capsules containing powder and one seizure of liquid which also contained 4-MEC.</p> <p>2013: Nine custom seizures in total 2237g of white powder; one police seizure of powder which also contained 4-MEC and three seizures of white powder from venues</p> <p>No date given: One seizure from a venue of powder which also contained alpha-PVP and pentedrone</p>
Germany	<p>09/2011 – 03/2013:</p> <p>Police seizures: 21 packages each of 1g and 20 capsules each of 0.5g</p> <p>2011: 27 police seizures (i) 101.8g powder (also contained ketamine), (ii) 29.56g powder and (iii) remainder (form and weight not given) which also contained lidocaine, butylone, flephedrone,</p>

	<p>4-MEC, MDPBP, caffeine and ketamine</p> <p>2012: Six police seizures in total 106.32g powder (range 0.02g – 66.3g and no weight for five seizures which also contained 2C-E, caffeine, MXE, AM-2201, 4-fluoramphetamine and nicotine); six seizures of unspecified form, total weight 177.66 (range 5.75g – 68.5g); one seizure of four packages each weighing 1g; one of 20 capsules containing powder each weighing 0.5g; one of two pills printed with ‘Yellow Submarine’ and 18 seizures (form not specified) which also contained sildenafil, lidocaine, caffeine, benzocaine, TFMPP, 2C-E, 4-fluoramphetamine, flephedrone and taurine</p> <p>2013: Three police seizures in total 361g light brown and cream powders (range 22.7g – 258g); five seizures of unspecified form total weight 1182.57g (range 0.17g – 1000g which also contained pentedrone and caffeine) and six seizures of unspecified form and weight which also contained TFMPP, lidocaine, caffeine, flephedrone and pentedrone</p> <p>Date not specified: 13 police seizures in total 4202.81 powder (range 0.94g – 2568g) some of which also contained caffeine; two seizures of 102g (24g and 78g each) of green tablets which also contained caffeine and 81 packages (61 and 20) which also contained caffeine and lidocaine</p>
Greece	<p>2011: police seizure of white powder. 169,8 grams of the substance was packed in 2 plastic bags and 16,8 grams in 67 packages labelled: ‘Decorated sand for ornamental plants’. Each package contained 0.25 gr of MDPV and it costed €12.</p>
Hungary	<p>2009: Six police seizures in total 551 tablets (in one 300 yellow tablets with heart imprint 8.1mm diameter)</p> <p>2010: 25 police seizures in total 133g powder and 20 seizures in total 645 tablets</p> <p>2011: 10 customs seizures in total 15153.5g of powder (range 207.4g – 3729.4g)</p> <p>266 police seizures in total 9579g powder and 104 seizures in total 5509 tablets</p> <p>2012: Four customs seizures in total 553.9g of powder (range 1.8g – 515g); two seizures of powder on herb in total 156g (21.6g</p>

	<p>and 134.4g each) and one seizure in total 483.9g of tablets</p> <p>66 police seizures in total 5730g of powder and nine seizures in total 8522 tablets</p> <p>2013: 7 police seizures in total 24g of powder and four seizures in total 26 tablets</p>
Ireland	<p>2010: Seven police seizures in total 4390.2g powder</p> <p>2010 – 2012: 242 small police seizures</p> <p>2013: One police seizure not weighed</p>
Italy	<p>2010: University laboratory analysis of 0.5g 'Ivory Wave' obtained from Internet</p> <p>2012: Two police seizures of powder (0.012g white powder also contained 3-fluoromethcathinone, weight of other not specified) and one seizure of two capsules containing powder called 'Yellow Submarine'</p> <p>2013: Five police seizures in total 13547.15g powder (range 30.145g – 5446g)</p> <p>Jan 2014: Three police seizures in total in 25547.65g powder (range 1.85 – 25045g)</p>
Latvia	<p>2010: Three customs seizures in total 2002.0259g powder (range 2.0259g – 1000g)</p> <p>Two police seizures in total 120.525g powder (range 4.935g – 115.59g)</p> <p>2011: Two customs seizures in total 117.081g powder (74.164g and 42.917g each)</p> <p>20 police seizures of total in 647.9839g powder (range 0.0443g – 426.4825g, one batch also contained 3FMC) and one seizure of liquid weighing 0.0851g</p> <p>2012: 22 police seizures in total 1873.679g powder (range 0.0843g – 1715g; other constituents were methamphetamine, 4-MEC, mephedrone and methylone)</p> <p>2013: 10 police seizures in total 65.0734g powder (range 0.1654g – 55.4008g)</p>
Lithuania	<p>2010: One customs seizure of 2.7g white powder</p> <p>2012: One customs seizure of 1.29992g powder and one seizure of two reddish tablets</p> <p>13 police seizures in total 13.81g of unspecified form</p>

	<p>2013: Two customs seizures in total 3.916g powder (0.937g and 2.979g each) and one seizure of 5.545g of tablets</p> <p>Five police seizures in total 5.5g unspecified form</p>
Malta	<p>2011: police seizure of 30 packets of white powder amounting to 15 grams. The packets were found in a parcel sent from Prague, Czech Republic</p>
Netherlands	<p>2012: Two tablets, two powders and one capsule sold to consumers analysed by Drugs Information and Monitoring System (DIMS)</p> <p>2013: Seven powders sold to consumers analysed by Drugs Information and Monitoring System (DIMS)</p>
Poland	<p>2010: 16 police seizures in total 26.56g of white, cream and beige powders (range 0.07g – 8.41g, some batches also contained metylone, butylone, pentedrone, lidocaine, buphedrone, acetaminophen, MPBP, pFPP, pMeOPP, 4-FMC, 4-MEC, methedrone); 33 capsules (weight 0.3-0.38g each, also contained methylone, MDPBP, MPPP, lidocaine, procaine, butylone) and two pink tablets (weight 0.72g each)</p> <p>Seven sanitary inspector seizures from shops in total 33.02g powder (range 0.09g – 6g, which also contained 4-MEC, MPBP, MPPP, methedrone, pentedrone, metylone, butylone, caffeine, lidocaine, buphedrone, pFPP, MBZP, BZP, DBZP); 35 pink and 16 grey tablets (weight approx. 0.7g which also contained butylone and lidocaine); two white capsules (weight of powder 0.33g which also contained pFPP) and four red capsules (weight of powder 0.45g which also contained MBZP, BZP, DBZP and caffeine) and 4.8g of plant material</p> <p>Two prosecutor seizures in total 4.96g white powder (range 0.96g – 4g which also contained lidocaine, caffeine and butylone) and one seizure of five white-red capsules (weight of powder 0.36g – 2.10g which also contained MPPP, lidocaine, procaine, dimethocaine, methylone and D2PM) and 10 white-orange capsules (weight of powder 0.4g)</p> <p>2011: Customs seizures of 119 packets of powder (weight not given which also contained 2-DPMP, lidocaine, methylone, 4-MEC, 3-FMC, penthedrone, isopenthedrone, pMeOPP, butylone,</p>

	<p>buphedrone)</p> <p>23 police seizures in total 402.892g white and beige powders (range 0.02g – 118.74g which also contained caffeine, lidocaine, 4-MEC, MPPP, MDPBP, BMDP, pentylone, pFPP, TFMPP, creatine, 2-AI, methedrone, buphedrone, pMeOPP, benzocaine, mephedrone, AEPEA, pentedrone, 3,4-DMMC, methylone, cocaine, JWH-210, JWH-018, methedrone, 2C-P, MXE, 2C-E, 2-DPMP and naphyrone); one yellow-black capsule (weight of cream powder 0.27g), three yellow-green capsules (weight of powder 0.25g), three transparent capsules (weight of powder 0.4g which also contained mephedrone), one capsule (weight of powder 0.33g which also contained mephedrone); 98 pink tablets (weight range 0.71g – 0.75g, some of which also contained lidocaine)</p> <p>Four seizures by regional prosecutor in total 32.45g beige and white powders (range 0.06g – 1.39g some of which also contained 4-FA, bupherone); 15 white-orange capsules, 16 with gray-blue powder (weight of powder in one capsule 0.35g), 24 capsules with beige powder (weight of powder 0.27g – 0.33g), 22 capsules with white powder (weight in one capsule 0.33g) (the capsules also contained mephedrone, butylone, naphyrone, methedrone and metylone)</p> <p>One sanitary inspector seizure from a shop of 0.09g white powder</p> <p>2012: Eight police seizures in total 156.71g white and beige powders (range 0.12g – 38.04g some of which also contained 2C-E, 2-DPMP, EP, piracetam, caffeine, lidocaine, 4-MEC, creatine and amphetamine); one transparent capsule weighing 0.4g and four blotter papers with Bugs Bunny symbols (which also contained 2-DPMP, ethylphenidate and piracetam)</p> <p>One seizure by regional prosecutor of white powder weight 1.38g</p> <p>2013: 72 police seizures in total 244.66g white, cream and bright yellow powders (range indeterminable, some of which also contained 2-DPMP, EP, MXE, methylphenidate, lidocaine and methylone)</p> <p>Two law enforcement seizures in total 556.06g white or beige powder (range 1g – 498.17g some of which also contained BZP,</p>
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	<p>TFMPP, naphyrone, caffeine, buphedrone and 4-MEC)</p> <p>One regional prosecutor seizure of 3g white powder (which also contained butylone and lidocaine)</p> <p>Two samples from shop of 1.05g cream powder (range 0.19g – 0.86g)</p> <p>October 2010-November 2012 sanitary inspection seizure of 887 products (powder, tablets and capsules which also contained lidocaine, methylone, 4-MEC, fluoroamphetamine, caffeine, methedron, MDPBP, butylone, pFPP, methedrone, BMDP, buphedrone, TFMPP, naphyrone, 2-CE, pentedrone, 5-HTP, creatine, RCS-4, FMC, JWH-122 and JWH-081)</p>
Portugal	<p>2011: 15 police seizures in total 556.558g powder (range 0.376g – 231g, four batches also contained 4-MEC, four mephedrone, two flephdrone with caffeine and one methylone with 4-MEC); four seizures of 107 capsules containing powder (range 8 – 50) and one seizure of 214 tablets (which also contained 4-MEC)</p> <p>2012: 18 police seizures in total 2161.726g powder (range 0.42g – 1025g, five batches also contained lidocaine, two methylone, one benzocaine, one 4-MEC and one 4-MEC with butylone) and one seizure of five tablets</p> <p>2013: 34 police seizures in total 5711.981g powder (range 0.146g -1715.335g, eight batches also contained lidocaine, two butylone with methylone, two butylone with methylone with MDPBP, one methylone, one caffeine, one flephedrone, one N-ethylcathinone with 4-MEC with 3,4 DMMC with caffeine and one AKB48 with JWH-122 with JWH-220 with JWH-250)</p>
Romania	<p>No date reported: Two police seizures in total 25.79g powder (25.41g and 0.38g each, the latter also contained heroin) and 15 tablets</p>
Slovakia	<p>2012: Two customs seizures in total 0.496g white powder (0.218g and 0.278g each, the latter also contained 2-DPMP and buphedrone)</p> <p>22 police seizures in total 107.255g of white, light brown, light green, cream and brown powder (range 0.223g – 53.315g). Most also contained 2-DPMP, buphedrone, MABP, bk-MDMA and ethcathinone</p>

Slovenia	<p>2010: Police seizure of 0.68g of white powder (also contained butylone)</p> <p>2011: Customs seizure of 1.1g of white powder (also contained 4-MEC)</p> <p>2012: Police seizure of 6.68g of white powder</p>
Spain	<p>2011: 34 unspecified seizures in total 3129.15g powder</p> <p>2012: 79 police seizures in total 637g powder; two seizures in total 30 tablets and one seizure of 11 tablets</p> <p>2013: 76 unspecified seizures in total 2080g powder (In each year other substances were found with MDPV but no information was provided)</p>
Sweden	<p>2010: Police seizure in total 3597g powder and 178mL of liquid Customs seizure of 4382g of powder</p> <p>2011: Police seizure in total 811.81g powder; 140 tablets and 49mL of liquid Customs seizure of 1243g of powder and 26 tablets</p> <p>2012: Police seizure in total 2296.36g powder and 528mL of liquid Customs seizure of 1581g of powder and 14 tablets</p> <p>2013: 42 police seizures in total 1899.02g powder (range 0.01g – 984.33g); three seizures in total 24.5 tablets (range 1-21.5); two of 38mL liquid (19mL each); and two other forms (2.52g dried crushed plant material and 0.71g partially combusted material) Six customs seizures in total 3120.25g of powder (range 10g-1000g and two batches also contained methylone)</p>
Turkey	<p>2010: One police seizure of 1.4g of grey powder</p>
UK	<p>2008: TICTAC laboratory analysis 33g of obtained from Internet</p> <p>2009: Three police seizures in total 2.111g powder (range 0.261g – 1.3g, some of which also contained MDMA and ketamine) and 44 law enforcement seizures in total 10.4681kg powder (range indeterminable)</p> <p>2010: One police seizure of 0.55g powder (which also contained TFMPP) and one seizure of 3 tablets 49law enforcement seizures in total 10.8878kg powder(range indeterminable)</p> <p>2011: 107 police seizures in total 16958.389g powder (range indeterminable), some batches also contained 1-Naphyrone, 4-</p>

	<p>MMC, bk-MDMA, BMDDB, 3-FMC, 4-FMC, 4-MMC, bk-MBDB, cocaine, D2PM, MDPBP, PMMA methylethcathinone, TFMPP, MBZP); nine seizures of 54 tablets (five of which weighed 9.75g) and six seizures of unspecified number of tablets weighing 12.75g (some of which contained methylmethcathinone and TFMPP)</p> <p>301law enforcement seizures in total 6260.71g powder (range indeterminable and some batches also contained 4-FMC, TFMPP and paracetamol); 18 seizures of 1271 tablets, 29 seizures of tablets weighing total of 5258.5g and three seizures of four capsules containing powder which also contained unspecified substances.</p> <p>2012: One police seizures of 5g off-white powder which also contained NEB, Alpha-PVP; one seizure of 1 capsule; one seizure of capsules weighing 4062g and one seizure of 4062g of unspecified form</p> <p>172 law enforcement seizures in total 15232.791g powder (range indeterminable) and six seizures of 90 tablets</p> <p>2013: Six police seizures in total 108.05g of powder (range indeterminable and some of which also contained methylone and other unspecified substances); one seizure of 19 tablets; one seizure of 686 tablets which weighed 260.66g; one seizure of unspecified number of capsules weighing 1g which also contained PVP and one seizure of vegetable matter unspecified weight</p> <p>1526<sup>#</sup> law enforcement seizures intotal 5422.023g<sup>##</sup> powder (range indeterminable and some of which contained methylone, MEC and MMC);92 seizures of unspecified form total weight 8803.5g and two seizures of an unspecified quantity of liquid</p> <p style="text-align: right;"># 743 cases may have been double counted ## 675.41g may have been double counted</p>
Norway	<p>2011: One seizure of 0.72g white powder also containing methoxetamine.</p> <p>2008: One police seizure of 1.184g of light brown powder</p> <p>2010: Two police seizures in total 5.366g of beige and white powders (range 0.084g – 5.282g, one also contained bk-MBDB)</p> <p>2011: 23 police seizures in total 920.694g of white, yellowish</p>

	<p>white, yellow and beige powders (range 0.19g – 487.3g, two batches also contained methamphetamine)</p> <p>2012: 18 police seizures in total 2624.175g of white and yellowish white powders (range 0.03g – 2481g, one batch also contained buphedrone, one methamphetamine and one methiopropamine with 4-MEC), one seizure of two tablets and one of 0.15g of powder and 3 capsules</p> <p>2013: Six police seizures in total 26.1g white and beige powders (range 0.22g – 11.45g) and one seizure of 98 purple tablets with spaceship/rocket logo</p>
Turkey	2010: seizure of 1.4g of grey powder

In a study in the United Kingdom, the content of ‘legal highs’ purchased from the Internet products were analysed for six months prior to the control of piperazines in December 2009 and for one month afterwards (Dargan, 2010). MDPV was found in four of the five products purchased December 2009; MDPV was not detected in any of the products purchased prior to December 2009.

Analysis of 17 products purchased from 12 Internet sites in 2010 in the United Kingdom found MDPV in four products that were labelled as NRG-1 (Brandt, 2010a); another study by the same group detected MDPV in four of 24 products purchased from Internet sites in the United Kingdom in 2010 (Brandt, 2010b). In a follow up to this study in 2011, MDPV was detected in one of two products that were bought from Internet sites in the UK and were supplied labelled as NRG-1 (Brandt 2011).

In a survey of Internet sites supplying psychoactive substances in Australia, 43 sites were identified over the 12 months from July 2011 and July 2012. A total of 212 chemically unspecified branded products (e.g. ‘White Lady’, ‘NRG-2’) were available and 86 chemically specified products; of these MDPV was one of the most commonly available compounds, along with 5,6-methylenedioxy-2-aminoindane, 5-iodo-2-aminoindane, methiopropamine, 5-methoxy-N,N-diallyltryptamine and 4-fluoromethcathinone. The number of sites selling each of the products was not specified (Bruno, 2013).

In the EMCDDA ‘snapshot’ survey of Internet sites selling new psychoactive substances conducted in January and June 2011, MDPV was available from 25 (8.0%) of the 314 online

shops identified to be selling new psychoactive substances in January 2011 and from 32 (5.1%) of the 631 online shops identified in July 2011 (EMCDDA, 2011). In the January 2012 snapshot, MDPV was available from 44 (6.3%) of the 693 online shops identified (EMCDDA, 2010).

Prior to the anonymous international online marketplace 'Silk Road' being closed down, MDPV was available from a number of retailers on the Silk Road (Sydney NDARC, 2013). In late October 2012 it was available from nine retailers and from ten in November and December 2012. In January 2013, nine sites were selling it and in February 2013, seven sites.

The price of MDPV reported to the EMCDDA varies across Europe, some examples of reported prices are: France 2-15€ per gram, Netherlands €160 for 5g or €35 for one gram and Spain 20€ per gram.

#### Published data

The annual "MixMag" Surveys reported on MDPV use in the 2009/10 and 2010/11 survey. In 2010/11, 4.4% respondents reported that they had ever used MDPV and 3% reported that they had used MDPV in the last year; the total number of respondents was not specified (MixMag, 2011). In the 2009/10 survey, 59% of respondents said they had ever used a 'legal high' of which 2% was reported to be MDPV; again the total number of respondents was not specified (MixMag, 2010). MDPV use was not reported in either the 2012 and 2013 MixMag / Global Drugs Surveys, although 12% of the 22,000 responders in 2013 said they had used drugs promoted as 'bath salts', 'legal highs' or 'research chemicals' in the previous 12 months and there is the potential that some of these products may have contained MDPV (MixMag, 2013).

In a self-report survey amongst University students in South Eastern USA in the first three months of 2012, 25 (1.07%) of 2349 respondents reported ever using "bath salts or MDPV" (Stogner, 2013). The most commonly used drugs were alcohol, marijuana and tobacco (87.8%, 58.1% and 55.7% of respondents respectively) whilst 12.8% had used hallucinogens and 12.5% 'Ecstasy' or club drugs.

Whilst there have been no co-ordinated national or European population surveys on MDPV use, a number of studies have been published concerning MDPV prevalence in various targeted groups in Europe which are usually based on biological sampling.

Urine samples from opioid-dependent patients receiving opioid substitution treatment at an out-patient clinic in Finland were analysed for the presence of MDPV (Ojanpera, 2011). 34 urine samples were collected between June 2009 and February 2010 and nine were found to be positive for MDPV; the authors suggested the opioid-dependent patients were using MDPV as a substitute for amphetamine.

MDPV has been found in the biological fluids of persons driving under the influence of drugs which is further explored in Section D3.4, 'Nature and extent of health consequence (e.g. acute emergencies, road traffic accidents)'. In a Finnish study, blood samples from drivers arrested for driving under the influence of drugs (DUID) were analysed for the presence of MDPV between the end of August 2009 and the end of August 2010 (Kriikku, 2011a). 259 samples (8.6%) were positive for MDPV which represented approximately 5.7% of all confirmed 4570 DUID cases (excluding the alcohol-only cases). 80% of the MDPV positive samples were also positive for amphetamine and 67% for benzodiazepines; 60 cases (23%) showed no other substance (or the concentrations of other substance found were "not expected to cause the behaviour leading to the arrest"). The concentrations of MDPV varied from 0.016 mg/L to 8.0 mg/L.

In another report from the same group in Finland, data was presented on drivers arrested for DUID in 2010 (it is likely that some individuals were included in both this paper and the paper described above as there is overlap between the study periods) (Kriikku, 2011b). A total of 4532 samples were analysed and 219 (4.8%) were found to contain MDPV at a median concentration of 0.06 mg/L (maximum concentration 8.4 mg/L). Of the MDPV positive cases, 89% were male and 96% were from Southern Finland. MDPV was commonly found together with amphetamine (79%) and benzodiazepines (76%); and a combination of MDPV, amphetamine and benzodiazepines was found in 63% of the MDPV positive cases.

A study in Denmark also analysed blood samples from drivers arrested for DUID (Pedersen, 2013). In 2011, blood samples from 1791 DUID cases were analysed; in 1335 cases the police requested a full screen for traffic-relevant drugs and in 456 cases only THC screening was requested. Amphetamine and cocaine were most frequently detected in the 1335 cases (in 383 (28.3%) and 335 (25.1%) samples respectively) and MDPV was detected in 3 samples (0.2% of those tested).

In 1335 urine samples collected from addiction treatment clinics for a one year period in Sweden and analysed for "Internet" drugs, MDPV was detected in 21 (24.1%) of 87 samples

found to be positive for these drugs (Al-Saffar, 2013). The most commonly detected substance was *o*-desmethyldramadol, found in 43 (49.4%) of the 87 samples.

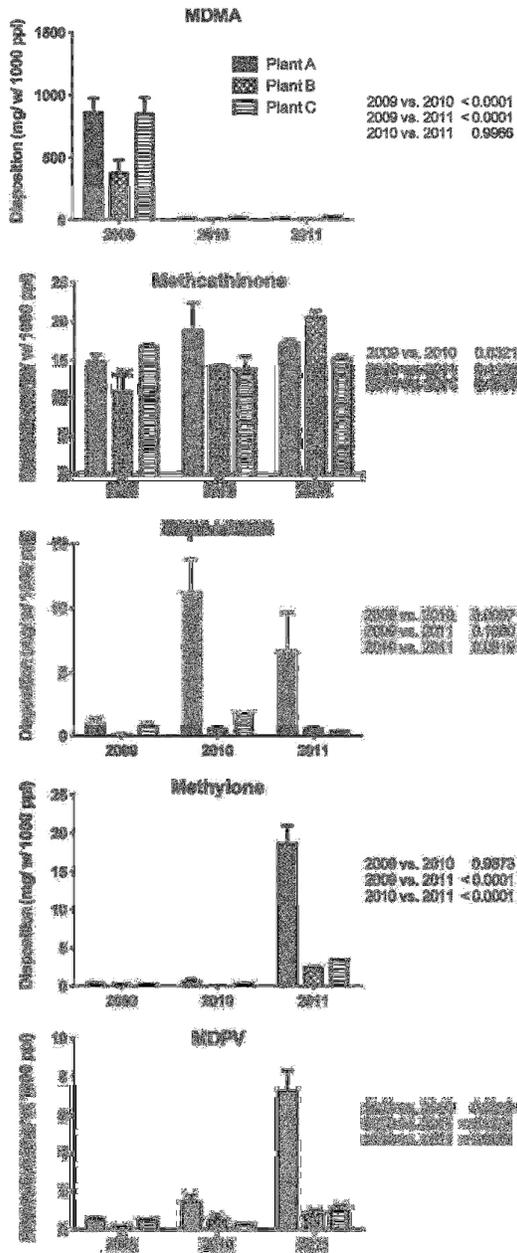
In a survey conducted at the largest needle exchange programme in Hungary, data on the substances used by injecting drug users (IDUs) was collected for one month between September and October 2011 (Csak, 2013). 183 clients, out of 461 who visited the needle exchange programme during the study period (39.7% response rate), agreed to answer a short questionnaire to identify the drug they had injected in the past 30 days (and if more than one was used, to list them by frequency of use); the age at which they started injecting regularly and the first substance they injected regularly. The characteristics of the respondents were compared to those of the 2572 people who registered in the needle exchange programme in 2011. 48.1% of the 183 responders stated that MDPV was their current primary injected substance and 45.9% stated amphetamine was their current primary injected substance. Over 40% of former amphetamine and opiate users had switched to MDPV, as had 78.6% of those previously using other drugs such as cocaine and mephedrone.

Drug samples submitted by users to Energy Control, a non-governmental organisation working among recreational drug users in risk and harm reduction in Spain, were analysed for the presence of cathinone derivatives (Caudevilla-Galligo, 2013). From the beginning of January 2010 until the end of June 2012, 6199 samples were analysed. 237 (3.8%) were believed to contain cathinone derivatives and were detected in 228 (96.2%) of these. 128 samples contained one psychoactive compound and 18 contained two or more. MDPV was detected in one of 51 cathinone derivative positive samples in 2010, 15 of 133 in 2011 and in none of the samples in the first six months of 2012 (total of 6.8% over the study period); methylone and mephedrone were the most frequently detected (24.9% and 24.5% respectively).

Analysis of MDPV and six other synthetic stimulants in wastewater from three independent wastewater treatment plants in Adelaide, Australia showed a marked change in detection over a three year period (wastewater samples were collected for six to eight weeks over May to July 2009 to 2011) (Chen, 2013). As shown in Figure 13, MDPV dispositions were low in 2009, rose slightly in 2010 and significantly increased in 2011 as did methylone disposition. MDMA dropped significantly in 2010 and remained low in 2011, and methcathinone remained similar throughout the study. Compared with disposition patterns of MDMA and methylone, which peaked at weekends, MDPV levels were relatively constant throughout the week. Although it is likely that this represents a different pattern of use it is not possible to be

certain that this is the explanation as there is limited pharmacokinetic data on MDPV in humans.

Figure 13. Weekly drug disposition (mg/week/1000 people) in each year and WWTP served area. Two-way analysis of variance with Tukey’s multiple comparisons. p values of multiple comparisons are displayed to the left of each figure.



In a report from the USA, over 3000 products seized in 1320 law enforcement cases in Arkansas were analysed for the presence of “new designer drugs” (Seely, 2013). Over the

three year period from January 2010 to December 2012 over 80% of the tablets, capsules and blotter papers tested were found to contain MDPV and caffeine; the main components of the powders were methylone, MDPV and pentedrone (breakdown of individual agents not provided).

## SECTION D. HEALTH RISKS

### D1. Acute health effects

#### D1.1. Animal Data

A number of animal models have investigated the potential for acute toxicity associated with MDPV – the effects studied include psychomotor and locomotor stimulant effects, thermoregulation and cardiovascular effects.

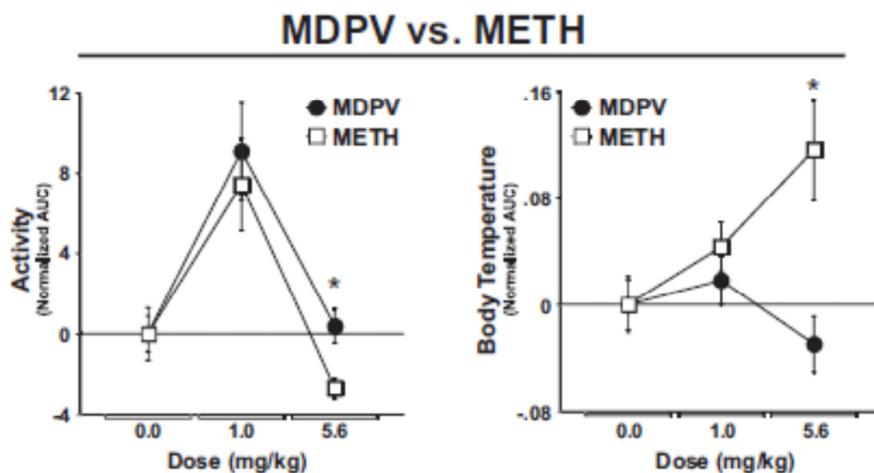
The original United Kingdom patent (Boehringer Ingelheim, 1969) gives a subcutaneous LD<sub>50</sub> value for MDPV of 175 mg/kg in the mouse while the estimated “dose required for stimulation of the central nervous system” was stated to be 0.2 mg/kg in the same animal model. For comparison, the LD<sub>50</sub> value and the stimulatory dose for ‘Benzedrine’ were 80 and 1.95 mg/kg, respectively, while for pyrovalerone the respective LD<sub>50</sub> and stimulatory dose values were 370 and 1.6 mg/kg in the mouse (Boehringer Ingelheim, 1969; Köppe H, 1969a, Köppe, 1969b).

In a study in eight male Wistar rats, the locomotor effects of MDPV were compared with *D*-methamphetamine (METH), 3,4-methylenedioxymethamphetamine (MDMA) and mephedrone using voluntary wheel running (Huang, 2012). The drugs were administered subcutaneously. MDMA and mephedrone both showed lower total wheel activity than saline control and this decreased with increasing drug doses. However, MDPV and METH were associated with locomotor stimulant effects. MDPV showed a biphasic pattern of locomotor effects with increased wheel activity at lower doses and reduced activity at higher doses. This was similar to the pattern of locomotor activity associated with METH administration. Counts of wheel rotation for MDPV at all the doses tested (0.5, 1.0 and 5.6 mg/kg) were higher in the early part of the hour long sessions compared to saline control, but were lower in the middle of the session after the two highest doses; with the highest dose the counts stayed low for the remainder of the session.

A study in male ICR Harlan mice also assessed locomotor activity associated with MDPV injection at doses of 1 – 17mg/kg (the route of injection was not specified in the paper) compared to saline vehicle (Marusich, 2012). 1mg/kg MDPV significantly increased locomotor activity for 60 minutes after administration; after 3 – 17mg/kg MDPV, locomotor activity was increased for the full 90 minute session. However, significant attenuation in the stimulant effect of MDPV was observed between during the first 10 minutes after MDPV administration and again at 30 – 90minutes with the 3 and 17mg/kg doses, and at 20-30 and 50-90 minutes with the 10mg/kg dose.

In another study, the psychomotor stimulant effects and effect on body temperature of MDPV and methamphetamine (1.0 and 5.6mg/kg) were studied in sixteen male Wistar rats (Aarde, 2013). MDPV at an ambient temperature of  $23 \pm 1$  °C resulted in a dose- and time-dependent increase in locomotor activity; activity was greatest early (30 -120 minutes) after MDPV injection. MDPV at ambient temperature of  $23 \pm 1$  °C resulted in small ( $< 0.5^\circ\text{C}$ ) increases in body temperature in a dose- and time-dependent manner. As shown in Figure 14, both locomotor activity and effect on body temperature were greater for MDPV than methamphetamine at 5.6mg/kg doses but not at 1.0mg/kg doses.

Figure 14: Mean  $\pm$  SEM area under the curve (AUC) calculations for locomotor activity and body temperature related to MDPV and methamphetamine (METH).



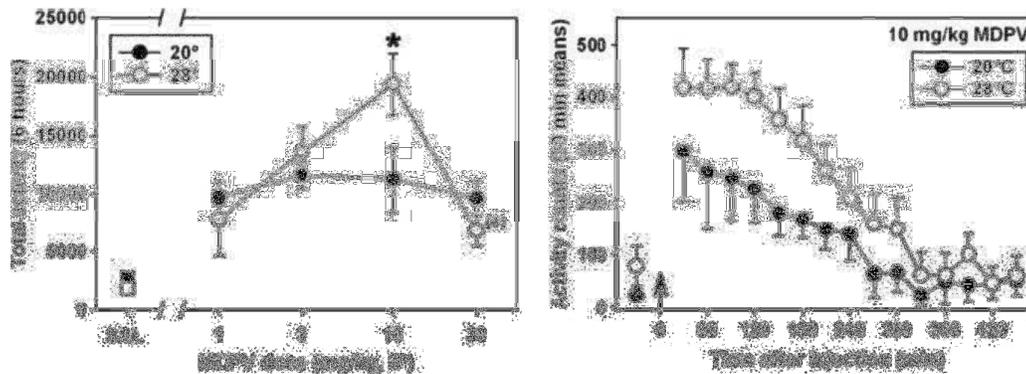
In another study, activity testing chambers with infrared beams were used to measure the locomotor stimulant effects of MDPV in male Swiss Webster mice. (Gatch, 2013) The horizontal activity (breaking the beams) was measured for eight hours within 10 minute periods following intra-peritoneal (IP) administration of either 0.9% saline or the test drug at a range of concentrations. MDPV was studied at doses of 0.3, 1, 3, 10 and 30 mg/kg; the other drugs studied were methamphetamine, cocaine, methylone, butylone, mephedrone, flephedrone and naphyrone. MDPV produced time-dependent and dose-dependent stimulation of locomotor activity at all doses studied. After doses of 1 and 3 mg/kg, MDPV caused stimulation within 10 minutes which lasted 190 minutes; the stimulant effects lasted 250 minutes after a dose of 10 mg/kg. For the 1, 3 and 10 mg/kg doses during the 30 minute period with maximal stimulant effects (10 – 40 minutes after administration), significant stimulant effects were seen ( $ED_{50}$   $1.26 \pm 0.08$  mg/kg). At the highest MDPV dose of 30 mg/kg, locomotor activity was initially depressed between 10 and 50 minutes after

administration, this was followed by locomotor stimulation that started at 80 minutes after administration and lasted for 300 minutes. This pattern in which low-moderate MDPV doses were associated with stimulation and higher doses were associated with initial depression followed by stimulation is similar to the effects that have been reported previously for amphetamine and that were seen with methamphetamine in this study. The increased locomotor activity associated with 1 – 10mg/kg of MDPV ( $ED_{50}$   $1.26 \pm 0.08$  mg/kg), was similar to that seen with mephedrone 3 and 10 mg/kg ( $ED_{50}$   $1.38 \pm 1.22$  mg/kg) and methylone ( $ED_{50}$   $1.48 \pm 0.35$  mg/kg); it was intermediate between cocaine 10, 20 and 40mg/kg ( $ED_{50}$   $7.24 \pm 0.14$  mg/kg) and methamphetamine 0.5 and 2mg/kg ( $ED_{50}$   $0.30 \pm 0.40$  mg/kg).

Another study in male Harlan Sprague-Dawley mice investigated both the locomotor and thermoregulatory effects of MDPV in comparison to saline vehicle and MDMA (Fantegrossi, 2013). The locomotor and thermoregulatory activity was measured using a surgically implanted intra-peritoneal radiotelemetry probe. Ambient temperature was maintained at two temperatures: 'cool' which was 20°C and 'warm' which was 28°C. After at least 60 minutes of baseline data collection, the mice were removed from the cage, injected with the test drug or saline (n=5 or 6) and then returned for 24 hours of data collection.

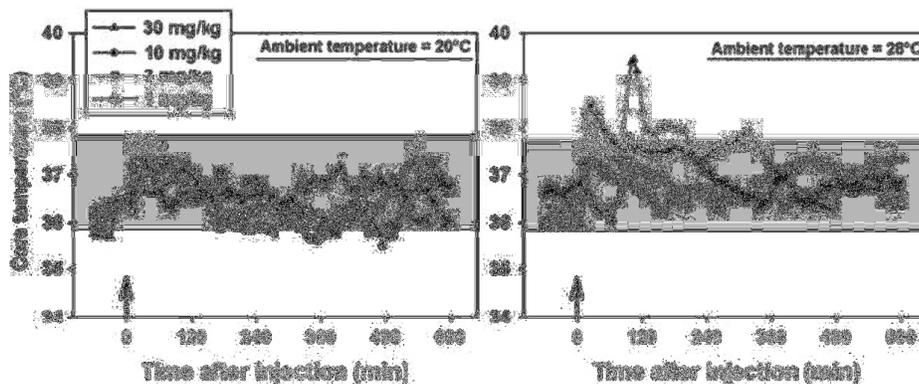
As shown in the left hand graph in Figure 15, MDPV increased locomotor activity above that seen with saline at all doses tested ( $p < 0.001$ ). At an ambient temperature of 20°C, the locomotor-stimulant effects of MDPV were not dose dependent. However, at an ambient temperature of 28°C, MDPV generated a biphasic dose–response curve for locomotor activity similar to that noted in the above studies. The locomotor stimulant effect of 10mg/kg MDPV was significantly greater at an ambient temperature of 28°C than at an ambient temperature of 20°C ( $p < 0.05$ ). In contrast to MDPV, the effects of MDMA on locomotor activity were not dependent on ambient temperature.

Figure 15: Locomotor activity in mice after MDPV or saline (SAL) at ambient temperatures of 20°C and 28°C.



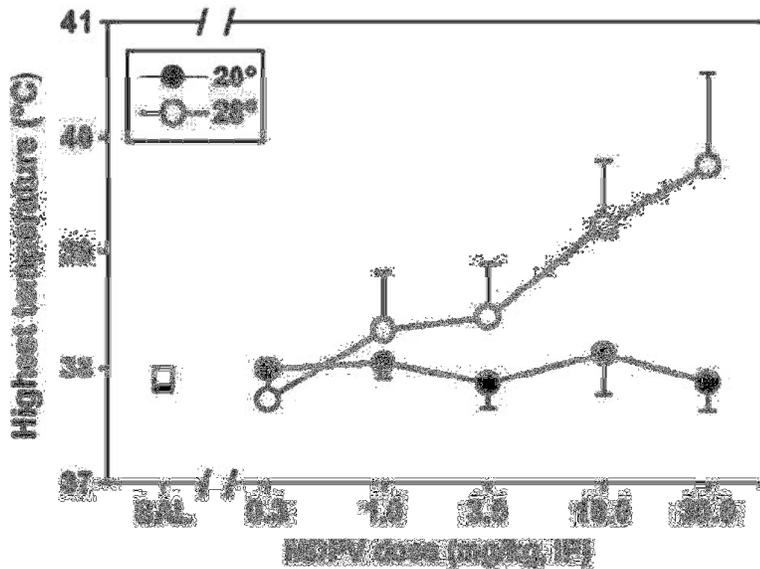
At an ambient temperature of 20°C and 28°C, mice treated with saline maintained core temperatures of 36 – 38.1°C. As shown in Figure 16, doses of MDPV from 1–30 mg/kg were not associated with an increase in core temperature outside the normal thermoregulatory range at 20°C ambient temperature; however, at an ambient temperature of 28°C, doses of 3, 10, and 30 mg/kg (but not 1 mg/kg) of MDPV were associated with an increase in core temperature outside the normal thermoregulatory range.

Figure 16: Effects of MDPV on core temperature at an ambient temperature of 20°C and 28°C



As shown in Figure 17, the mean maximum temperature in the mice increased with MDPV dose at an ambient temperature of 28°C but there was no increase in mean maximum temperature of the mice at an ambient temperature of 20°C.

Figure 17: Maximum temperature after saline (SAL) or MDPV at ambient temperatures of 20°C and 28°C



Another study has assessed the locomotor and cardiovascular stimulant effects of MDPV in male Sprague-Dawley rats (Aarde, 2013). Locomotor effects were studied in six rats and subcutaneous doses of MDPV (0.1 – 3.0mg/kg) were compared to cocaine (3 – 17mg/kg) and saline control. MDPV was associated with significant dose-related stimulation of forward locomotion ( $p < 0.0001$ ). These effects were also seen with cocaine, but MDPV was more potent than cocaine – the threshold dose of MDPV that stimulated significant forward locomotion was 0.3 mg/kg, compared with 10 mg/kg for cocaine. Additionally, MDPV induced significantly greater peak stimulant effects than cocaine ( $p < 0.001$  for 3.0 mg/kg MDPV vs 10mg/kg cocaine). Cardiovascular parameters were studied in four rats using telemetry transmitters inserted into the aorta to measure heart rate and blood pressure; subcutaneous doses of MDPV (0.1 – 3.0mg/kg) were compared to cocaine (3 – 17mg/kg) and saline control. MDPV administration was associated with tachycardia ( $F [4,25] = 32.61$ ,  $p < 0.0001$ ) and hypertension ( $F [4,25] = 3.05$ ,  $p < 0.05$ ). Cocaine administration was associated with tachycardia ( $F [3,20] = 6.15$ ,  $p < 0.01$ ) but not hypertension ( $F [3,20] = 1.10$ ,  $p = 0.37$ ). The peak increase in heart rate associated with MPPD administration was significantly greater with cocaine administration (3.0 mg/kg MDPV vs 10 mg/kg cocaine,  $p < 0.01$ ).

It would appear that only one study has assessed the potential for cytotoxicity associated with MDPV administration, this was an *in vitro* study in HEK 293 cells (Simmler, 2013a). Cell membrane integrity was maintained after incubation with 10 $\mu$ M and 100 $\mu$ M of MDPV for four hours and therefore cytotoxicity was not observed under these assay conditions.

## **D1.2. Human Data**

### **D1.2.1 User Reports**

A number of adverse effects have been reported by users to be associated with MDPV use. Psychological effects such as severe and prolonged anxiety attacks, agitation, irritability, depression and confusion have been reported (Psychonaut, 2009) as well as the physical effects listed in Section A3.2.1.

### **D1.2.2. MDPV associated acute toxicity**

Data on non-fatal intoxications related to MDPV is available from reports by the Member States to the EU Early Warning System as well as from the published scientific literature. Some of these reports have analytical confirmation of MDPV in biological samples or in the substance(s) used and some are based on user self-report.

A total of 524 non-fatal intoxications associated with MDPV have been reported by eight Member states (Belgium (2), France (18), Germany (6), Greece (2), Ireland (1), Italy (3), Slovakia (5) and Sweden (487)). Six Member States have reported a total of 110 analytically confirmed non-fatal intoxications associated with MDPV. These confirmed cases, which are described below and can be found in Table 6 were reported from: Belgium (2), France (4), Greece (1), Ireland (1 – analysis of substance taken), Italy (3) and Sweden (99). The remaining cases include cases based on user self-reports, with no analytical confirmation of MDPV in biological samples or the remaining. In addition, there are EU-based and non-EU based case reports published in the scientific literature which are presented below.

#### **Cases reported to the EU Early warning system**

Belgium reported two analytically confirmed linked non-fatal intoxications in which the patients presented were stimulated, hypertensive and tachycardic. Traces of cocaine and amphetamines were also detected in urine samples (not quantified). They both reported visual and auditory hallucinations and severe psychosis, paranoia and were aggressive. They were treated with antipsychotics and their status returned to normal after 3-4 days.

France reported four analytically confirmed non-fatal intoxication cases. In one case, a man was brought in to the emergency department by the police. In this case, delirium syndrome was reported, including hallucinations as well as rhabdomyolysis, tachycardia, hypotension, agitation, logorrhea and acute renal failure. The MDPV metabolite, pyrovalerone and cannabis were also detected in this case. In the second case, which was a 'forced

hospitalisation', paranoid psychosis and aggression were noted. The symptoms reported were tachycardia, mydriasis, hypertension, agitation, profuse sweating, trembling, scarification and rhabdomyolysis. In this case, the route of administration was nasal and oral and the MDPV had been bought on the Internet. Methylone (4400 ng/ml) was also detected in this case. In the last case, where the detection of MDPV was in a sample of hair, the patient had also bought MDPV via the Internet and the route of administration was nasal. Symptoms reported were mydriasis and paranoid psychosis. Cannabis and alcohol were also detected in this case. In the final case, a 39-year-old male presented to hospital after injecting MDPV and using 4-MEC (route not specified). He had abnormal movements, trismus, profuse sweating, visual disorders, insomnia, anorexia and vertigo. He also reported dysuria which lasted 24 hours; no further details were reported.

Greece reported a case of a 47-year-old male who was admitted to a hospital in Athens with a sudden loss of consciousness after ingestion of MDPV. According to the testimony of a witness, the patient had purchased MDPV from the Internet in powder form and it was taken orally. He required urgent intubation and was admitted to the Intensive Care Unit (ICU) due to multi-organ failure (hepatic impairment, rhabdomyolysis and renal insufficiency). Toxicological analysis was performed on a urine sample taken on admission. Screening tests for all groups of drugs of abuse was performed by immunoassay and his urine sample was positive for amphetamine type stimulants. The confirmation of MDPV in his urine was carried out using a GC/MS method.

Ireland reported a case of a case of a young man who presented with acute psychosis and subsequently developed hepatic failure following ingestion of butylone and MDPV. Further details are described below, taken from the academic study that was performed in this case.

Italy reported three analytically confirmed non-fatal intoxications. The first was from August 2011 when a 20 year old male was admitted to hospital very agitated with tachycardia (heart rate 115 bpm). He reported having consumed cannabis, alcohol and three white capsules. MDPV was found in urine (14 mg/L) and butylone was also present (concentration not provided). The patient was treated with benzodiazepines and discharged two days later. The second case was from October 2012 and involved a 38 years old male who presented at the emergency department with agitation, mild tachycardia (HR 105 bpm), distress and psychotic symptoms. He also reported visual and auditory hallucinations. He reported to have taken ecstasy and synthetic drugs generally named as 'mefre, crystal and energy' by nasal insufflation. MDPV was detected in blood (12 mg/L) and urine (17 mg/L). Urine screening of ketamine, atropine, scopolamine, levamisole, mephedrone, butylone, 4-MEC,

methoxetamine, APB (4) (isomers), 4-FA (5), and MDAI (6), resulted negative. The final case also occurred in October 2012 and involved a 27 years old male who presented at the emergency department. His father had found him in a state of agitation, confusion and anxiety. The patient reported having taken MDPV by intravenous injection for the last 3-4 days together with benzodiazepines to counteract the excitatory effect of MDPV. The MDPV had been purchased from the Internet as a 'bath salt'. Analysis of the patient's urine revealed MDPV (55 µg/L), alprazolam (113.79 µg/L) and hydroxyalprazolam (103.59 µg/L). Three days after admission, the patient returned to the hospital for a second urine analyses, as requested by sanitary authorities. The patient reported continuing his use of MDPV and this was confirmed by the detection of MDPV in urine at a concentration of 35 µg/L. The analyses also found chlordiazepoxide (13.03 µg/L), nordiazepam (61.55 µg/L), oxazepam (114.99 µg/L), diazepam (1.26 µg/L), temazepam (169.90 µg/L), alprazolam (10.43 µg/L) and alpha-hydroxyalprazolam (13.45 µg/L).

Sweden reported 487 non-fatal intoxications between 2007 and 2013 as follows: 2007 (1 case), 2008 (4), 2009 (15), 2010 (47), 2011 (32), 2012 (194) and 2013 (194). Of these, between 86 and 99 cases are known to be analytically confirmed (<sup>7</sup>). Two literature sources which describe a total of 99 non-fatal intoxications have been used for the purposes of describing the health risks. In the first report (Lindeman, et al., 2013), cases of stimulant toxicity were studied from one hospital in Sweden covering April-May for three consecutive years (2010 to May 2012). In April-May 2012 the number of patients with stimulant toxicity was 45 and 17 of these cases were examined toxicologically. Thirteen of these tested positive for MDPV and 12 of these were classified as chronic drug users with >60% noted to be HCV (Hepatitis C virus) positive. The second study (Bäckberg et al., 2013) focussed on the results of the STRIDA project which monitors trends in acute poisonings with novel recreational drugs in Sweden. The study summarises the results for the first 9 months in 2012 when MDPV was detected in 86 out of 321 samples. In 17 cases the symptoms were severe (Poisoning Severity Score - PSS 3 (Persson et al, 1998)) and consisted of extreme agitation, psychosis, hyperthermia, tachycardia, hypertension, myocardial infarction, rhabdomyolysis and renal failure. A few patients needed therapy with sedatives for several days due to prolonged symptoms. It was noted by the authors that among people that come to medical attention, the incidence of severe poisonings (PSS 3) was highest for MDPV.

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(<sup>4</sup>) (Aminopropyl)benzofuran

(<sup>5</sup>) 4-Fluoroamphetamine

(<sup>6</sup>) 3,4-Methylenedioxyaminoindane

(<sup>7</sup>) There is a potential that there may be an overlap of some cases reported by Lindeman et al., 2013 and the cases reported by Bäckberg et al., 2013

Table 6 below summarises the non-fatal intoxications reported to the EU Early Warning System in which there was analytical confirmation of MDPV in biological samples.

Table 6: Non-fatal intoxications in which MDPV has been detected in biological samples and that were reported to the EU Early Warning System by the Member States [EMCDDA Europol Joint Report Annex 2]

Country	Date	Sample type	MDPV result	Results for other substances	Notes
Belgium	Aug 2011 (F, 31)	Urine	+	cocaine (+) amphetamines (+)	First time MDPV use. Drug taken orally. Clinical features included hallucinations and severe psychosis, paranoia, visual and auditory hallucinations, aggressiveness, hypertension and tachycardia. Treated with antipsychotics and admitted to a psychiatric ward. Status normal after 3-4 days
Belgium	Aug 2011 (M, 34)	Urine	+	cocaine (+) amphetamines (+)	First time MDPV use. Drug taken orally. Clinical features included hallucinations and severe psychosis, paranoia, visual and auditory hallucinations, aggressiveness, hypertension and tachycardia. Treated with antipsychotics and admitted to a psychiatric ward. Status normal after 3-4 days This case is related to the case described above.

Country	Date	Sample type	MDPV result	Results for other substances	Notes
France	Date not specified (M, 27)	Not specified	+	pyrovalerone (+) cannabis (+)	Brought to the Emergency Department by the police. Clinical features included delirium, hallucinations, rhabdomyolysis, tachycardia, hypotension, agitation, acute renal failure. Man brought in to the emergency by the police.
France	Date not specified (M, 25)	Blood	366 ng/mL	methylone (4400 ng/mL)	Clinical features included tachycardia, mydriasis, hypertension, agitation, profuse sweating, trembling, scarification, rhabdomyolysis, paranoid psychosis, aggression. Route of administration: inhaled and oral, dose 10g. Bought on the internet. In combination with methylone. Forced hospitalization.
France	Date not specified (M, 22)	Hair	+	alcohol (+) cannabis (+)	Nasal insufflation. Clinical features: mydriasis, paranoid psychosis. Duration of effects: 2 days.
France	Date not specified	Not specified	+	4-MEC	MDPV injected. Patient had abnormal movements, trismus, profuse sweating, visual disorders, insomnia, anorexia and vertigo. He also reported dysuria which lasted 24 hours; no further details were specified.

Country	Date	Sample type	MDPV result	Results for other substances	Notes
Greece	2013 (M, 47)	Urine	+	+ ATS immunoassay - other immunoassays (MDPV only confirmed by GC-MS)	Sudden loss of consciousness after ingestion of MDPV bought from the Internet. Patient required urgent intubation and was admitted to the Intensive Care Unit due to multi-organ failure (hepatic impairment, rhabdomyolysis and renal insufficiency). The patient was in ICU for one week and required kidney dialysis for two weeks after discharge.
Italy	Aug 2011 (M, 20)	Urine	4 mg/L	butylone (+)	On admission, the patient was very agitated with tachycardia (Fc 115 bpm). He reported having consumed cannabis, alcohol and 3 white capsules. He was treated with benzodiazepine and discharged two days later.

Country	Date	Sample type	MDPV result	Results for other substances	Notes
Italy	Oct 2012 (M, 38)	Blood Urine	12 mg/L (blood) 17 mg/L (urine)	Urine: ketamine (-) atropine (-) scopolamine (-) levamisole (-) mephedrone (-) butylone (-) 4-methylethcathinone (-) methoxetamine (-) APB ( <sup>8</sup> ) isomers (-) 4-fluoroamphetamine (-) MDAI ( <sup>9</sup> ) (-)	The patient was admitted to the emergency department and reported nasal insufflation of ecstasy and synthetic drugs generally named as “mefre, crystal and energy”. Clinical features included agitation, tachycardia (105 bpm), distress, psychosis, visual and auditory hallucinations. During the first 24 hours, the patient was treated with fluids, benzodiazepines and haloperidol and transferred to a psychiatric ward.

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<sup>8</sup> (Aminopropyl)benzofuran

<sup>9</sup> 3,4-Methylenedioxyaminoindane

Country	Date	Sample type	MDPV result	Results for other substances	Notes
Italy	Oct 2012 (M, 27)	Urine	On admission: 55 µg/L Three days after admission: 35 µg/L	On admission: alprazolam (113.79 µg/L) hydroxyalprazolam (103.59 µg/L) 3 days after admission: chlordiazepoxide (13.03 µg/L) nordiazepam (61.55 µg/L) oxazepam (114.99 µg/L) diazepam (1.26 µg/L) temazepam (169.90 µg/L) alprazolam (10.43 µg/L) alpha-hydroxyalprazolam (13.45 µg/L)	On arrival in the emergency department the patient reported having using MDPV intravenously, for the last 3-4 days together with benzodiazepines to counteract the excitatory effect of MDPV. Clinical features included psychomotor agitation, confusion and anxiety. Anamnestic information from the patient revealed previous use of pentedrone and 3-methylmethcathinone, the patient had abandoned these for decreased interest in these substances. Three days after admission, the patient had a second urine analysis, and reported having continued his use of MDPV. The MDPV was purchased via Internet and marketed as "bath salts"

Country	Date	Sample type	MDPV result	Results for other substances	Notes
Sweden	Jan – Sep 2012	Blood Urine	+	Result for other substances was positive for 15/17 cases with severe symptoms. Benzodiazepines (7) were the most frequently identified substances. Medicines included buprenorphine, tramadol and fentanyl.	From a total of 86 cases, in 17 cases the clinical features were severe (Poisoning Severity Score - PSS 3) and consisted of extreme agitation, psychosis, hyperthermia, tachycardia, hypertension, myocardial infarction, rhabdomyolysis and renal failure. “A few” patients needed therapy with sedatives for several days due to prolonged symptoms [Bäckberg et al., 2013]
Sweden	Apr-May 2012	Not specified	+	None reported	Twelve of the 13 cases described were classified as chronic drug users with >60% noted to be HCV-positive [Lindeman et al., 2013]

## France

France reported 14 cases of non-fatal intoxication associated with MDPV where there was no analytical confirmation of MDPV in biological samples.

Between December 2011 and June 2013, five cases involving males aged 20 to 35 years were reported via the Sintes system in which MDPV had been insufflated and cocaine also used. Paranoia and neurological effects (such as uncontrolled movement and “a sensation of cold liquid in the brain, arms and legs”) were reported. In four of these cases, MDPV was confirmed in powders collected from the patients and contained MDPV (2), MDPV and PVP or MDPV, PVP and pentedrone. In a separate case in 2013 a 35-year-old male used MDPV and methadone and developed respiratory depression, he also became paranoid and socially isolated. A powder from the patient in this case was found to contain MDPV, PVP and caffeine. No further clinical details were available for these cases.

In the remaining eight cases were reported, but no date was specified in seven of these reports:

Case 1: A 28-year-old male injected 50 mg of MDPV four or five times a day (length of time and route not specified) and also used buprenorphine. He developed fatigue and sleep disorder with pain at the injection site. He also became anxious with intellectual stimulation, an obsession to consume MDPV and ‘psychic withdrawal symptoms’ (sic). The patient became withdrawn from others and was absent from work; no further details were specified.

Case 2: A 24-year-old male injected MDPV and also used MDMA and cathinones (route not specified). He presented to hospital confused and agitated following a suicide attempt. No further details were specified.

Case 3: A 48-year-old male presented to hospital with chest pain, tachycardia and a sensation of warmth having injected MDPV (route not specified). No further details were specified.

Case 4: A 35-year-old male developed anxiety and agitation with facial erythrosis and dry mucous membranes after insufflating a gram of MDPV. No further details were specified.

Case 5: A 32-year-old male became paranoid with a loss of focus, sensation of cold and electrical discharge in his heels after insufflating MDPV. He also reported weight loss, a reduced appetite and insomnia; no further details were specified.

Case 6: A 30-year-old male presented to hospital with insomnia and psychomotor agitation having injected MDPV (route not specified). No further details were specified.

Case 7: A 33-year-old male developed social phobia after inhaling MDPV and using buprenorphine and heroin. No further details were specified.

In 2012, a 41-year-old male presented to hospital after injecting powder that was subsequently found to contain MDPV, although no MDPV was detected in his blood (the timing of this sample is not specified). He was in respiratory distress, had tetany, malaise and language disorders. No further details were specified.

#### Germany

In 2013, the Poison Control Centre reported six inquiries in context with the substance MDPV. In five of the inquiries, said to be from young people, the callers were 'afflicted with tachycardia, agitation and mentally disordered'.

#### Greece

In October 2011, a 22-year-old male patient was brought to hospital by his parents. He presented with: severe agitation, confusion, disorganised behaviour, auditory and visual hallucinations and thought incoherence; he had been like this for one day or so. He had a chest x-ray consistent with pneumonia and had elevated CPK (>10.000 U/L) and elevated hepatic enzymes (SGOT 219 U/L, SGPT 68 U/L), LDH 464 U/L). After treatment with haloperidol and diazepam he showed signs of improvement. His psychiatric state had improved by the third day in hospital when he admitted previous use of LSD and cannabis for the last year. He said he had ordered MDPV powder from a Chinese site on the Internet. He admitted having inhaled the powder twice, but was adamant that he started showing symptoms after the first use, taking the second dose in a failed attempt to ease his anxiety. The patient discharged himself before toxicological samples could be taken.

#### Slovakia

Five cases were reported which occurred between February and March 2012. The cases involved males aged between 22 and 24 years who ingested MDPV and developed

tachycardia, hypertension, mydriasis, nausea, agitation and palpitations (actual heart rate, blood pressure and temperature were not reported). One patient was seen by a psychiatrist three days after ingestion with ongoing insomnia, euphoria and auditory hallucinations. The products used also contained buphedrone, 2-DPMP, methylone and piracetam.

#### Sweden

As reported above, Sweden reported a total of 487 non-fatal intoxications related to MDPV which were reported via the Swedish Poisons Information Service from 2007. Between 86 and 99 of these are known to be analytically confirmed and have been recorded in Table 6 and have been reported in the scientific literature by Lindeman et al., 2012 and Bäckberg et al., 2013, see further details below.

#### ***Case reports published in the literature***

There is the possibility that some of these cases are included in the reports from national focal points and are already detailed above. The information is presented here in order to provide more detailed information including contextual information, where available.

#### ***EU non-fatal intoxication cases – analytically confirmed***

##### France

A 47-year-old man was brought to a psychiatric Emergency Department with a 3 day history of restlessness, behavioural change and delirium (Sadeg, 2014). On arrival, he was suspicious, anxious, and delirious with delusional thoughts. He was tachycardic (heart rate not specified). He was admitted to a psychiatric unit and treated with loxapine and diazepam. The next day his clinical features had settled and the medication was stopped. He had three previous presentations with similar features. He had purchased "NRG-3" from an Internet site and had been using it by nasal insufflation for a few months. MDPV was detected both in the "NRG-3" product and in a serum sample.

##### Ireland

A 28-year-old male, with bipolar affective disorder, had a witnessed tonic-clonic seizure in the community after ingesting 12 "stimulant tablets" and was taken to ED in Ireland (Frohlich, 2011). On arrival his GCS was 5/15 and he was tachycardic (190 bpm) with a systolic blood pressure of 230 mmHg, temperature of 39.5°C and he was sweating profusely. He was intubated and transferred to ICU where he was treated with cooling, mechanical ventilation, labetalol and phenytoin; he was extubated 10 hours later. He developed rhabdomyolysis with a creatine kinase of 112,000 IU/L and acute renal failure which was treated

conservatively without requiring renal replacement therapy. Two days post ingestion he developed acute liver failure with a peak INR of 2.8, the following day peak ALT was 2500 IU/L and he was treated with N-acetylcysteine for three days. Four days post ingestion he was discharged from ICU and admitted to a psychiatric unit where he received prolonged treatment for a relapse of his psychosis. The remaining tablets were analysed and found to contain MDPV and butylone.

A study of the enquiries to the National Poisons Information Centre in Ireland on cases involving synthetic cathinones was undertaken following legislation controlling the use of benzylpiperazine in Ireland in 2009 (Herbert JX, 2011). In the 18 months after the ban 116 enquiries (about 117 patients) were received regarding 'bath salts' or 'plant feeder pills'. The active ingredients were identified from police forensic laboratory analysis of purchased products. MDPV was detected in 6.8% of products; other commonly encountered cathinones were mephedrone (31.6%) and methylone (14.5%); active ingredients were not identified in 39.3% of products. The majority (86.2%) of the enquiries were from hospital EDs and involved males (68.4%); the age range of all the patients was 14 – 42 years (mean 24.2, median 22.5). The most commonly reported clinical features were tachycardia (40.2%), agitation (25.6%), mydriasis (21.4%), chest pain (18.6%) and hypertension (14.5%); the actual heart rate / blood pressures were not reported nor where the criteria that were used to determine tachycardia / hypertension in the cases. The Poisons Severity Score was used to rate the severity of the exposures and two had no symptoms (PSS 0), 20 had minor symptoms (PSS 3), 90 had moderate (PSS 2) and none had severe (PSS 3); there were no fatalities. No breakdown was provided to be able to determine which clinical features were present in the cases that had used a product containing MDPV.

#### Italy

A 27 year old male presented to the Emergency Department with agitation, delirium, hallucinations and depression for the previous week (Favretto, 2012). No other clinical details were reported. He reported MDPV use but could not remember when he had used it. MDPV and benzodiazepines were detected in the urine.

In a study undertaken by the Pavia National Toxicology Information Centre in Italy from January 2010 – October 2011, biological samples were analysed from 192 patients with suspected "new recreational drugs of abuse" toxicity in Italy (Lonati, 2012). One (0.52%) sample was positive for MDPV - no clinical details were reported for this case.

#### Poland

There is a cases series of three patients from Poland with analytically confirmed MDPV use (Adamowicz, 2013):

Case 1: a 25 year old female was arrested for possessing narcotics. She had slurred speech, abnormal papillary reflex, pale skin and “wobbly lifting”; no further clinical details are available. Blood MDPV was 306 ng/mL and diazepam was also detected.

Case 2: a 19 year old male was stopped from routine traffic control. He had slurred speech and poor reactions to light; no further clinical details are available. Blood MDPV was 124 ng/mL; THC, THCCOOH, JWH-018 5-hydroxyindole were also detected.

Case 3: a 32 year old female was involved in a motor vehicle accident and did not know where she was or that she had hit any cars; no further clinical details are available. Blood MDPV was 200 ng/mL; fluoxetine and norfluoxetine were also detected.

#### Sweden

As noted above, the Swedish Poisons Information Service was contacted regarding MDPV, on a total of 487 occasions between 2007 and 2013. Further details about some of these cases are available from the scientific literature. Enquiries to the Swedish Poisons Centre during 2008 and 2009 were analysed for cases involving synthetic cathinones, in combination with 52 hospital records (Hagerkvist, 2010). In total 150 cases were identified most frequently involving mephedrone (100 cases) or MDPV (50 cases), it is not specified if there were any co-ingestions. The age range of the patients was 14 – 38 years (no average age or median is given) and the majority were male (71%). The most common route of use was oral (54%), nasal insufflation (20%) and intravenous (7%) and the most common clinical effects were tachycardia (53%), restlessness (33%), mydriasis (25%) and hypertension (14%); the actual heart rate / blood pressures were not reported or the criteria to determine tachycardia / hypertension. The Poisons Severity Score (PSS) was used to rate the severity of the exposures and 54% had minor symptoms (PSS1), 22% had moderate (PSS2), none had severe (PSS3) and there was one fatality, attributed to mephedrone. No breakdown was provided to be able to determine which clinical features were present in the cases that had used MDPV.

In 2010 the Swedish Poisons Information Centre began a joint initiative with the Karolinska Institute and Karolinska University Laboratory, known as STRIDA, to look at the problems of new psychoactive substances (Helander, 2013). Emergency departments around the country sent blood and urine samples from cases in which patients self-reported the use of

such drugs or when use of NPS was suspected by medical staff. In the first 12 months, 103 samples were received which included 22 cases involving synthetic cannabinoid receptor agonists and 11 cases involving substituted cathinones. The most commonly reported clinical features in the substituted cathinone group were tachycardia and agitation/restlessness (each 64%), mydriasis (55%) and hypertension (45%). The cathinones were used orally, the age range was 19 – 32 years (mean 25.2 years) and 91% were male. MDPV was detected in 3 samples (2.9% of all samples and 27% of the cathinone-positive samples); it is not possible to determine from the information available in the report which of the reported clinical features were present in the patients in whom MDPV was detected.

Another report from the STRIDA project in Sweden, reported analysis of urine and/or blood samples from 321 patients in 2012 (Bäckberg, 2013). MDPV was detected in 86 (26.8%) samples and 17 of these had severe clinical features (Poisoning Severity Score (PSS) 3) with extreme agitation, psychosis, hyperthermia, tachycardia, myocardial infarction, rhabdomyolysis and renal failure. No further clinical details were included and no information on the proportion of patients with these individual clinical features.

The enquiries to the Swedish Poisons Information Centre regarding MDPV rose sharply in the first half of 2012, with most coming from Vasteras a city in central Sweden (Lindeman, 2013). Records from the hospital there identified 45 patients with 'stimulant' toxicity in April and May 2012, requiring hospitalisation for a total of 109 days. Ten patients were treated in ICU for 45 days. MDPV toxicity was suspected in 82% of the cases and unspecified biological samples from 17 patients were analysed; 14 (76%) of these were positive for MDPV.

#### United Kingdom

A 31-year-old male who had purchased what he believed to be naphyrone (sold as "Energy-1") from the Internet (Wood, 2011). After ingesting 1g of the powder dissolved into wine, he experienced an 'intense high' similar to that he had experienced following previous use of MDMA. He presented to the ED approximately 30 hours later with agitation, anxiety and prolonged insomnia. On examination he had a normal heart rate (75 bpm), was mildly hypertensive (153/86 mmHg) and had a normal temperature (36.4°C); apart from his agitation and anxiety the only other clinical sign on presentation was dilated pupils (5mm). The patient declined a dose of oral lorazepam and after four hours of observation he was asymptomatic and discharged. Subsequent analysis of a serum sample taken at the time of ED presentation and the powder that was ingested by the patient detected MDPV and butylone.

### ***EU non-fatal intoxication cases – not analytically confirmed***

#### Germany

In Germany in 2013, the Poison Control Centre North received six enquiries regarding MDPV; five young patients were tachycardic (heart rate or other physiological parameters not reported), agitated and “mentally disordered” and one patient suffered from stomach-ache. The Poison Control Centre for the Federal States of Hessen and Rheinland Pfalz had two enquiries regarding MDPV with 13 enquiries from hospital doctors/rescue services; no further details were available on these cases.

#### Netherlands

A 27-year-old HIV-positive male in the Netherlands inhaled 1g ‘Ivory Wave’, considered to contain MDPV, and presented to hospital two days later with sudden left-sided weakness (Boshuisen, 2012). He had felt agitated and confused earlier but on the day of admission fell to the ground and could not get up. On examination his blood pressure was 140/70 mmHg, pulse 110 bpm, temperature normal. The patient had left-sided gaze palsy, left-sided central facial palsy, partial homonymous hemianopia, paralysis of his left arm and mild proximal and severe distal weakness of his left leg with a Babinski sign. A CT brain scan showed right middle cerebral artery (MCA) infarction and he was treated within four hours of the onset of symptoms with recombinant tissue plasminogen activator with minimal improvement. The patient was transferred to another hospital where, four days after his stroke, a brain MRI scan showed a large right MCA infarction with haemorrhagic transformation. His neurological deficits recovered slightly and he was transferred to a rehabilitation clinic where he made a complete recovery within two months.

#### Hungary

The first report from Hungary described five patients who were admitted acutely to a psychiatric unit after developing psychotic symptoms related to self-reported MDPV use (Szily, 2013). They had no medical history of schizophrenia or other psychotic illnesses and all recovered after treatment with low-dose anti-psychotics (risperidone, olanzapine, haloperidol and zuclopenthixol) and benzodiazepines. No information on other clinical features was included.

A further report from Hungary, and published in Hungarian, included 15 cases (13 male, 2 female; age 21 – 50 years) of self-reported MDPV use (Kalapos, 2011). It was reported that these patients had hepatotoxicity (“lowered GOT, GPT and gamma-GT”, elevated urobilinogen), “intoxication” (>40% cases), decreased appetite, paranoia and delusions,

aggression, “withdrawal” (>30% cases), muscular pain, pallor and hypersomnia. It was noted that “treatment with clonazepam and if necessary risperidone” was given to “alleviate delusions”. No further clinical details were described.

Another report from Hungary contains some information on 54 cases (42 male, 10 female) of acute intoxication related to self-reported MDPV use (Andrássy, 2013). The most common route of use of MDPV (proportion not stated) was nasal insufflation, injection was the route of use in 28% of cases. Clinical features reported were tachycardia, hypertension (heart rate and blood pressure not stated), agitation, muscle rigidity, lack of appetite, xerostomia, bruxism, itching and skin erosion, psychosis, paranoia, hallucinations, “out of time feeling”. There was one case of rhabdomyolysis (clinical details or the creatinine kinase result are not available).

Farkas et al., describe 5 cases: a 21 year old male, 36 year old female, 20 year old female, 32 year old female and a 44 year old male in Hungary of hospital presentations related to self-reported use of MDPV (Farkas, 2013). Two patients developed hepatotoxicity (it is not stated whether these patients had hyperpyrexia and/or rhabdomyolysis) with “elevated GGT, GOT, GPT”. Other features reported included dysphoria, paranoia, anxiety, aggression, hallucinations, suicidal ideation, depersonalisation and anorexia; no further clinical details are available.

### ***Non-EU non-fatal intoxication cases - analytically confirmed***

A 19-year-old male presented to an ED in Mississippi, USA with auditory and visual hallucinations which had begun several hours prior to his presentation; he stated that voices were urging him to kill unspecified people and someone was trying to steal his thoughts (Kyle, 2011). The patient denied drug and alcohol use and homicidal or suicidal ideations. The patient’s physical examination was unremarkable (blood pressure 140/80 mmHg, heart rate 95 bpm, temperature 37.1°C). After a psychiatric examination, in which he exhibited illogical thought processes, anxiety and paranoia he was admitted to an in-patient psychiatric unit with a psychosis of unknown cause and treated with promethazine and risperidone. The next day the patient said he was no longer hearing voices and wanted to go home. A urine toxicology screen detected MDPV, caffeine, cotinine (nicotine metabolite) and promethazine. When told of these results, the patient admitted smoking a product purchased for US\$20 from the Internet; initially he had felt euphoric but soon began to hallucinate. The patient said he had suffered hallucinations, confirmed by family members, when he had used similar

product two months previously. He was discharged in a stable condition the day after his admission.

A 25-year-old male was taken to an ED in Virginia, USA by the police as he had been found very agitated with altered mental status (Borek, 2012); according to his girlfriend he had injected 'bath salts' (amount not specified). On presentation the patient was not speaking, was tachycardic (175 bpm) with a normal blood pressure (148/66 mmHg) and he was significantly hyperthermic (rectal temperature 41.3°C). He had dilated pupils, rightward deviation of the eyes and "combativeness" requiring physical restraint by multiple members of staff. He was sedated, intubated, ventilated and admitted to the Intensive Care Unit (ICU). His pulse and blood pressure decreased over the next hour, and with the application of ice packs and cooling blankets his temperature normalised. Over the next two days he developed renal failure (peak creatinine 10.2 mg/dL), fulminant hepatic failure (peak AST 16,688 IU/L, peak ALT 9,085 IU/L), disseminated intravascular coagulation (peak INR >9.3, platelet nadir  $16 \times 10^9/L$ ) and rhabdomyolysis (peak CK 235,377 IU/L). An initial echocardiogram showed decreased global left ventricular systolic function with an ejection fraction of 30%. He remained critically ill, sedated, intubated and receiving haemodialysis until he was extubated on his 9<sup>th</sup> day in hospital; his mental status normalized by the 13<sup>th</sup> day and he was discharged on the 19<sup>th</sup> day. His liver function tests, coagulation and creatinine kinase all normalised prior to discharge from hospital; however, he required ongoing haemodialysis for a month after admission until his creatinine normalised. An admission urine sample was positive for MDPV at a concentration of 140ng/mL.

A 41-year-old female nasally insufflated "Blue Magic" 'bath salts' over the two days prior to presentation to a hospital in Indianapolis, USA (Mugele, 2012). On presentation she was agitated but orientated, on examination she had a normal blood pressure (99/64 mmHg), heart rate (98 bpm) and temperature (36.7°C); she had spontaneous myoclonus but no nystagmus or hypertonicity. Eight hours after presentation she became severely agitated, developed hallucinations and became hyperthermic (40.1°C) with tachycardia (130 bpm) and mildly hypertensive (152/85 mmHg). The patient was given lorazepam and diazepam but her symptoms did not improve so she was sedated, intubated and transferred to the ICU of a tertiary hospital where a fentanyl infusion was started for ongoing sedation and analgesia. On arrival her vital signs had improved (heart rate 81 bpm, blood pressure 119/57 mmHg) and her temperature was normal (37.3°C). On the second day the patient was hyperreflexic with inducible clonus on dorsiflexion and increased tone in her lower extremities. Due to concern about serotonin syndrome, fentanyl was stopped and sedation continued with propofol and benzodiazepines; when sedation was reduced she became

more agitated and combative and on the fourth day cyproheptadine was commenced (initial 12mg then 8mg four hours later followed by 8mg every six hours), given via nasogastric tube, for serotonin syndrome. The patient developed aspiration pneumonia and a pneumothorax and was finally extubated on the seventh day. On day 8 the cyproheptadine was stopped but restarted the next day as the patient had inducible clonus of the ankles and bilateral patellar hyperreflexia; these clinical features resolved by the 11<sup>th</sup> day when the drug was discontinued and the patient discharged home on the 12<sup>th</sup> day. A urine sample from the time of ED presentation was found to have a MDPV concentration of 3,100ng/mL. Her blood ethanol concentration was 23mg/dL. The authors stated in their report that they felt that the patient's serotonin syndrome related to MDPV was worsened by the use of fentanyl.

A case series from the ToxIC Network Database in the USA reported on 40 cases of presentations to hospital after use of a "bath salt" product (Froberg, 2012). Analytical testing was undertaken in 57.5% of the cases and MDPV was identified in 78% of these (concentrations were not reported and it is not clear whether analysis was of blood or urine samples). The clinical features reported in the whole group (these are not broken down to be able to determine the features present in those who were positive on MDPV screening) were: tachycardia (HR > 100bpm) 70%, systolic hypertension (SBP > 140 mmHg) 35%, hyperthermia (> 100°C) 15%, agitation 57.5%. Hypokalaemia (potassium < 3.5 mmol/L) was present in 27.5% and acidosis (bicarbonate < 20 mmol/L) in 37.5%. Treatment included benzodiazepines (72.5%), antipsychotics (30%), intubation (22.5%). Most (85%) patients were admitted to hospital and the mean length of stay in those admitted was 5.1 days.

A 23-year-old male, with a previous psychiatric history, was taken by ambulance to an ED in California, USA due to his bizarre behaviour, suicidal ideation and agitation following nasal insufflation of a white powder 'bath salt' from an unlabelled vial (Thornton, 2012). On presentation he was tachycardic (109 bpm) with a normal blood pressure (133/68 mmHg), diaphoretic with a normal temperature (36.9°C), had mydriasis and was experiencing visual, auditory and tactile hallucinations. Due to his agitation he had to be physically restrained and was given intravenous lorazepam (6mg) and droperidol (2.4mg) over 90 minutes. He remained sedated for five hours and on waking was no longer hallucinating or suicidal. Following psychiatric assessment, a diagnosis of schizoaffective disorder, bipolar disorder or psychosis secondary to drug use was suggested and he was discharged within eight hours of arrival with planned follow up. Analysis of the remaining product detected MDPV (143 µg/mg product), flephedrone (142 µg/mg product) and caffeine (102 µg/mg product). A urine immunoassay was positive for tetrahydrocannabinoids; serum and urine samples were subsequently analysed using LC-TOF/MS and MDPV (serum 186 ng/mL, urine 136 mg/L),

lephedrone (serum 346 ng/mL, urine 257 ng/mL) and caffeine (serum 387 ng/mL, urine 367 ng/mL) were detected.

A 37-year-old male, with a history of right nephrectomy due to trauma, was taken to an ED in Arizona, USA agitated and aggressive having ingested 'bath salts' four hours previously (Levine, 2012). Following ingestion, he had felt 'hot' and therefore sat in the bath for approximately four hours. On arrival he was agitated, tachycardic (153 bpm) and hyperthermic (39°C); his blood pressure was not reported. He was intubated to facilitate transfer to an ICU in a tertiary hospital, where on arrival his creatinine kinase was 90,168 IU/L. He was then extubated and he complained of diffuse mild myalgia, although his paraspinal muscle compartments were soft. Approximately 12 hours later creatinine kinase was 350,000 IU/L and his creatinine 451 µmol/L with a urine output of 345 mL in the previous 24 hours despite receiving 8545 mL of fluids. Haemodialysis was commenced and surgery undertaken where the deep paraspinal compartments of the lumbar spine were noted to be "tight" and necrotic muscle from the deep erectors was resected; further resection was required two days later. MDPV was detected in an admission urine sample along with caffeine, hydrocodone and propofol. The serum concentrations of MDPV seven and ten hours after seeking medical care were 120 ng/mL and 89 ng/mL respectively. The patient remained in renal failure on haemodialysis five months later; no detail on whether this resolved was presented in report which was only published in abstract form.

In a retrospective review of enquiries to the Carolinas Poison Centre in North Carolina, USA 409 human exposures were identified as having used 'bath salts' or 'plant food' and the following case report was included (Murphy, 2013). A 22-year-old male snorted a product he referred to as 'eight ballz' multiple times a day for five days prior to presentation at an ED. He was pacing continually, had not slept and developed twitching movements of his arms and tongue with auditory and visual hallucinations. On arrival he was tachycardic (140 bpm) with a blood pressure of 156/77 mmHg, respiration rate of 22 breaths/min and a temperature of 36.9°C. He had choreoathetoid movements of his arms and legs and writhing movements of his tongue; these abnormal movements were not controlled by 2 mg of IV lorazepam and he subsequently received 4 mg of IV lorazepam and 2.5 mg of IV haloperidol; his abnormal movements resolved after this therapy. He had a slightly raised creatinine kinase (990 IU/L) and white blood cell count ( $18.9 \times 10^9/L$ ). The patient's serum concentration of MDPV was 72 ng/mL and urine concentration 2400 ng/mL, analysis of the product confirmed the presence of MDPV and benzocaine.

There is a small series of four patients presenting to an ED in Missouri, USA in which all of whom had insufflated 'bath salts' (Spencer, 2011a). There was one fatality – this case is described in Section D1.2.5. Case 1 and 2: Two 32-year-old females presented to the ED soon after use with shortness of breath, palpitations and chest pressure. One patient had Parkinsonian-type features including resting tremor, bradykinesia and was also reported to have ECG changes (these were not further described in the report). Urine analysis of samples showed MDPV concentrations of 0.1mcg/mL and 0.52 mcg/mL. Case 3: A 35-year-old male presented with tachycardia and shortness of breath after use; on analysis a urine sample was positive for MDPV at a concentration of less than 0.05mcg/mL; no further clinical details were described.

In another small case series from Philadelphia, USA, documenting the use of ketamine as a novel drug for the management of agitated delirium in four paediatric patients, one case described the use of ketamine in the management of MDPV-related acute toxicity ;the other cases were primary psychiatric disorders (2) or "acid" (presumed LSD) ingestion (1) (Kopec, 2013). A 16-year-old male presented to hospital with erratic behaviour. He was tachycardic, agitated and aggressive towards the staff (full clinical details not provided). His violent behaviour continued despite him receiving 2.5mg intravenous lorazepam. He was then given 2.5mg/kg (200mg) intramuscular ketamine and was adequately sedated in six minutes; he received a further 2.5mg intravenous lorazepam when he woke. The patient subsequently admitted that he had ingested 'bath salts' and a urine sample confirmed the presence of MDPV (no concentration reported).

In a case series from Dayton, Ohio, USA (Marinetti, 2013) eight cases are described with analytical confirmation of MDPV use:

Case 1: A 23-year-old male was hospitalised following a motor vehicle accident; no further clinical detail is available. Blood MDPV was <10 ng/mL, THCCOOH was also detected.

Case 2: A 32-year-old male was arrested for driving under the influence of drugs; no further clinical detail is available. Blood MDPV was 29 ng/mL; lidocaine and oxycodone were also detected.

Case 3: A 30-year-old male was found collapsed in vehicle; no further clinical detail is available. Blood MDPV was 24 ng/mL; methyldone, clonazepam, 7-AMC, alprazolam and citalopram were also detected.

Case 4: An adult male was the victim of robbery facilitated by drugging; no further clinical detail is available. Blood MDPV was 52 ng/mL; lorazepam and temazepam were also detected.

Case 5: A 25-year-old male was in a vehicular homicide/assault; no further clinical detail is available. Blood MDPV was 6 ng/mL; no other drugs were reported to have been detected.

Case 6: A 25-year-old male was evading police; no further clinical detail is available. Blood MDPV was 368 ng/mL; tramadol and benzocaine were also detected.

Case 7: A 44-year-old male was stabbed during domestic dispute; no further clinical detail is available. Blood MDPV was 21 ng/mL.

Case 8: A 32-year-old female was arrested for driving under the influence of drugs; no further clinical detail is available. A urine sample was positive for MDPV and benzocaine was also detected.

Three cases of “hallucinatory delirium” were reported following the use of ‘bath salts’ in North Carolina, USA (Penders, 2011):

Case 1: A young adult male presented to ED hyperactive, angry and fearful about unknown individuals tapping on his window; no further clinical details were included. He agreed to in-patient treatment with oral risperidone and within two days was free from paranoid ideas. The patient was discharged on the fifth hospital day, having started to take ‘bath salts’ orally about six weeks prior to admission.

Case 2: A young adult female was admitted to the psychiatric unit of a community hospital believing that people were repeatedly invading her home, although her husband had video evidence that no one was there. He said she had been insufflating ‘bath salts’ (called ‘White Horse’) daily for two weeks prior to admission. The patient was fearful, inattentive with behavioural withdrawal; no further clinical details were included. She was treated with oral risperidone and by the third hospital day she was much improved.

Case 3: A middle-aged male was taken to an ED by the police; he contacted the police because he was concerned that people had entered his home and were shooting him with laser beams. He reported that he had been using ‘synthetic cocaine’ known as ‘White Horse’

for approximately the previous week. In ED he was hyperactive with visual and auditory hallucinations of threatening people; no further clinical details were included. He was admitted to a psychiatric unit where he was treated with oral haloperidol; by the third hospital day he was no longer paranoid or hallucinating.

On recovery each patient appeared to have memory distortion or lack of recall about their use of 'bath salts' prior to the development of their paranoid psychotic delirium. The contents of the packets of drugs used by all patients were analysed and found to contain only MDPV.

A 29-year-old man presented to an ED in Virginia, USA extremely agitated with diaphoresis, mydriasis, tachycardia (190bpm) hypotension (systolic blood pressure 50 mmHg) and hyperthermia (42.9°C, unknown route) having ingested 'White Girl', marketed as a 'super pure stain remover' (Troendle, 2013). He became increasingly unwell with myocardial infarction, rhabdomyolysis, hepatotoxicity, acute kidney injury and coagulopathy (results not specified). The patient was aggressively cooled and hydrated, received benzodiazepines, phenylephrine and haemodialysis. He was discharged with no sequelae after two weeks in hospital. The container of 'White Girl' used by the patient was obtained and on analysis the contents were found to be MDPV.

In a retrospective study of cases of exposures to 'bath salts' reported to the two poisons centres in Louisiana and Kentucky, USA between August 2010 and February 2011, 236 patients were identified (Spiller, 2011). The age range was 16 – 64 years (mean 29 years, SD 9.4) and 184 (78%) were male. Clinical features were not reported for individual agents, but for the whole group were reported to include: agitation (194, 82% of the patients); combative violent behaviour (134, 57%); tachycardia (132, 56%); hallucinations (94, 40%); paranoia (86, 36%); confusion (83, 34%); myoclonus (45, 19%); hypertension (41, 17%); chest pain (40, 17%); mydriasis (31, 13%); blurred vision (7, 3%); and catatonia (1, 1%). The mean heart rate for those with tachycardia was  $124 \pm 15.5$  (range 100 – 178) bpm. Twenty-two (9%) had elevated CK concentrations (mean reported CK in those with elevated CK was 1,825 IU/L, range 301 – 4,400 IU/L) and ten (4%) had hypokalaemia (mean potassium concentration in those with hypokalaemia was 2.9 mmol/L, range 2.1 – 3.4 mmol/L). 18 live patients had blood and/or urine samples that were analysed; 13 (out of 17 cases) had MDPV detected in blood/ serum at concentrations ranging from 24 – 241 ng/mL and three (out of five cases) had MDPV detected in urine at concentrations ranging from 34 – 1386 ng/mL (mean 856 ng/mL). In addition citalopram, diazepam, diphenhydramine, hydrocodone and zolpidem were detected in blood/serum and alprazolam, citalopram,

diphenhydramine, hydrocodone and methamphetamine in the urine. One fatality was reported in a 21-year-old following a self-inflicted gunshot after a delusional episode; MDPV blood concentration was 170 ng/mL and MDPV urine concentration 1400 ng/mL.

In February 2011 in Michigan, USA, the poisons centre was designated an agent of the state so it could receive case reports directly to enable mandatory reporting of cases of exposures to 'bath salts', considered to contain MDPV or mephedrone (Centers for Disease Control and Prevention, 2011). From 11<sup>th</sup> November 2010 to 31<sup>st</sup> March 2011, 35 patients presented to the ED following ingestion, inhalation or injection of 'bath salts' and the most common clinical features reported were agitation (n=23, 66%) tachycardia (22, 63%) and delusions/hallucinations (14, 40%). The age range was 20 – 55 years (median 28 years) and 19 (54%) were male. There was one fatality with biological confirmation of MDPV, marijuana and prescription drug use; MDPV was considered to be the primary factor contributing to this death. In response to the cluster of cases the proprietor of the shop from which the 'bath salts' were purchased was ordered to remove the products from sale; analysis of products was undertaken and MDPV was detected in a product that was being marketed as 'White Rush'.

#### ***Non-EU cases – not analytically confirmed***

A 37-year-old male was taken to an ED in Texas, USA three days after he had used three doses of 'bath salts' (presumed to contain MDPV) intravenously over a 15-hour period (Sutamewagul, 2014). His initial blood pressure was 103/66 mmHg, pulse 88 bpm, temperature 36.6°C and he had severe, uncontrolled choreoathetotic movements; he had acute kidney injury and rhabdomyolysis (creatinine 1344 μmol/L, creatine kinase 44,570 IU/L) and a raised white blood cell count (24,900/μL). He became disorientated and agitated and on his fourth day in hospital his blood pressure ranged from 170/112 to 104/36 mmHg, his maximum heart rate was 122 bpm and his temperature was 39.7°C. The patient remained in hospital for six days, with three days in ICU where he was treated supportively with intravenous fluids, haloperidol and lorazepam. An initial urine drug screen was negative for benzodiazepines, amphetamines, barbiturates, cannabinoids, cocaine and opiates; it is not clear what methodology was used for this screen and whether this would have picked up MDPV and/or other synthetic cathinones.

A 27-year-old male was brought to an ED in Tennessee, USA due to severe agitation but on arrival in the ED he was orientated and could provide a reliable history (Sivagnanam, 2013). He reported inhaling and injecting a mixture of MDPV and mephedrone a few hours prior to

presentation and on examination was tachycardic (117 bpm), hypotensive (90/60 mmHg) and pyrexial (38.4°C). He remained hypotensive the next day (blood pressure not specified) and cardiogenic shock was suspected and so an echocardiogram was performed which showed dilated cardiomyopathy with an ejection fraction (EF) of 15-20% and global hypokinesia. He was treated with intravenous norepinephrine for less than six hours and his mean arterial pressure was kept over 60 mmHg. The patient was treated conservatively and was discharged stable and asymptomatic on day five; a left heart catheterisation was negative for coronary heart disease. An echocardiogram repeated at a 20 week follow up showed an EF of 52% and significant improvement in hypokinesia.

Paranoid psychosis was reported in a couple who were taken to an ED in Pennsylvania, USA following protracted nasal insufflation of 'Powdered Rush', considered to contain MDPV (Antonowicz, 2011). The 27-year-old female and 32-year-old male called the police claiming an unknown person was breaking into their home; on arrival the police found them barricaded into their bedroom, convinced they were about to be killed but the danger was imagined. In ED the female was tachycardic (heart rate not specified), diaphoretic and still convinced she was in danger; she was transferred to an in-patient psychiatry unit on an involuntary commitment and oral risperidone was started. By the fifth hospital day she had no further delusions and was discharged on a tapering dose of risperidone. The male was tachycardic and hypertensive (heart rate and blood pressure not specified) in ED and observed there for 24 hours. The couple both had a history of opiate dependence and had insufflated 'Powdered Rush' for five to six days and had not slept for four days prior to admission.

In a case series of three patients presenting to an ED in North Carolina, USA (Penders, 2012) all developed excited delirium after using 'bath salts' presumed to contain MDPV; although there was no analysis of either biological samples or the bath salt product(s). Case 1: A 31-year-old had contacted the police as he was concerned that his home was being invaded by threatening individuals. He was brought to hospital confused and agitated requiring restraint. He was admitted to ICU, dehydrated and hallucinating with acute kidney failure, hyperkalaemia and rhabdomyolysis (results not included in the report). He was treated supportively with hydration and intramuscular haloperidol over three days and his symptoms resolved. Case 2: A 30-year-old male was taken to hospital agitated, paranoid and behaving violently, handcuffed by police. On arrival he was unresponsive and had to be intubated; he was in sinus rhythm with a heart rate of 150 bpm and a creatine kinase of 6599 IU/L. The patient was admitted to ICU with acute renal failure and rhabdomyolysis (peak creatine kinase 32,880 IU/L) and although he was extubated "within a few hours" he went on

to develop acute respiratory distress syndrome and had to be re-intubated. He was also very agitated with a “high tolerance to sedatives and analgesia”; his length of stay in ICU is not documented but he appears to have recovered. Case 3: A 26-year-old male was taken to hospital by the emergency services confused, anxious and diaphoretic; he had to be restrained and was handcuffed. On arrival his heart rate was 170bpm, his temperature 41°C and he was admitted to ICU with a creatine kinase of 6599 IU/L. No further clinical information is provided but from the information provided it appears that the patient recovered; it was his second episode of hospitalisation after using ‘bath salts’.

A 50-year-old male in Oregon, USA, with a history of methamphetamine dependence, required three psychiatric in-patient admissions in a 15-day period following the use of ‘bath salts’ (assumed to contain MDPV); he injected these ‘bath salts’ intravenously at an estimated dose of one quarter to one half a gram daily (Lajoie, 2012). He would typically present agitated and fearful of attacks by ‘gangbangers’, with tachycardia, chest pain, psychosis; in addition, on the third presentation he had lacerations which required suturing. His psychotic agitation resolved with olanzapine and lorazepam and after his third hospitalisation he agreed to a 12-month treatment programme for his substance use disorder. No further clinical details were available in the report.

In a descriptive account of the use of ‘bath salts’ by a 33-year-old male in Michigan USA (Winder, 2013), the patient reported that smoking or insufflating products stated to contain MDPV resulted in “more attenuated, subtle high with realistic auditory and visual hallucinations”. However as these products were more expensive than those containing mephedrone he could not afford to use them; after two months of using the ‘bath salts’ that were assumed to contain MDPV he joined a substance use disorder out-patient treatment programme.

A 26-year-old female was admitted to hospital in Delaware, USA with suicidal ideation; she was found confused in the middle of a street suffering auditory hallucinations urging her to harm herself; no other clinical features were reported (Gallucci, 2011). The patient was treated with risperidone and her symptoms resolved within 48 – 72 hours. Panic attacks and auditory hallucinations had started about six weeks before the patient’s presentation when she started using ‘bath salts’ presumed to contain MDPV and she had been insufflating about half a gram per week.

A 30 year-old male was taken to an ED in Missouri, USA following suicidal threats (Stoica, 2013). The patient described hearing voices and believed people were trying to steal from

him; he had been injecting 'bath salts', presumed to contain MDPV, mixed with water three to four days prior to presentation. The patient had a long history of substance misuse and his past psychiatric history was uncertain; on admission to hospital he was manipulative, asked for medications and tried to negotiate the doses with physicians whilst he denied hallucinations and his thought processes appeared logical. He was treated with valproic acid and trazodone and discharged after three days with a diagnosis of resolved substance-induced psychotic disorder.

In a report from North Carolina, USA, Electroconvulsive therapy (ECT) was used to treat persistent psychosis in a 26-year old female who had insufflated 'bath salts', presumed to contain MDPV, for several months (Penders, 2013). The patient developed distressing visual hallucinations five months after her initial use of 'bath salts'. She had no response to risperidone and haloperidol and a minimal improvement with lurasidone; she also on citalopram and trazodone. The patient was admitted 13 months after she began using 'bath salts' and after two ECT treatments reported a significant reduction in visual hallucinations. After two further ECT treatments she was discharged to out-patient care having reported improved mood and less social anxiety. The patient did not return for further out-patient ECT but eight months later was reported to continue to have occasional hallucinations but diminished psychotic symptoms.

In a retrospective search of enquiries to the Carolinas Poison Centre in North Carolina, USA 409 human exposures were identified as having used 'bath salts' or 'plant food' between January 2010 and December 2011 (Murphy, 2013). The most commonly reported clinical features were tachycardia (n= 218, 53.3%), agitation/irritability (109, 50.4%) and hallucinations/delusions (109, 26.7%). The age was recorded in 380 cases, the mean was 28.8 years (range 21 months – 68 years) and median 27 years.

In Missouri, USA the poison centre received 116 enquiries about 'bath salts', assumed to contain MDPV, in the first four months of 2011 compared to a total of 22 enquiries about 'bath salts' in 2010; no clinical details were provided and no analysis of either drug product or biological samples was carried out to confirm that these 'bath salt' products contained MDPV (Spencer, 2011).

### **D1.2.3. MDPV associated deaths**

There have been a total of 108 deaths associated with MDPV reported to the EU Early Warning System by 8 Member States and Norway in which MDPV has been detected in post-mortem biological samples and/or implicated in the cause of death: Austria (1), Finland

(40), France (1), Hungary (1), Ireland (8), Poland (3), Sweden (21), United Kingdom (32) and Norway (1). In addition there have been reports in the scientific literature of deaths from EU countries and non-EU countries. The deaths reported in these scientific papers, in some cases may have been already reported to the EU Early Warning System and are presented here in order to provide more detailed information including contextual information, where available. The non-EU cases include 33 cases from the US and one case from Japan in which MDPV has been detected in biological samples and/or implicated in the cause of death.

The data on deaths associated with MDPV need, like all data on drug-associated deaths, to be interpreted carefully. Detection of a drug in post-mortem samples does not necessarily mean that this drug is responsible for, or has contributed to, death. It should be noted that in some of these deaths it is likely that other drugs and/or other medical conditions or trauma may have contributed to and/or been responsible for death. There is also the possibility that the number of deaths associated with MDPV may be under-reported because MDPV was not screened for in post-mortem samples, or samples were not taken for toxicological analysis.

### ***Deaths reported to the EU Early Warning System***

#### *Austria*

Austria reported one death which occurred in January 2012. The case involved a 'young man' who died from butylone (bk-MBDB) overdose in combination with MDPV, methylone and 4-MEC. No further details were provided.

#### *Finland*

Finland reported 40 deaths which occurred between September 2009 and August 2013. The cases were all analytically confirmed and where the concentration of MDPV was reported (20 cases) it ranged from 20-4800 mg/mL in blood; in all but one case, up to seven other substances were detected. In fourteen cases, five or more substances were detected in addition to MDPV. The most frequently encountered other substances detected were diazepam (22 cases), amphetamine (14), buprenorphine (14), temazepam (9), alprazolam (8), ethanol (7), morphine (3) and pregabalin (3). Causes of death reported were accidental poisoning (22 cases), suicidal poisoning (4), suicide resulting from crushing injuries (2), suicide by hanging (2), suicide by carbon monoxide poisoning (1), unspecified intoxication (1), unspecified death and cirrhosis of liver (1), accidental injury to thoracic aorta (1),

accidental death due to multiple rib fractures (1), infective myocarditis disease (1) and homicide (1). The cause of death was not yet registered in three cases.

#### France

France reported one death that occurred in October 2012. The cause of death was drowning. MDPV was present at a concentration of 106 µg/L (blood) and 760 µg/L (urine). Other drugs detected were PVP (10) (blood 40 µg/L; urine 295 µg/L), pentedrone (blood 33 µg/L; urine 110 µg/L), hydroxyzine (blood 194 µg/L), nordiazepam (blood 47 µg/L), oxazepam (blood 8 µg/L), cannabinoic acid (blood 15.7 µg/L) and ethanol (blood 0.3 g/L). No further details were provided.

#### Hungary

Hungary reported one death from November 2011 in which MDPV was analytically confirmed. The case was noted to be an “Indirect death’ (f. e. fatal traffic accidents)’. No further details were provided.

#### Ireland

Ireland reported eight analytically confirmed deaths associated with MDPV. There were four deaths in the period from 2010 to 2011, where it was stated that MDPV was the ‘drug implicated in the cause of death by coroner’. A further 4 deaths were reported for 2012, where it was stated that MDPV was ‘not necessarily the drug implicated in the cause of death by coroner’. No further information was provided on these eight cases.

#### Poland

Poland reported three deaths associated with MDPV. The first death was in September 2010 and the reported cause of death was ‘metabolic dysfunction’ caused by MDPV. The concentration of MDPV determined in blood was 430 ng/mL and ephedrine was also detected at a concentration of 324 ng/mL. No further details were available. The second and third cases were reported from 2011. One of the cases involved a road traffic collision where one driver suffered severe injuries, resulting in his death. During the police investigation, packages of white powders, called ‘Ivory Speed’ and ‘Exclusive Dust’ were found (Adamowicz et al., 2013). MDPV was detected in blood at a concentration of 38 ng/mL and buphedrone was also detected at a concentration of 127 ng/mL. The third case involved a man with a history of drug addiction who was found unresponsive after a night of partying. A witness reported that he had taken a product called ‘Speedway’ while at the party. The post

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<sup>(10)</sup> Pyrrolidinovalerophenone

mortem examination showed emaciation, external hydrocephalus and atherosclerosis. The man also suffered from human immunodeficiency virus (HIV) infection (Adamowicz et al., 2013). MDPV was detected in blood at a concentration of 17 ng/mL and in addition clonazepam (1.2 ng/mL) and 7-aminoclonazepam (96 ng/mL) were also detected.

#### Sweden

Sweden reported twenty-one deaths: 3 in 2010, 3 in 2011, 9 in 2012 and 6 in 2013. Brief comments were reported as follows: in 2010 the deaths were intoxications involving several substances (not further described); in 2011 none of the three deaths related only to MDPV; in 2012 there were several accidents, death by hanging and intoxications with several drugs (not further described); and in 2013 there was one car accident and intoxications with several drugs (not further described).

#### United Kingdom

The United Kingdom reported 32 deaths that occurred between January 2010 and an unspecified date in 2013 (12 in 2010, 8 in 2011, 12 in 2012 and 1 in 2013).

Where reported, the causes of death were noted to be hanging (7 cases), cardiac-related causes (11) (5), drug toxicity (4), drowning (2), carbon monoxide poisoning (2), asphyxia (1), multiple injuries (suicide) (2), hypovolemic shock due to laceration of left forearm associated with partial transection of cephalic vein (1). In the remaining cases the cause was either unascertained or not specified. In the cases of drug toxicity, MDPV was normally present with other drugs. Where reported, the most common other substances present were mephedrone (9 cases), 4-fluoromethcathinone (7), cocaine (4), amphetamine (4) and MDMA (3), although a range of other controlled drugs and medicines were also detected. MDPV was not the sole cause noted in any of the cases and was specifically implicated as a contributory factor in nine of the cases.

#### Norway

Norway reported one death in 2012 in which MDPV was detected during the toxicological examination of blood. The cause of death in this case was not reported and no further information was provided.

Table 7 below summarises the deaths in which there was analytical confirmation of MDPV in post-mortem biological samples and that were reported to the EU Early Warning System.

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<sup>(11)</sup> Specifically: heart attack (1 case), cardiac arrest (1), cardiac failure (1), coronary artery disease (1) and ischemic heart disease (1).

Table 7: Deaths Reported to EU Early Warning System and included in the Annex to the EMCDDA Joint Report on MDPV [EMCDDA Europol Joint Report Annex 2]

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
1	Austria	Jan 2012 (M)	Not specified	+	butylone (+) methylone (+) 4-methylethcathinone (+) cocaine (+)	Butylone (bk-MBDB) overdose in combination with methylone, 4-methylethcathinone and cocaine
2	Finland*	Sept 2009	Urine  Blood	+ (urine)	Blood: olanzapine (0.7 mg/L) methadone (0.4 mg/L) chlorprothixen (0.1 mg/L) diazepam (0.03 mg/L) amphetamine (8.4 mg/L)	Accidental death, poisoning by narcotics
3	Finland	Sept 2009	Blood	40 mg/mL	ethanol (1.5 g/kg) buprenorphine (0.001 mg/L)	Accidental death, poisoning by narcotics

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
4	Finland	Oct 2009	Blood	+	diazepam (0.1 mg/L) temazepam (0.3 mg/L) morphine (0.6 mg/L) amphetamine (0.88 mg/L) THC ( <sup>12</sup> ) (<LOQ)	Accidental death, poisoning by drugs or medicaments
5	Finland	Oct 2009	Urine  Blood	+ (urine)	Blood: alprazolam (0.1 mg/L) tramadol (1.4 mg/L) methadone (0.2 mg/L) diazepam (0.02 mg/L)	Accidental death, poisoning by drugs or medicaments
6	Finland	Oct 2009	Blood	840 mg/mL (estimated value)	levomepromazine (2.4 mg/L) trimipramine (0.3 mg/L) oxycodone (2.2 mg/L)	Suicide, poisoning by drugs or medicaments

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<sup>12</sup>Δ9-tetrahydrocannabinol, the main psychoactive substance in cannabis

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
7	Finland	Oct 2009	Urine  Blood	+ (urine)	Blood: zolpidem (0.4 mg/L) citalopram (0.9 mg/L) oxazepam (1.7 mg/L) olanzapine (0.2 mg/L) propranolol (2.1 mg/L)	Suicide, propranolol poisoning
8	Finland	Feb 2010	Blood	4800 mg/mL	Blood: morphine (0.08 mg/L) amphetamine (1.6 mg/L)	Homicide, multiple injuries of neck
9	Finland	Feb 2010	Urine	+	temazepam (0.9 mg/L) diazepam (0.4 mg/L) amphetamine (7.3 mg/L)	Suicide Hanging
10	Finland	Feb 2010	Blood	1800 mg/mL	methadone (1.3 mg/L) temazepam (0.3 mg/L) diazepam (0.1 mg/L) amphetamine (0.06 mg/L) buprenorphine (0.0044 mg/L)	Accidental death, poisoning by drugs or medicaments

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
11	Finland	Feb 2010	Urine  Blood	+ (urine)	Blood: tramadol (5.3 mg/L) valproate (19 mg/L) THC ( <sup>13</sup> ) (0.0061 mg/L)	Accidental death, poisoning by drugs or medicaments
12	Finland	Feb 2010	Blood	70 mg/mL	ethanol (0.22 g/kg) amphetamine (0.16 mg/L)	Accidental death, Injury of thoracic aorta
13	Finland	Feb 2010	Blood	+	metoclopramide (0.3 mg/L) diazepam (0.1 mg/L) oxycodone (0.13 mg/L)	Accidental death, poisoning by drugs or medicaments
14	Finland	Feb 2010	Blood	+	None reported	Disease, infective myocarditis

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<sup>13</sup>Δ9-tetrahydrocannabinol, the main psychoactive substance in cannabis

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
15	Finland	Mar 2010	Blood	1200 mg/mL	ethanol (1.3 g/kg) venlafaxine (8.7 mg/L) levomepromazine (0.4 mg/L) mirtazapine (0.3 mg/L) nordiazepam (0.05 mg/L) codeine (0.53 mg/L) buprenorphine )0.0032 mg/L)	Accidental death, poisoning by drugs or medicaments
16	Finland	Mar 2010	Blood	+	ethanol (0.36 g/kg) venlafaxine (0.9 mg/L) alprazolam (0.05 mg/L) diazepam (0.34 mg/L) buprenorphine (0.0076 mg/L)	Accidental death, poisoning by drugs or medicaments
17	Finland	Apr 2010	Blood	60 mg/mL	oxazepam (0.46 mg/L) temazepam (0.096 mg/L) nordiazepam (0.024 mg/L) amphetamine (0.11 mg/L) buprenorphine (0.70 mg/L)	Accidental death, poisoning by drugs or medicaments

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
18	Finland	Jun 2010	Liver  Muscle	+ (liver)	Muscle: ethanol (0.51 g/kg)	Suicide, hanging
19	Finland	Jun 2010	Blood	40 mg/mL	nordiazepam (0.12 mg/L) morphine (0.15 mg/L) codeine (0.02 mg/L) amphetamine (0.20 mg/L) oxycodone (<LOQ) THC ( <sup>14</sup> ) (+)	Accidental death, poisoning by narcotics
20	Finland	Sep 2010	Blood	20 mg/mL	methadone (0.3 mg/L) temazepam (0.13 mg/L) oxazepam (0.15 mg/L) nordiazepam (0.026 mg/L) amphetamine (+)	Accidental death, poisoning by narcotics

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<sup>14</sup>Δ9-tetrahydrocannabinol, the main psychoactive substance in cannabis

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
21	Finland	Oct 2010	Blood	530 mg/mL	diazepam (0.033 mg/L) DPMP <sup>(15)</sup> (+) methydone (+)	Accidental death, poisoning by narcotics
22	Finland	Feb 2011	Hair  Blood	+ (hair)	Blood : amitriptyline (4.3 mg/L) hydroxyzine (1.1 mg/L) citalopram (0.7 mg/L) perfenazine (0.21 mg/L)	Suicide, poisoning by drugs or medicaments
23	Finland	Feb 2011	Urine  Blood	+ (urine)	Blood: alprazolam (0.018 mg/L) methadone (0.4 mg/L) diazepam (0.13 mg/L)	Disease, other and unspecified cirrhosis of liver
24	Finland	Apr 2011	Blood	+	alprazolam (0.44 mg/L ) clonaxepam (0.12 mg/L) amphetamine (0.42 mg/L) buprenorphine (0.00042 mg/L)	Suicide, crushing injury of skull

<sup>15</sup> (Diphenylmethyl)piperidine.

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
25	Finland	May 2011	Hair  Blood	+ (hair)	Coronary blood: temazepam (1.1 mg/L) quetiapine (0.3 mg/L) methadone (0.2 mg/L) diazepam (0.029 mg/L)	Accidental death, poisoning by drugs
26	Finland	May 2011	Hair  Liver	+ (hair)	Liver: temazepam (+) methadone (+) quetiapine (+)	Accidental death, poisoning by drugs  This case has a connection to case 25. The two deceased were found together
27	Finland	May 2011	Blood	110 mg/mL	nordiazepam (0.20 mg/L)	Suicide, toxic effect of carbon monoxide (COHb <sup>(16)</sup> 71% )
28	Finland	Jun 2011	Urine	+	diazepam (0.30 mg/L) buprenorphine (0.0037 mg/L) alprazolam (+) clonazepam (+)	Suicide, crushing injuries involving other combinations of body regions

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<sup>16</sup> Carboxyhaemoglobin

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
29	Finland	Jul 2011	Blood	30 mg/mL	methadone (0.6 mg/L) temazepam 0.22 mg/L diazepam (0.15 mg/L) buprenorphine (0.0017 mg/L)	Accidental death, poisoning by drugs or medicaments
30	Finland	Oct 2011	Blood	170 mg/mL	2,3-DMMC ( <sup>17</sup> ) (0.01 mg/L) amphetamine (1.8 mg/L)	Accidental death, poisoning by narcotics
31	Finland	Oct 2011	Blood	190 mg/mL	methadone (1.1 mg/L) mirtazapine (0.07 mg/L) oxazepam (0.077 mg/L) amphetamine (0.24 mg/L) pregabalin (3.7 mg/L)	Accidental death, poisoning by drugs or medicaments
32	Finland	Jan 2012	Hair	+	buprenorphine (+) verapamil (+) propofol (+) diazepam (+)	Accidental death, poisoning by narcotics

<sup>17</sup> 2,3-dimethylmethcathinone

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
33	Finland	Apr 2012	Blood	130 mg/mL	fentanyl (0.0097 mg/L) clonazepam (0.005 mg/L)	Accidental death, poisoning by narcotics
34	Finland	Jul 2012	Blood	1700 mg/mL	olanzapine (0.3 mg/L) alprazolam (0.005 mg/L) GHB ( <sup>18</sup> ) (1500 mg/L)	Accidental death, poisoning by narcotics
35	Finland	Jul 2012	Blood	80 mg/mL	ethanol (0.23 g/kg) isopropylalcohol (0.1 g/kg) diazepam (0.048 mg/L) buprenorphine (0.0079 mg/L)	Accidental death, poisoning by narcotics
36	Finland	Jul 2012	Blood  Vitreous humor	590 mg/mL  (blood)	Blood:  $\alpha$ -PVP ( <sup>19</sup> ) (0.60 mg/L) amphetamine (1.6 mg/L)  Vitreous humor: ketamine (+)	Accidental death, multiple fractures of ribs

<sup>18</sup> Gammahydroxybutyrate

<sup>19</sup>  $\alpha$ -Pyrrolidinovalerophenone

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
37	Finland	Nov 2012	Urine  Blood	+ (urine)	Blood: diazepam (0.064 mg/L) buprenorphine (0.00066 mg/L) pregabalin (4.4 mg/L) amphetamine (< LOQ)	Disease, intoxication -psychoactive substances
38	Finland	Dec 2012	Blood	30 mg/mL	doxepine (1.5 mg/L) citalopram (1.9 mg/L) quetiapine (1.3 mg/L) $\alpha$ -PVP (0.070 mg/L) buprenorphine (0.029 mg/L) temazepam (<LOQ)	Suicide, doxepin poisoning
39	Finland	Jan 2013	Urine	+	ethanol (1.6 g/kg) alprazolam (0.005 g/L) diazepam (0.45 g/L) codeine (0.15 g/L) buprenorphine )0.0006 g/L)	Cause of death not yet registered
40	Finland	Apr 2013	Blood	30 mg/mL	trimethoprim (1.6 mg/L)	Cause of death not yet registered

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
41	Finland	Aug 2013	Urine	+	alprazolam (0.044 mg/L) diazepam (0.092 mg/L) THC <sup>20</sup> (0.0051 mg/L) buprenorphine (0.0012 mg/L) fentanyl (0.0082 mg/L) pregabalin (4.0 mg/L)	Cause of death not yet registered

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<sup>20</sup> $\Delta$ 9-tetrahydrocannabinol, the main psychoactive substance in cannabis

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
42	France	Oct 2012	Blood  Urine	106 µg/L (blood) 760 µg/L (urine)	PVP (40 µg/L in blood) (295 µg/L in urine) pentedrone (33 µg/L in blood) (110 µg/L in urine) hydroxyzine (194 µg/L in blood) nordazepam (47 µg/L in blood) oxazepam (8 µg/L in blood) cannabinoic acid (15.7 µg/L in blood) ethanol (0.3 g/L in blood)	Cause of death was drowning
43	Hungary	Nov 2011	Not specified	+	Not reported	Noted to be in 'Indirect death' (f. e. fatal traffic accidents)
44-47	Ireland	Jan 2010 – Dec 2011	Not specified	+	Not reported	'Drug implicated in the cause of death by coroner'

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
48-51	Ireland	Jan 2012 – Dec 2012	Not specified	+	Not reported	MDPV 'Not necessarily implicated in the cause of death' (by coroner)
52	Norway	2012	Blood	+	None reported	Cause of death not reported.
53	Poland	Sep 2010	Blood	430 ng/mL	ephedrine (324 ng/mL)	Cause of death: 'metabolic dysfunction' caused by MDPV
54	Poland	2011	Blood	38 ng/mL	buphedrone (127 ng/mL)	Indirect death: car accident. During inspection of the deceased driver, the police revealed packages of white powders, with the names Ivory Speed and Exclusive Dust and a note 'collector's product for field stone rinsing' [Adamowicz et al., 2013]
55	Poland	2011	Blood	17 ng/mL	clonazepam (1.2 ng/mL) 7-aminoclonazepam (96 ng/mL)	Death after a night of partying, a witness testified that the man had taken a product called Speedway.  The autopsy showed emaciation, external hydrocephalus and atherosclerosis. Deceased with a history of drug addiction, HIV+ [Adamowicz et. all 2013]

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
56-58	Sweden	2010	Not specified	+	None reported	3 cases The deaths were intoxications involving several substances (not further described)
59-61	Sweden	2011	Not specified	+	None reported	3 cases None of the 3 deaths related only to MDPV
62-70	Sweden	2012	Not specified	+	None reported	9 cases There were several accidents, death by hanging and intoxications with several drugs (not further described)
71-76	Sweden	2013	Not specified	+	None reported	6 cases There was one car accident and intoxications with several drugs (not further described)

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
77-78	United Kingdom	Jan-Dec 2010	Blood  Urine	+	<u>Case 1</u> fluoromethcathinone (+) mirtazapine(+) olanzapine (+) amphetamine (+)  <u>Case 2</u> fluoromethcathinone (+) ibuprofen(+) 	2 cases  Case 1 – hit by train Case 2 – bag over head

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
79-81	United Kingdom	Jan-Dec 2011	Blood  Urine	+	<u>Case 1</u> ketamine (+)  <u>Case 2</u> quetiapine (+)  <u>Case 3</u> fluoromethcathinone (+) MDMA <sup>(21)</sup> (+) methyone (+) MDAI <sup>(22)</sup> (+) 5-IAI <sup>(23)</sup> (+) methoxetamine (+) AMT <sup>(24)</sup> (+)	3 cases  Case 1 – hanging Case 2 – no circumstances reported Case 3 – found at home

<sup>21</sup> Methylenedioxymethylamphetamine (commonly known as 'ecstasy')

<sup>22</sup> 3,4-Methylenedioxyaminoindane

<sup>23</sup> 5-Iodoaminoindane

<sup>24</sup> Alpha-methyltryptamine

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
82-91	United Kingdom **	Jan-Dec 2012	Blood  Urine	+	None reported	<p>11 cases</p> <ul style="list-style-type: none"> <li>6 cases of hanging</li> <li>1 case murder victim</li> <li>1 case murder suspect</li> <li>2 cases found dead at home</li> <li>1 case found in a canal</li> <li>1 case found dead in a car (carbon monoxide poisoning)</li> </ul> <p>(One of the cases is a duplicate, although it is not certain which one, hence this group is counted as 11 cases – see death 99)</p>
92	United Kingdom	Jan-Dec 2013	Blood  Urine	+	methadone (+) morphine (+) mirtazapine (+) diazepam (+) zopiclone (+) codeine (+)	Methadone intoxication

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
93	United Kingdom	Jan 2010 (M, 57)	Blood	0.01 mg/L	N-desalkyl-4-methylmethcathinone (+)	Coronary artery disease in the presence of MDPV.  Coroner's verdict: open verdict/unascertained.
94	United Kingdom	Feb 2010 (M, 34)	Blood  Gastric	+ (blood)	fentanyl (24 ng/mL in blood) (37 µg in gastric sample) cannabis (+)	Fentanyl toxicity implicated.  Coroner's verdict: open verdict/unascertained.
96	United Kingdom	Jul 2010 (M, 26)	Blood  Gastric	+ (blood) + (gastric)	pyrovalerone (+ in blood) (+ in gastric sample) THC-acid <sup>(25)</sup> (+ in blood) lignocaine (+ in antemortem blood) amiodarone (+ blood, therapeutic use suspected)	Cause of hypovolaemic shock, laceration of left forearm associated with partial transection of cephalic vein.  Toxic effects of pyrovalerone and MDPV. Coroner's verdict accidental / misadventure.

<sup>25</sup>Δ9-tetrahydrocannabinolic acid, a breakdown product of Δ9-tetrahydrocannabinol, the main psychoactive substance in cannabis

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
97	United Kingdom	Apr 2010 (F, 45)	Blood	+	+) GBL <sup>(26)</sup> (+) methyldone (+)	Mixed drug toxicity. Implicated: methedrone, GBL and methyldone. Cause of death non-dependent abuse of drugs.  Coroner's verdict: open verdict/unascertained.
98	United Kingdom **	Nov 2010 (F, 29)	Blood  Urine	<LOD (blood)  + (urine)	alcohol (63 mg/100mL in blood) (118 mg/100mL in urine)  mephedrone (<LOD <sup>(27)</sup> in matrix unknown) cocaine (+ in urine) levamisole (+ in urine) quinine (+ in urine)	Multiple injuries. Had taken a variety of substances and alcohol.  Coroner's verdict: suicide. Implicated drugs alcohol, mephedrone and MDPV

<sup>26</sup> Gammabutyrolactone

<sup>27</sup> Limit of detection – the lowest amount that can be detected by the method used.

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
99	United Kingdom	Jun 2010 (M, 39)	Blood	0.13µg/L	alcohol (175 mg/100mL) citalopram (0.12 mg/L) diazepam (85 µg/L) temazepam (99 µg/L)	Carbon monoxide poisoning, alcoholic liver disease. Implicated- 4-fluoromethcathinone and mephedrone  Coroner's verdict: suicide.
100	United Kingdom	Apr 2010 (M, 29)	Blood  Urine	0.11 mg/L	4-fluoromethcathinone (0.21 mg/L in blood) (23.62 mg/mL in urine) mephedrone (<0.05 mg/L in urine) ibuprofen (+ blood)	Asphyxia. Implicated: 4-fluoromethcathinone and mephedrone.  Coroner's verdict: accidental/misadventure.

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
101	United Kingdom	Jun 2010 (M, 38)	Blood  Urine	0.41 mg/L (blood)  0.75 mg/L (urine)	amphetamine (+ blood) mephedrone (0.05 mg/L in blood) (0.05 mg/L in urine) 4-fluoromethcathinone (0.55 mg/L in blood) (6.51 mg/L in urine)	Cardiac arrest caused by either multiple drug toxicity or excited delirium  Coroner's verdict: accidental/misadventure
102	United Kingdom	Jun 2010 (M, 33)	Unspecified	1.5 mg/L	alcohol (57 mg/100 mL) benzodiazepine (7.4 mg/L) TFMPP <sup>(28)</sup> (1.9 mg/L) lignocaine (+)	Cause of death unascertained.  Coroner's verdict: open verdict/unascertained.

<sup>28</sup> Trifluoromethylphenylpiperazine

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
103	United Kingdom	Feb 2011 (M, 37)	Blood  Nasal swab	+ (blood) + (nasal swab) both low level	amphetamine (0.04 µg/mL in blood) (+ on nasal swab) lignocaine (+ on nasal swab) benzocaine (+ on nasal swab) sertraline (+ in blood) diazepam (+ in blood)	Hanging.  Coroner's verdict: open verdict/unascertained.
104	United Kingdom	Apr 2011 (M, 24)	Blood	1.63 mg/L	MDMA <sup>(29)</sup> (7460 µg/L) cocaine (929 µg/L) benzoylecgonine (1.89 mg/L) mephedrone (0.17 mg/mL) diazepam (3284 µg/L) nordiazepam (1138 µg/L)	Drowning and multiple drug overdose. Implicated- MDMA, cocaine and mephedrone  Coroner's verdict: accidental/misadventure

<sup>29</sup> Methylenedioxymethylamphetamine (commonly known as 'ecstasy')

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
105	United Kingdom**	May 2011 (M, 53)	Blood  Urine	+	MDPBP <sup>(30)</sup> (1.55 mg/l in blood), (94.2 mg/l in urine) pentylone (0.34 mg/l in blood) (29.4 mg/l in urine) mephedrone (+ in matrix unknown) cocaine (+ in urine)	Cause of death: ischemic heart disease and illicit use of cathinones. Implicated drugs: mephedrone, MDPBP and pentylone  Coroner's verdict accidental/misadventure
106	United Kingdom	Dec 2011 (M, 56)	Not specified	+	MDMA <sup>(21)</sup> (+) cocaine (+) cathinone (+)	MDMA, cocaine, MDPV and methylmethcathinone toxicity. Implicated: ecstasy, cocaine and cathinones  Coroner's verdict: open verdict/unascertained
107	United Kingdom	Aug 2011 (M, 27)	Unspecified	+	None reported	MDPV and heart attack.  Coroner's verdict: open verdict/unascertained

<sup>30</sup> 3,4-Methylenedioxy- $\alpha$ -pyrrolidinobutyrophenone

	Country	Date	Biological sample	MDPV result	Results of toxicological analysis for other substances	Notes
108	United Kingdom **	Apr 2012 (M, 31)	Blood	<0.1 mg/L	AMT ( <sup>31</sup> ) (0.89 mg/L)	Cause of death cardiac failure, MDPV and AMT drug toxicity plus left ventricular hypertrophy and obesity.  Coroners' verdict: accidental/misadventure

In this table LOD is the limit of detection and LOQ is the limit of quantification.

\* All cases in Finland are from a medico-legal source and include suspect and unnatural deaths, non-related to poisoning.

\*\* The United Kingdom reported data on fatal intoxications from two separate sources, ROAR Forensics and the national programme for Substance Abuse Deaths (np-SAD). It should be noted that based on case specific details, case 108 is believed to be a duplicate of one of the cases reported in the aggregated data from 2012 and has been counted once only.

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<sup>31</sup> Alpha-methyltryptamine

### ***Case reports published in the literature***

There is the possibility that some of the cases noted below refer to cases reported by national focal points and are already detailed above. The information is presented here in order to provide more detailed information including contextual information, where available.

### ***EU cases***

#### **Finland**

Brief details are included in a study from Finland of the results of post-mortem toxicology screening of 7105 deaths in 2010; these comprised approximately 14% of all deaths in Finland in 2010 (Kriikku, 2011b). MDPV was found in blood and/or urine in 13 cases, all of these were male and the median (range) age was 38 (20 – 47) years. The median (range) MDPV concentration in post-mortem blood in the 8 cases in which quantitative analysis was carried out was 0.13 (0.02 – 4.8) mg/L. MDPV was not the “sole cause of death in any of these cases”; no clinical information was provided, or information on other drugs detected, or the causes of death for these cases.

#### **Hungary**

In 571 autopsies performed in South-East Hungary, MDPV was detected in two cases (Tóth, 2013). A 19 year old male died following a high speed car crash where his car left the road and hit a building. Post mortem MDPV concentrations were 22.2 ng/mL in blood and 20.1 ng/mL in urine. Other substances detected included alcohol (blood 0.16 g/L, urine 0.31 g/L), THC (urine 10.2 ng/mL), 4-FMC (urine 13.8 ng/mL), 3,4-DMMC (blood 53.2 ng/mL, urine 199 ng/mL) and amphetamine (urine 13.7 ng/mL). In the second case, a 22 year old male died after jumping from a window on the 9<sup>th</sup> floor of a student hostel. MDPV was detected at post mortem in urine (44 ng/mL) only; other substances detected included alcohol (urine 0.2 g/L), codeine (blood 16.6 ng/mL, urine 222 ng/mL) and amphetamine (blood 25 ng/mL, urine 2942 ng/mL).

#### **Poland**

There has been a study from Poland of the detection of MDPV, along with other drugs, in two fatalities (Adamowicz, 2013).

Case 1: A male driver (age not reported) died when his car crashed into a truck. Several packages of Ivory Speed and Exclusive Dust were found on him during external inspection. Post mortem blood analysis was positive for MDPV (38 ng/mL) and buphedrone (127 ng/mL).

Case 2: A male with underlying drug addiction was found dead after a night of partying, where he was reported to have used a product called “Speedway”. Post mortem blood analysis was positive for MDPV (17 ng/mL), clonazepam (1.2 ng/mL) and 7-aminoclonazepam (96 ng/mL).

### ***Non-EU cases***

In the first reported death attributed to MDPV (Murray, 2012) from North Carolina, USA, a 40-year-old man, with a history of bipolar disorder and previous cocaine abuse, insufflated and injected ‘bath salts’. Soon afterwards he became aggressive, delusional and removed all his clothes and ran outside; the police were called and the patient remained aggressive and was physically restrained as he was taken to hospital. 2mg intramuscular lorazepam failed to sedate the patient and his observations were blood pressure 131/72 mmHg, a respiratory rate of 24 breaths/min and heart rate 164 bpm with widened QTc interval and peaked T waves on his ECG. Within five minutes of his arrival in hospital he developed bradycardia and suffered a cardiac arrest with pulseless electrical activity (PEA). Standard advanced cardiac life support measures were initiated and after 30 minutes of resuscitation, return of spontaneous circulation was achieved. Immediately following resuscitation the rectal temperature was 40.8°C, blood pressure 70/32 mmHg, serum potassium 7.4 mmol/L and creatinine 265 µmol/L; a repeat ECG showed sinus bradycardia with a rate of 56 bpm with peaked T waves and a prolonged QRS duration of 240 msec (the T-wave and QRS changes are consistent with hyperkalemia). The patient was transferred to a tertiary hospital where, despite intensive supportive care and haemodialysis started 17 hours post presentation, he developed coagulopathy (INR > 9.3), rhabdomyolysis (creatinine kinase 75,952 IU/L), oliguric renal failure (creatinine 377 µmol/L) and hepatic failure (ALT 6,623 IU/L). The patient also developed malena with anaemia (haemoglobin 63 g/L) and thrombocytopenia (platelets  $11 \times 10^9/L$ ). 42 hours after his initial presentation the patient was declared brain dead and treatment was stopped. At the first hospital a urine screen was positive for opiates and urine and serum samples taken on arrival at the tertiary centre were positive for acetaminophen, caffeine, cotinine, lidocaine, trimethoprim and MDPV; the concentration of MDPV in the urine was 670 ng/mL and in the serum 82 ng/mL. The authors hypothesised that the trimethoprim was an adulterant in the ‘bath salts’ as the patient was not known to be taking any medications containing trimethoprim.

In the second report of a fatality in Baltimore Maryland, USA, attributed to MDPV a 39-year-old male with a history of depression and drug and alcohol abuse, was found outside his

residence delusional and dressed inappropriately for the weather. (Kesha, 2013). He was taken to the ED where whitish powder was seen around his mouth and he said he had used 'bath salts'. The patient became agitated and was transferred to ICU where he was sedated and ventilated. He developed ventricular tachycardia (treated with amiodarone and defibrillation) and was hyperthermic with a temperature of 41.7°C. Rapidly he became bradycardic leading to asystole but despite atropine, electrocardiac pacing and further resuscitation he died approximately 12 hours after presenting to ED. A post-mortem drug screen was positive for diphenhydramine, promethazine, diazepam, nordiazepam and MDPV. The concentration of MDPV found in heart blood was 0.7mg/L and in peripheral blood 1 mg/L.

In two cases of fatalities attributed to MDPV in Texas, USA, both patients developed disseminated intravascular coagulation (DIC) (Young, 2013).

Case 1: A 20-year-old male suffered convulsions after insufflating 'bath salts' and was unresponsive when emergency medical services arrived on scene. On arrival in the hospital he had narrow complex tachycardia (165 bpm) treated with intravenous adenosine and cardioversion without effect; his blood pressure fluctuated from 120/55 to 80/55 mmHg and his temperature was 39.6°C. The patient was intubated and transferred to a tertiary care centre. On arrival his heart rate was 140 bpm, blood pressure 140/60 mmHg and temperature 40.5°C; a chest x-ray was consistent with pneumonitis. The patient developed DIC but despite intensive supportive care he became pulseless; cardiopulmonary resuscitation was commenced but he died eight hours after arrival at the tertiary facility. MDPV and diazepam were detected in the blood and MDPV and diltiazem were detected in the urine.

Case 2: A 48-year-old female was found unresponsive after ingesting 'bath salts' and when the emergency medical services arrived she was tachycardic (175 bpm) and tachypnoeic (30 breaths per min) with a blood pressure of 100/59 mmHg and GCS of 7/15. On arrival in the hospital she became hostile and remained tachycardic, received intravenous lorazepam, adenosine and esmolol and was transferred to a tertiary care centre. There the patient was intubated on arrival and admitted to ICU; she was hypertensive (220/110 mmHg), tachycardic (148 bpm) and pyrexial (39.4°C) with bloody diarrhoea and no urine output. On hospital day two she became hypotensive and anuric and developed DIC and rhabdomyolysis; despite intensive supportive care the patient died on hospital day four. Her blood concentration of MDPV was 29ng/mL.

Amongst a larger series of cases reported to the Michigan Poison Control Centre involving 'bath salts' there was one fatality with biological confirmation of MDPV, marijuana and prescription drug use. MDPV was considered to be the primary factor contributing to the death but no clinical details were given (Centers for Disease Control and Prevention, 2011).

In a retrospective study of cases of exposures to 'bath salts' reported to the two poisons centres in Louisiana and Kentucky, USA between August 2010 and February 2011, 236 patients were identified (Spiller, 2011). One fatality was reported in a 21-year-old following a self-inflicted gunshot after a delusional episode; MDPV blood concentration was 170 ng/mL and MDPV urine concentration 1400 ng/mL in this case.

There was one fatality reported in a series of four patients presenting to an ED in Missouri, USA (Spencer, 2011). A 30-year-old male became agitated after a day of snorting 'bath salts' and the police were called. On their arrival he jumped out of a second storey window and was found later dead in a nearby creek. His blood MDPV concentration was 0.33mcg/mL, but the medical examiners conclusion on the cause of death was not given in the paper.

There are two reports of MDPV detection in two fatalities in Maryland, US (Cawrse, 2012). A 21 year old female was reported to be suicidal and had left her property in her vehicle; after she was located by the police, a high-speed car chase ensued and following collision with a second car the vehicle stopped on a bridge. She was subsequently found dead in a river below the bridge. Post mortem MDPV concentrations were: heart blood 0.47 mg/L, liver 0.53 mg/kg, kidney 0.49 mg/kg and bile 0.58 mg/L; methylone (heart blood 0.06 mg/L, liver 0.14 mg/kg, kidney 0.16 mg/kg and bile 0.42 mg/L) and morphine (0.031 mg/L, biological matrix not specified) were also detected. The cause of death was determined to be drowning. A 35 year old female was found in bed with sharp force trauma to her neck and a gunshot wound at the back of her neck. Post mortem MDPV concentration in heart blood was 0.03 mg/L (not detected in other biological matrices analysed); in addition, methylone was detected: heart blood 1.1 mg/L, urine 0.22 mg/L, liver 1.3 mg/kg, kidney 0.91 mg/kg). The cause of death was determine to be a homicide; she was found with a 38 year old male who had committed suicide; he had methylone but not MDPV detected in his post mortem biological sample analysis.

There is a report from Nebraska, USA of two deaths in individuals who had injected a product from a head shop that was analysed and found to contain MDPV (Kirschner, 2012):

Case 1: A 43 year old man was found dead by the police by a lake. He had been camping with his girlfriend; his girlfriend reported that he had been acting "wierd" and so she locked herself in a car and found him dead the following morning. Earlier that day he had injected (route not specified) a glass cleaner called "hookah" bought from a head shop. A post-mortem revealed multiple small abrasions and contusion, but no major trauma; there was also single vessel coronary artery disease. Serum MDPV was 160 ng/mL.

Case 2: The neighbour of a 37 year old man reported that he was naked and screaming and called an ambulance. The man was found in cardiac arrest, resuscitation was unsuccessful. Paramedics found needles and drug paraphernalia at the scene. The wife of the deceased noted that he had chronic pain and when it was not relieved by analgesics such as tramadol he injected "Srystal Clean Hookah & Pipe Cleaner". A post-mortem showed three-vessel coronary artery disease and rib fractures consistent with cardiopulmonary resuscitation. MDPV, tramadol and caffeine were detected in the blood, serum MDPV was 340 ng/mL.

In Upper East Tennessee, USA there were two reported deaths where MDPV was detected (Wright, 2013). A 46 year old male was found dead on the floor next to his bed several days after using the bath salt "Drone". In the days prior to his death, he had complained of "weakness, difficulty walking, increased falling, nausea and vomiting". In addition he had significant underlying cardiovascular, renal, endocrine and respiratory medical issues and an extensive history of drugs abuse. Post mortem MDPV concentration was 39 ng/mL in blood and 760 ng/mL in urine; metoclopramide (490 ng/mL) was detected in blood. The cause of death was determined to be diabetic ketoacidosis. In a second case, a 40 year old male, again with previous drug abuse, HIV infection and extensive respiratory, cardiovascular and mental health issues was found dead on his bedroom floor. There was a previous history of snorting and/or smoking "bath salts". Post-mortem MDPV concentration was 130 ng/mL and 3,800 ng/mL in blood and urine respectively. A urine immunoassay screen was positive for caffeine, barbiturates, bupropion, dextromethorphan, diphenhydramine, phenothiazines; femoral blood analysis revealed a butalbital (5.1 µg/mL) and dextromethorphan / levomethorphan (250 ng/mL).

In Ohio, USA, a 39 year old male with a background history of schizophrenia, depression and drug abuse, including snorting "bath salts", was found face up in his bed unresponsive; he had last been seen alive 4.5 hours before (Wyman, 2013). Two unopened packages of synthetic cannabinoid receptor agonist products ("Demon" and "Flame") and empty jars of "Tranquillity" and "Infinity bath salts" were found with / near his body. Analysis of a range of post mortem biological matrices for MDPV was undertaken: heart blood 0.5 µg/mL; femoral

blood 0.44 µg/mL; urine >5 µg/mL; gastric fluid >2 µg/mL (50 mL); bile 0.88 µg/mL; CSF 0.41 µg/mL; lung 0.6 µg/g; kidney 0.84 µg/g; liver 0.98 µg/g; muscle 0.56 µg/g; spleen 0.64 µg/g; brain – parietal 0.36 µg/g; brain – cerebellum 0.42 µg/g; brain – lentiform nucleus 0.3 µg/g; brain – frontal 0.3 µg/g; brain – occipital 0.42 µg/g; brain – medulla 0.42 µg/g; heart 0.12 µg/g; and hair: 11,660 pg/mg. Other drugs detected included methydone (urine “positive”, hair 1,332 pg/mg), caffeine (blood, concentration not reported), fluoxetine (blood 0.29 µg/mL), lamotrigine (blood <0.4 µg/mL), risperidone and hydroxyrisperidone (blood 6.8 and 6.3 ng/mL, respectively), ibuprofen (blood, concentration not reported), nicotine/cotinine (blood, concentration not reported), pseudoephedrine (blood 130 ng/mL) and benztropine (10 ng/mL).

In a review of analytical cases of 32 by the Montgomery County Coroner’s Office and Miami Valley Regional Crime Laboratory in Dayton, Ohio, USA, there were 18 post-mortem cases where MDPV was detected (Marinetti, 2013).

Case 1: 37 year old male died in a motor vehicle accident, where he was the at fault driver. Post mortem analysis: MDPV (heart blood 56 ng/mL, bile 412 ng/mL, vitreous 33 ng/mL), THC (heart blood 15 ng/mL), methydone (heart blood 31 ng/mL, bile >400 ng/mL, vitreous >200 ng/mL).

Case 2: 20 year old male died in a motor vehicle accident, where he was the at fault driver. Post mortem analysis: MDPV (cavity blood 31 ng/mL, urine “positive”)

Case 3: 39 year old male known user of “Posh” bath salt, which normally resulted in him becoming manic and uncontrollable. Found dead at home. Post mortem analysis: MDPV (femoral blood 91 ng/mL, vitreous 132 ng/mL, urine >200 ng/mL), lidocaine (100 ng/mL). Analysis of product confirmed this also contained lidocaine.

Case 4: 29 year old male reported to have snorted bath salts and later found hanging. Post mortem analysis: MDPV (heart blood 129 ng/mL, vitreous 20 ng/mL), THC (“historic use”).

Case 5: 34 year old male using heroin with a friend, who when he regained consciousness found him unresponsive. Post mortem analysis: MDPV (femoral blood 185 ng/mL, urine >200 ng/mL, vitreous 195 ng/mL), morphine (femoral blood 24 ng/mL), fluoxetine (femoral blood 760 ng/mL), norfluoxetine (femoral blood 1,600 ng/mL), trazadone (femoral blood 70 ng/mL) and mirtazepine (femoral blood <50 ng/mL).

Case 6: 46 year old male whose mental status became “altered” at home, who became hypotensive and then coded (died) in hospital. Post mortem analysis: MDPV (heart blood 10 ng/mL, hospital blood MDPV <5 ng/mL, brain 16 ng/mL, liver 12 ng/g, vitreous 17 ng/mL), DPH (hospital blood 230 ng/mL), alprazolam (15 ng/mL) and tramadol (heart blood <50 ng/mL).

Case 7: 33 year old female found dead in hotel room with ‘bath salt’ containers. Post mortem analysis: MDPV (femoral blood 46 ng/mL, urine >200 ng/mL, vitreous 48 ng/mL), morphine (femoral blood 90 ng/mL), hydrocodone (179 ng/mL), citalopram (320 ng/mL), benzoylecgonine (>700 ng/mL) and alprazolam (50 ng/mL).

Case 8: 47 year old male with history of illicit and prescription drug abuse found unresponsive. Post mortem analysis: MDPV (peripheral blood 162 ng/mL, heart blood 280 ng/mL, urine 13,900 ng/mL, liver 3,720 ng/g, bile >750 ng/mL, CSF 105 ng/mL, brain 168 ng/g, vitreous: 159 ng/mL), oxymorphone (peripheral blood 43 ng/mL), diazepam (peripheral blood 313 ng/mL), nordiazepam (peripheral blood 494 ng/mL), temazepam (peripheral blood 33 ng/mL) and DPH (peripheral blood 80 ng/mL).

Case 9: 33 year old male found dead, potentially after two days, with straws and White Horse brand bath salts nearby. Post mortem analysis revealed MDPV (liver >4,800 ng/g), ethanol (0.044g/dL), trazadone (liver “positive”) and beta-phenethylamine (liver “positive”).

Case 10: 43 year old female found unresponsive in bed. Post mortem analysis: MDPV (peripheral blood 18 ng/mL, heart blood 28 mg/mL, brain <20 ng/g, CSF 14 ng/mL, liver 52 ng/g, vitreous 14 ng/mL), fentanyl (peripheral blood 8ng/mL), norfentanyl (peripheral blood <1 ng/mL), trazodone (peripheral blood 540 ng/mL), gabapentin (peripheral blood 6,800 ng/mL), norvenlafaxine (peripheral blood 220 ng/mL), tramadol (peripheral blood <50 ng/mL), diazepam (peripheral blood 301 ng/mL) and nordiazepam (peripheral blood 281 ng/mL).

Case 11: 51 year old male with severe depression found inside a motorcycle trailer with a mason jar with minimal red liquid residue in it. Post mortem analysis: MDPV (femoral blood 129 ng/mL, liver 388 ng/g, vitreous 191 ng/mL), bupripion/metabolite (femoral blood 24 and 216 ng/mL respectively), morphine (femoral blood 40 ng/mL), oxycodone (femoral blood <20 ng/mL), diazepam (femoral blood 303 ng/mL) and nordiazepam (femoral blood 229 ng/mL).

Case 12: 32 year old male, known heavy user of bath salts, found dead hanging from an electric cord on a fence in a field. Post mortem analysis: MDPV (heart blood 133 ng/mL, peripheral blood 102 ng/mL, urine 6100 ng/mL, brain 136 ng/g, liver: 256 ng/g, CSF >200 ng/mL, vitreous 205 mg/mL, bile >200 ng/mL), chlorpheniramine (peripheral blood <50 ng/mL) and dextromethorphan (peripheral blood 60 ng/mL).

Case 13: 32 year old male, known drug user, found unresponsive and nude lying in a bath tub with empty jar of K-2 spice herbal incense nearby. Post mortem analysis: MDPV (heart blood 56 ng/mL, peripheral blood 36 ng/mL, brain 148 ng/g, liver 668 ng/g, vitreous 130 ng/mL, CSF 52 ng/mL), citalopram (peripheral blood 200 ng/mL), JWH-122 (peripheral blood "positive"), JWH-210 (peripheral blood "positive") and trazodone (peripheral blood 50 ng/mL).

Case 14: 53 year old female with extensive past medical history found unresponsive. Concerns raised by family, but analysis not undertaken until after body had been embalmed. Post mortem analysis: MDPV (cavity blood "positive", brain 20 ng/g, liver 432 ng/g, bile 140 ng/mL, vitreous 48 ng/mL, spleen 80 ng/g, CSF 33 ng/mL), benzoylcecgnoine (cavity blood <1,000 ng/mL), morphine (cavity blood 212 ng/mL), alprazolam (cavity blood 15 ng/mL), promethazine (cavity blood 200 ng/mL), citalopram (cavity blood 1,100 ng/mL), diphenhydramine (cavity blood 330 ng/mL), dextromethorphan (cavity blood 140 ng/mL), trazodone (cavity blood 140 ng/mL) and cyclobenzaprine (cavity blood 380 ng/mL).

Case 15: 19 year old male initially involved in minor road traffic accident and did not seek medical attention. Presented two days later with headache and chest pain, discharged with analgesia. Represented five days later with increasing shortness of breath and died during intubation in the ER. Post mortem noted several large bilateral pulmonary emboli. Post mortem analysis: MDPV (femoral blood 63 ng/mL, urine >200 ng/mL), cyclobenzaprine (femoral blood 60 ng/mL), dextromethorphan (femoral blood <50 ng/mL), midazolam (femoral blood <10 ng/mL), hydromorphone (femoral blood <5 ng/mL) and ethanol (0.012 g/dL).

Case 16: 33 year old male, with reported history of use of bath salts and cross-dressing, found suspended by a rope from a pole attached to his bed. Post mortem analysis: MDPV (urine "positive"), pentylone (femoral blood "positive"), amphetamine (femoral blood <50 ng/mL) and pyrovalerone (femoral blood 42 ng/mL).

Case 17: 24 year old male, with a history of abuse of prescription medication, cocaine and bath salts) found hanging from a tree. Post mortem analysis: MDPV (femoral blood 640 ng/mL, brain 896 mg/g, liver 6,080 ng/g, bile 1,880 ng/mL, vitreous 940 ng/mL).

Case 18: 32 year old female with morbid obesity found unresponsive on the floor at home. Drugs (heroin and bath salts) and related paraphernalia were found in her pockets. Post mortem analysis revealed: MDPV (femoral blood 47 ng/mL, urine “positive”), nordiazepam (femoral blood 12 ng/mL), free morphine (femoral blood 37 ng/mL), 6-MAM (vitreous 7 ng/mL), alpha-PVP (urine “positive”), and methedrone (urine “positive”).

In a review of 486 calls to the Carolinas Poisons Center, 11 hospital records and charts were reviewed, of which there was one death where MDPV was detected (Murphy, 2013). This was of a 38 year old man was reported to have difficulty breathing and was found partially naked and in asystole on arrival of emergency services; no further clinical details were included in the report. A bottle of “Q bath salts” was found in the home. Post mortem analysis: MDPV (serum 0.22 mg/L), 7-aminoclonazepam (serum 0.083 mg/L), benzyoylecgonine (serum 0.031 mg/L), fluoxetine (serum 0.89 mg/L, liver 36 mg/kg), norfluoxetine (serum 0.33 mg/L, liver 11 mg/Kg) and tramadol (serum 0.83 mg/L).

A 35 year old female was brought into hospital in Hiroshima, Japan, “unconscious” and pronounced dead on arrival (Namera, 2013). The police found three empty syringes and a “straw” in her handbag. Post mortem analysis of heart blood was positive for MDPV (1,200 ng/mL) and  $\alpha$ -pyrrolidinobutiophenone ( $\alpha$ -PBP) (200 ng/mL). Due to concerns regarding long-term use of MDPV, hair analysis was undertaken. This analysis was positive for MDPV (16-22 ng per 10mm hair segment) and  $\alpha$ -pyrrolidinovalerophenone ( $\alpha$ -PVP) (0.8-1.2 ng/10mm hair segment).

## **D2. Chronic Health Effects**

### **D2.1. Animal Data**

There have been no animal studies that have investigated the potential for chronic toxicity associated with MDPV.

### **D2.2. Human Data**

To date there have been no reported studies investigating chronic long-term physical health effects relating to MDPV use. However there is the potential for long-term physical harm as a direct result of acute MDPV toxicity (e.g. prolonged seizures resulting in cerebral hypoxia or

renal damage requiring long-term dialysis). A number of published cases illustrate the potential for chronic toxicity related to complications of acute MDPV toxicity.

A 37-year-old male, with a history of right nephrectomy due to trauma, was admitted to hospital having ingested 'bath salts' that were assumed to contain MDPV; there was no analysis of either the product used by the patient or of biological samples to confirm that this was MDPV (Levine, 2012). He developed renal failure and remained on haemodialysis five months later; no detail on whether this resolved was presented in the abstract.

A 25-year-old male developed renal failure after injecting 'bath salts' that were assumed to contain MDPV (Borek, 2012). He required haemodialysis for a month after admission until his creatinine normalised. An admission urine sample was positive for MDPV at a concentration of 140ng/mL.

A 27-year-old HIV-positive male inhaled 1g 'Ivory Wave', considered to contain MDPV, and presented to hospital two days later with sudden left-sided weakness (Boshuisen, 2012). A CT brain scan showed a right middle cerebral artery (MCA) infarct (stroke) and he was transferred to a rehabilitation clinic with ongoing left sided neurological motor weakness - he made a complete recovery from this stroke within two months.

### **D3. Factors Affecting Public Health Risks**

#### **D3.1. Availability and quality of the new psychoactive substance on the market (purity, adulterants etc)**

As reported in Section C., is available from Internet based suppliers of new psychoactive substances or research chemicals; MDPV has been found in brick and mortar head shops and other retail outlets supplying new psychoactive substances; there are also reports of MDPV being available from street level drug dealers.

In the EMCDDA 'snapshot' surveys of Internet sites selling new psychoactive substances conducted in January and June 2011, MDPV was available from 25 (8.0%) of the 314 online shops identified to be selling new psychoactive substances in January 2011 and from 32 (5.1%) of the 631 online shops identified in July 2011 (EMCDDA, 2011). In the January 2012 snapshot, MDPV was available from 44 (6.3%) of the 693 online shops identified (EMCDDA, 2012).

As noted in Section C, prior to Silk Road being closed down, MDPV was available from a number of retailers on the Silk Road (Sydney NDARC, 2013). In late October 2012 it was available from nine retailers and from ten in November and December 2012. In January 2013 nine sites were selling it and in February 2013 seven.

Analysis of the seizures summarised in the table in Section C. suggests that although some samples have been of pure MDPV with no adulterants, MDPV is often found in combination with one of more active pharmaceutical ingredient (other new psychoactive substance, classical recreational drug or pharmaceutical medicine).

Examples of the active pharmaceutical ingredients that have been found in MDPV containing products are:

i) New psychoactive substances: mephedrone, methedrone, methylone, pMeOPP, JWH-122, JWH-081, JWH-018, JWH-210, JWH-250, JWH-220, AM-2201, 2C-P, naphyrone, MDPBP, 4-MEC, alpha-PVP, butylone, methoxetamine, BZP, TMPP, 3-fluoromethcathinone, flephedrone;

ii) Classical, classified recreational drugs: cocaine, ketamine, methamphetamine, MDMA;

iii) Pharmaceutical medicines: piracetam, lidocaine, benzocaine, ethylphenidate, paracetamol, levamisole, sildenafil, diltiazem, trimethoprim.

### **D3.2. Availability of the information, degree of knowledge and perceptions amongst users concerning the psychoactive substance and its effects**

There is no published information on the degree of knowledge and perceptions amongst users concerning MDPV and its effects, other than that which is available on Internet discussion forums as summarised in Section D.1.2.1.

### **D3.3. Characteristics and behaviour of users (including risk factors, vulnerability, etc.)**

There no information available on the characteristics and behaviours of those who use MDPV. It is likely that these will be similar to those using other stimulant drugs such as MDMA and cocaine; and/or to those using other cathinones such as mephedrone.

### **D3.4. Nature and extent of health consequence (e.g. acute emergencies, road traffic accidents)**

The acute health effects of MDPV have been discussed in Section D1.2, and as summarised, there have been numerous presentations to hospitals in Europe with acute toxicity associated with MDPV use. There is no currently available data to suggest that the impact of these acute health effects would be any different to that from other similar stimulant drugs such as MDMA or cocaine, or cathinones such as mephedrone.

As summarised in Section C, MDPV has been detected in both non-fatal and fatal road traffic accidents, although it is difficult to be certain of the role of MDPV in these reports. Four countries, Finland, Germany, Sweden and the United Kingdom have reported the detection of MDPV in cases of driving under the influence of drugs (DUID) as detailed below:

#### Finland

Since 2009, Finland has recorded a total of 518 cases of DUID where MDPV has been identified in blood samples. There were 80 cases in 2009; 219 cases in 2010, 111 cases in 2011, 84 cases in 2012 and 24 cases in 2013. Other substances were present in a large number of these cases. Further details are provided below.

#### Germany

In 2013, MDPV was detected in two cases of DUID and at the Department of Forensic Medicine at the University of Bonn.

#### Sweden

In 2011, MDPV was detected in blood in four cases of DUID or other crimes and in 2012 in five cases. In 2012 MDPV was detected in urine in five cases; samples from three prisoners and two cases of other crime.

#### United Kingdom

In 2013, MDPV was detected in a blood sample from one case of DUID.

There are also published reports in the scientific literature of the detection of MDPV in cases of DUID from Finland Denmark.

In the first of these studies from Finland, blood samples from drivers arrested for driving under the influence of drugs (DUID) were analysed for the presence of MDPV between the end of August 2009 and the end of August 2010 (Kriikku, 2011a). 259 samples (8.6%) were positive for MDPV which represented approximately 5.7% of all confirmed 4570 DUID cases

(excluding the alcohol-only cases). 80% of the MDPV positive samples were also positive for amphetamine and 67% for benzodiazepines; 60 cases (23%) showed no other substance (or the concentrations of other substance found were “not expected to cause the behaviour leading to the arrest”). The concentrations of MDPV varied from 0.016 mg/L to 8.0 mg/L.

In another report from the same group in Finland, data was presented on drivers arrested for DUID in 2010 (it is likely that some individuals were included in both this paper and the paper described above as there is overlap between the study periods) (Kriiku, 2011b). A total of 4532 samples were analysed and 219 (4.8%) were found to contain MDPV at a median concentration of 0.06 mg/L (maximum concentration 8.4 mg/L). Of the MDPV positive cases, 89% were male and 96% were from Southern Finland. MDPV was commonly found together with amphetamine (79%) and benzodiazepines (76%); and a combination of MDPV, amphetamine and benzodiazepines was found in 63% of the MDPV positive cases.

A study in Denmark also analysed blood samples from drivers arrested for DUID (Pedersen, 2013). In 2011, blood samples from 1791 DUID cases were analysed; in 1335 cases the police requested a full screen for traffic-relevant drugs and in 456 cases only THC screening was requested. Amphetamine and cocaine were most frequently detected in the 1335 cases (in 383 (28.3%) and 335 (25.1%) samples respectively). MDPV was detected in 3 samples (0.2% of those tested).

### **D3.5. Long-term consequences of use (e.g. irreversible toxicity leading to deterioration of health in later life)**

There is currently no animal or human data on the chronic health effects of MDPV and in particular, there have been no long-term follow up studies to determine whether MDPV users are at greater risk of health deterioration later in life, or of developing chronic or life-threatening medical conditions.

### **D3.6. Conditions under which the new psychoactive substance is obtained and used, including context-related effects and risks (e.g. continuous dancing in hot environments, other substances used)**

As noted in Section D3.1. MDPV is readily available from a variety of Internet suppliers, in brick and mortar retail outlets and from street level drug dealers. There is limited data available on where MDPV is used, although it is likely that it is used in the same environments as other stimulant drugs such as MDMA, amphetamine and cocaine. This would be within home environments, bars/pubs, discotheques/nightclubs and outdoor music festivals.

## **SECTION E. SOCIAL RISKS**

### **E1. Individual social risks**

There is no published data to be able to determine the impact of MDPV on individual social risks; in particular there is no data on the effects of MDPV on fertility, pregnancy and lactation.

### **E2. Possible effects on direct social environment**

There is no published data to be able to determine the impact of MDPV on the direct social environment.

### **E3. Possible effects on society as a whole**

As summarised in D.3.4., there have been reports of detection of MDPV in cases of driving under the influence of drugs from Finland, Germany, Sweden and the United Kingdom. There is also a study in the scientific literature relating to Denmark.

There is no other published data or information from Europol to be able to determine the impact of MDPV in this area.

### **E4. Economic costs**

As noted in Section D1.2., there are reports of acute health effects relating to MDPV use. These appear to involve short assessments within the Emergency Department, however some individuals have had more severe clinical features requiring intensive care unit admission and other have had more prolonged features and/or have required admission to psychiatric facilities due to ongoing symptoms. Also, as summarised in D2.2., there are some reported of individuals who have developed complications related to acute MDPV toxicity such as renal failure requiring ongoing dialysis (n=2) or a stroke that has required ongoing medical treatment/rehabilitation for a period of a few months (n=1).

### **E5. Possible effects related to the cultural context, for example marginalisation**

There is no specific data in relation to use in marginalised groups, and it is likely that MDPV will be used by similar cohorts that use other stimulants and/or other cathinones.

### **E6. Possible appeal of the new psychoactive substance to specific population groups within the general population**

There is no data to suggest that MDPV is being marketed to, or has specific appeal to particular sub-population groups.

## **SECTION F. Involvement of organised crime <sup>(32)</sup>**

### **F1. Evidence that criminal groups are systematically involved in production, trafficking and distribution for financial gain**

Europol did not report any evidence of production, trafficking and/or distribution by criminal gangs of MDPV. As summarised in Section C., there have been reports of tablets with markings that would normally be associated with other recreational drugs or new psychoactive substances. It is possible, therefore, that criminal groups may be involved in the production of MDPV tablets that mimic other substances on the market.

### **F2. Impact on the production, trafficking and distribution of other substances, including existing psychoactive substances as well as new psychoactive substances**

As show in Section C, MDPV has been detected in both police and border seizures in combination with a range of new psychoactive substances and/or classical recreational drugs. It is not possible to determine whether this was intentional adulteration of MDPV with these substances or the adulteration of these substances with MDPV. In addition, it is possible that in some circumstances the mixing with other substances could have been done by the end user.

### **F3. Evidence of the same groups of people being involved in different types of crime**

There is no published data or information from Europol to be able to determine the impact of MDPV in this area.

### **F4. Impact of violence from criminal groups on society as a whole or on social groups or local communities (public order and safety)**

Europol have reported that they have received no information on incidents of violence in connection with the production, wholesale and/or trafficking of MDPV in Europe.

### **F5. Evidence of money laundering practices, or impact of organised crime on other socioeconomic factors in society**

Europol report that no information was received by them on incidences of money laundering in connection with the production, wholesale and/or distribution of MDPV in Europe.

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<sup>(32)</sup> Detailed information is available in the *Europol-EMCDDA Joint report on MDPV*;

**F6. Economic costs and consequences (evasion of taxes or duties, costs to the judicial system)**

There is no published data or information from Europol to be able to determine the impact of MDPV in this area.

**F7. Use of violence between or within criminal groups**

Europol have reported that no information was received by them on incidences of violence in connection with the production and/or distribution of MDPV in Europe.

**F8. Evidence of strategies to prevent prosecution, for example through corruption or intimidation**

There is no published data or information from Europol to be able to determine the impact of MDPV in this area.

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