3,4-Methylenedioxypyrovalerone (MDPV)

Critical Review Report

Agenda item 4.13

Expert Committee on Drug Dependence

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Contents

Summary

(*R*/*S*)-1-(Benzo[*d*][1,3]dioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one, also known as 3,4-methylenedioxypyrovalerone (MDPV), has emerged in recent years as a recreational substance with psychostimulant properties. Its preparation for potential use as a central nervous system stimulant has been described in the 1960s in response to the exploration of alternatives for its 4-methylphenyl analogue pyrovalerone and racemic amphetamine. Although it was originally claimed that MDPV showed more favourable properties, such as reduced toxicity when compared to amphetamine, it was not developed as a medicinal product.

The detection of MDPV on the street market in Tokyo has been first published in 2007 and preliminary work indicated that oral administration of MDPV caused an increase in striatal dopamine levels in mice, thus, pointing towards a potential mechanism of action. The first official notification submitted to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) by a European member state was 2008. Since then, it has become clear that the presence of MDPV, along with a range of other cathinone analogues, has spread across the globe as a reflection of modern forms of trade within a globalised world. As was the case with many other emerging substances with psychoactive properties, commonly used terms include "legal highs", "bath salts" or "new psychoactive substances" (NPS) in the attempt to highlight the fact that many, if not most, did not originally fall under any legislative control and that detailed data on both pre-clinical and clinical levels were normally less well explored. The number of reports received from some UN member states indicated that MDPV was among the most commonly detected cathinone representatives.

It has become increasingly clear in recent years that the psychoactive and behavioural profile of MDPV, for example demonstrated by drug discrimination and self-administration studies, shows significant similarities to psychomotor stimulants such as cocaine and methamphetamine. On the pharmacological level it has been convincingly demonstrated that key targets of MDPV include monoamine transporters and that it functions as a catecholamine-selective transport blocker. MDPV may be more potent and efficient than cocaine in the ability to induce locomotor activation, tachycardia and hypertension. Microdialysis studies in conscious rats have also shown that MDPV was more potent than cocaine in its ability to elevate extracellular dopamine levels in nucleus accumbens which implicates reward circuitry. The capacity of MDPV to potentially induce an excessive dopaminergic tone, in combination with inhibition of norepinephrine uptake and potentially reduced ability to provide compensatory serotonergic transmission, appears to form the basis for a variety of symptoms observed in emergency departments such as severe agitation, violent behaviour, tachycardia, psychosis, profuse diaphoresis, paranoia and anxiety. The currently available research literature indicates that MDPV may show a high potential for abuse.

1. Substance identification

A. International Nonproprietary Name (INN)

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B. Chemical Abstract Service (CAS) Registry Number

687603-66-3 (free base)

24622-62-6 (hydrochloride salt)

1388142-27-5 (*R*-enantiomer; form not specified)

1388142-28-6 (*S*-enantiomer; form not specified)

1246820-09-6 (deuterated D_8 hydrochloride salt)

1246912-12-8 (deuterated D_8 base)

C. Other Names

3,4-Methylenedioxypyrovalerone, methylenedioxypyrovalerone, MDPV

D. Trade Names

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E. Street Names

Examples include MDPV, MDPK, Magic, Super coke, Peevee, New Ivory Wave, Kannibaldrogen, Apdamm, Aakkoset, Bath salt, MP, MP4 and MP3.[1] However, the list of product names known or suspected to contain MDPV may vary significantly between batches, producers and countries.

F. Physical properties

MDPV HCl is a white crystalline powder.

G. WHO Review History

MDPV was not previously pre-reviewed or critically reviewed. A direct critical review is proposed based on information brought to WHO's attention that MDPV is clandestinely manufactured, of especially serious risk to public health and society, and of no recognized therapeutic use by any party. Preliminary data collected from literature and different countries indicated that this substance may cause substantial harm and that it has no medical use.

2. Chemistry

A. Chemical Name

IUPAC Name: (*R*/*S*)-1-(Benzo[*d*][1,3]dioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one

CA Index Name:

Examples include:

3,4-Methylenedioxypyrovalerone

MDPV

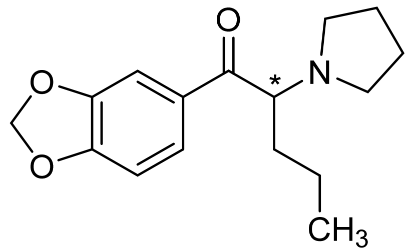
1-(1,3-Benzodioxol-5-yl)-2-(1-pyrrolidinyl)-1-pentanone

3',4'-(Methylenedioxy)-2-(1-pyrrolidinyl)-valerophenone
1-(3',4'-Methylenedioxyphenyl)-2-pyrrolidino-1-pentanone

Note: the ending 1-pentanone may also be replaced with pentan-1-one

B. Chemical Structure

Free base:



Note: Asterisk (*) refers to a chiral centre

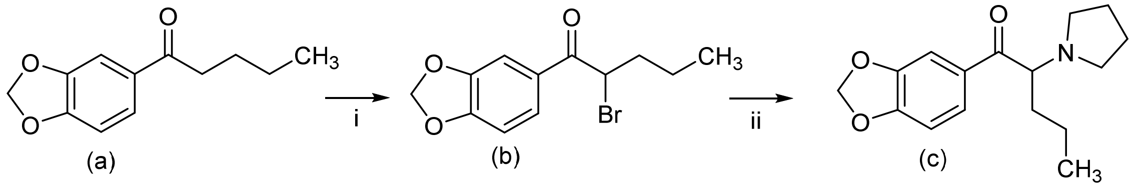
Molecular Formula: $C_{16}H_{21}NO_3$ (base)
Molecular Weight: 275.35 g/mol
Melting point: 229-231 °C hydrochloride salt (isopropanol/diethyl ether),[2,3] 238-239 °C hydrochloride salt.[4]
Boiling point: --
Fusion point: --

C. Stereoisomers

The presence of a chiral centre at the α-carbon of the side chain gives rise to the enantiomeric pair of *S*-MDPV and *R*-MDPV, respectively. Currently, it appears that data about their optical rotation or potential to display distinguishable pharmacological properties have not been published. MDPV is most likely to be available as the racemic mixture.

D. Synthesis

A key procedure used for MDPV includes the α-bromination (step i) of the pentan-1-one precursor (a) and formation of the 2-bromopentan-1-one intermediate (b). Reaction with pyrrolidine (step ii) gives MDPV (c) which may then be converted into a range of salts. The ketone species (a) may be obtained from a number of precursors including benzo[*d*][1,3]dioxole, i.e. 1,2-(methylenedioxy)benzene. One of several alternatives may include the oxidation of the ephedrine-type 2-(pyrrolidin-1-yl)pentan-1-ol precursor as well.[2,3,5,6]



E. Chemical description

MDPV, i.e. (*R*/*S*)-1-(benzo[*d*][1,3]dioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one, contains a 2-amino-1-phenylpropan-1-one nucleus which forms the structural basis for many cathinone-based substances that are known to interact with a range of targets found, for example, in the central nervous system.

F. Chemical properties

MDPV HCl is a water-soluble white crystalline powder but may also be encountered in various shades of beige/brown when encountered as a street sample. MDPV free base has been reported to appear as a brown or yellow-green amorphous powder.[1] The hydrochloride salt has also been described to be soluble in methanol and chloroform.[4]

G. Chemical identification

MDPV, as well as many other cathinones, have been extensively characterized in recent years. The first report on the detection of MDPV was published in Japan in 2007 which described the identification of nine "new designer drugs" obtained from the purchase of 99 uncontrolled substances between April 2006 and March 2007 in Tokyo. Analytical data provided for MDPV included time-of-flight (TOF) and electron ionisation (EI) mass spectrometry (MS), full scan ultraviolet (UV) and nuclear magnetic resonance spectroscopy (NMR).[7] The first report to feature MDPV in the English scientific literature was available in 2008 and contained gas chromatography-mass spectrometry (GC-MS) and UV full scan diode array data.[8] Further MS and NMR data obtained from a seized sample were published in 2009.[9] Similar data, including the display of a Fourier transform infrared (FTIR) spectrum, was provided in 2010[4] and the first investigation on MDPV metabolism was also published in the same year.[10,11] A range of presumptive spot/colour tests have been presented for MDPV and other cathinones in 2012.[12] Several immunoassays have been described for the detection of MDPV and other cathinones. Under certain conditions, examples of cross-reactivity have been described.[13,14] MDPV has also been reported to result in false-positive phencyclidine (PCP) immunoassay results.[15]

3. Ease of convertibility into controlled substance

Not applicable. MDPV may be easily reduced to its (pentan-2-yl)pyrrolidine counterpartalthough this would not be considered a substance under international control.

4. General pharmacology

Similar to other well-established psychostimulants, a key principle involved in the molecular mechanisms of MDPV is the interaction with transport proteins that lead to the elevation of extracellular neurotransmitter levels, most notably, dopamine (DA), norepinephrine (noradrenaline, NE) and serotonin (5-HT), respectively. However, an important question, especially when dealing with the implementation of *in-vitro* assays, relates to the ability of a psychostimulant to act as a monoamine re-uptake inhibitor (e.g. cocaine-like) or as a substrate-type releaser (amphetamine-like). In the latter case, this may be achieved by transporter-mediated translocation of the drug into the cytoplasm in exchange of the monoamine which may be exacerbated by additional release from vesicular storage, thus leading to increasing monoamine availability for further release.[16] Increasing research indicates that MDPV shows cocaine-like properties which means that it functions as an uptake blocker and the following sections are aimed to provide a summary. The key targets of interest normally include the evaluation of drug action at the dopamine (DAT), norepinephrine (NET) and serotonin (SERT) transporters.

4.1. Pharmacodynamics

In-vitro pharmacology

MDPV was shown to be a catecholamine-selective transporter blocker in a variety of *in-vitro* assays with IC_{50} values in the low nM range while SERT inhibition was not found to play a significant role (Table 1).[17-19] For example, when using a transporter-mediated uptake and release assay with rat brain synaptosomes, Baumann et al. reported that MDPV was a 50-fold more potent DAT blocker (IC_{50} = 4.1 nM vs. 211 nM) and a 10-fold more potent NET blocker (IC_{50} = 26 nM vs. 292 nM) when compared to cocaine. The fact that cocaine showed higher potency to inhibit SERT-mediated uptake (IC_{50} = 313 nM vs. 3349 nM for MDPV, Table 1), revealed that MDPV exhibited catecholamine selectivity whereas cocaine was observed to be non-selective with regards to these three targets.[17] In contrast to amphetamine (EC_{50} = 5.8 nM for DAT, EC_{50} = 6.6 nM for NET and EC_{50} = 698 nM for SERT), however, MDPV did not show any efficacy to release any of three [^{3}H]monoamines from synaptosomes which indicated that MDPV was not a transporter substrate. [17] Further confirmation for cocaine-like rather than amphetamine-like properties of MDPV were provided using a variety of cell-line based work (Table 1). [18-23]

Inspection of Table 2 reveals that MDPV has also been investigated for its ability to interact with additional biological targets that are commonly involved in psychoactive effects elicited by other substances. For example, the vesicular monoamine transporter type 2 (VMAT2), known to play an important role in vesicular storage release with a number of amphetamine-type substrates,[24] did not appear to show the same level of interaction with MDPV.[18] These results were reminiscent of the work published by Cozzi et al. who found that methamphetamine and MDMA were VMAT2 substrates ([^{3}H]5-HT uptake into bovine chromaffin granules) whereas methcathinone and methylone were not.[25]

Radioligand binding and functional activity studies (Table 2) carried out, for example, with a number of 5-HT or DA receptor subtypes indicated that MDPV may only display low efficacy and potency at these targets, thus, giving reason to believe that these targets may be less relevant when accounting for the psychoactive properties of MDPV.[18,19] While MDPV was a low potency partial agonist at the 5-HT_{1A} receptor, it was found to be an antagonist with very low potency at the 5-HT_{2A} and 5-HT_{2C} receptors (Table 2). Interestingly, MDPV showed high membrane permeability when assessing transendothelial transport through immortalized human brain capillary endothelial cells (TY09) and recent work suggests that there might be a possible involvement of an active transport mechanism with regards to MDPV.[19]

Table 1. MDPV *in-vitro* uptake and release data [a]

Uptake [a]			Release [b]			Affinity			Ref
DAT IC_{50}/nM	NET IC_{50}/nM	SERT IC_{50}/nM	DAT EC_{50}/nM (E_{max} %)	NET EC_{50}/nM (E_{max} %)	SERT EC_{50}/nM (E_{max} %)	DAT K_i/nM	NET K_i/nM	SERT K_i/nM	
4.1	26	3349	2.3 (24) (inactive) [c]	13 (24) (inactive) [c]	inactive	--	--	--	Baumann et al.[17]
--	--	--	[d]	[d]	[d]	--	--	--	Cameron et al.[20]
28	--	--	[e]	[e]	[e]	--	--	--	Cameron et al.[21]
12.6	18.8	1380	> 100 µM (4.8)	> 100 µM (6.9)	> 100 µM (18)	19.4 [f]	107 [f]	1250 [f]	Eshleman et al.[18]
31	44	9300	> 100 µM	--	> 100 µM	10 [g]	80 [g]	2860 [g]	Simmler et al.[19]
31	--	--	IC_{50} 280 [h]	--	--	--	--	--	Simmler et al.[22]
135	--	--	[i]	[i]	[i]	--	--	--	Kolanos et al.[23]

[a] Ref[17]: rat brain synaptosomes ([^{3}H]DA, [^{3}H]NE, [^{3}H]5-HT); Ref[18]: HEK-hDAT, HEK-hNET, HEK-hSERT ([^{3}H]DA, [^{3}H]NE, [^{3}H]5-HT); Ref[19]: HEK-hDAT, HEK-hNET, HEK-hSERT ([^{3}H]DA, [^{3}H]NE, [^{3}H]5-HT); Ref[21]: HEK-hDAT ([^{3}H]DA); Ref[23]: HEK-hDAT ([^{3}H]DA)

[b] Ref[17]: rat brain synaptosomes ([^{3}H]MPP$^+$ for DAT, NET; [^{3}H]5-HT for SERT); relative to maximum release; Ref[18]: HEK-hDAT, HEK-hNET, HEK-hSERT ([^{3}H]DA, [^{3}H]NE, [^{3}H]5-HT); data normalised to maximal effects of methamphetamine (hDAT and hNET) and *p*-chloroamphetamine (hSERT); Ref[19]: HEK-hDAT, HEK-hNET, HEK-hSERT ([^{3}H]DA, [^{3}H]NE, [^{3}H]5-HT); release expressed as percent reduction in monoamine cell content at maximal drug concentration (100 mM) compared with controls; Ref[22]: HEK-hDAT.

[c] Low-efficacy releasing activity due to uptake blockade rather than release; confirmed with HEK-hDAT-mediated efflux of [^{3}H]MPP$^+$ experiments.

[d] *Xenopus* oocytes expressing hDAT were voltage-clamped to -60 mV; MDPV (10 µM) produced cocaine-like current which confirmed inhibition of endogenous leak current of hDAT (MDPV concentrations 0.01 to 30 µM); MDPV more efficacious than cocaine regarding endogenous hDAT leak but potency was similar (EC_{50} ~ 0.3 µM); drug responses expressed as a percentile of DA pre-pulse peak current (100 %).

[e] Voltage clamp experiments set up as above [d]; confirmed that MDPV more potent than cocaine as uptake inhibitor, i.e. increased ability to block endogenous leak current; mephedrone/MDPV mixtures were also evaluated: at equal access to transporter, dissimilar dissociation rates observed and mephedrone acted more quickly than MDPV; MDPV blockage longer-lasting than cocaine.

[f] Inhibition of [^{125}I]RTI-55 binding (0.04 nM) at HEK-hDAT, HEK-hNET, HEK-hSERT.

[g] *N*-Methyl-[^{3}H]nisoxetine and indatraline (NET), [^{3}H]citalopram and indatraline (SERT) and [^{3}H]WIN35,428 and indatraline (DAT]).

[h] Inhibition of methamphetamine-induced DA release (10 µM); HEK-hDAT ([^{3}H]DA); drug combinations: 10 µM methamphetamine with bupropion, methamphetamine, or MDPV in different concentrations; residual radioactivity in cells after methamphetamine alone defined 100% DA release. Baseline (0% release) defined as remaining radioactivity following drug treatment.

[i] Two-electrode voltage-clamp techniques as above [d]; MDPV exposure (10 µM) reduced the hDAT-mediated inward current (12.1% recovery based on first DA application) elicited by DA; similar to above [d], MDPV acted as a DAT inhibitor.

Table 2. MDPV *in-vitro* data in addition to Table 1.	Ref
MPDV and cocaine on dopamine clearance: fast-scan cyclic voltammetry in mouse striatal slices (male CB57/BL6 mice); EC_{50} = 115 nM more potent than cocaine (EC_{50} = 308 nM) at inhibiting dopamine clearance.	Baumann et al.[17]
Inhibition of [^{3}H]DHTB binding to hVMAT2 [a]: K_i = 990 µM. Comparison: K_i = 661 µM (MDMA); K_i = 920 µM (methamphetamine). Inhibition of hVMAT2 [^{3}H]5-HT uptake [b]: IC_{50} >100 µM. Comparison: IC_{50} = 5.8 µM (MDMA); IC_{50} = 4.72 µM (methamphetamine). hVMAT2 [^{3}H]NE release assay [c]: EC_{50} = 148 µM with efficacy (E) of 35.8% [d]. Comparison: EC_{50} = 114 µM, E = 63% (MDMA); EC_{50} = 79 µM, E = 95.% (methamphetamine). Inhibition of binding to 5-HT receptors [e]: K_i h5-HT_{1A} = 14.8 µM; K_i h5-HT_{2A} = 207 µM; K_i h5-HT_{2C} = 107 µM. Comparison with LSD: K_i h5-HT_{1A} = 1.32 nM; K_i h5-HT_{2A} = 0.15 nM; K_i h5-HT_{2C} = 1.29 nM. MDPV did not show any measureable affinity for dopamine receptor subtypes up to 10 µM. Potency and efficacy at 5-HT receptors [f]: h5-HT_{1A}: EC_{50} = 60.8 µM, E = 69%; h5-HT_{2A}: IC_{50} = 270 µM, E = 67.7%; h5-HT_{2C}: IC_{50} >1 mM, E = 24.5%. Comparison: LSD h5-HT_{1A}: EC_{50} = 5.8 nM, E = 107.8%; ketanserin h5-HT_{2A}: IC_{50} = 2.98 nM, E = 95.9%; SB-242084 h5-HT_{2C}: IC_{50} = 0.28 nM, E = 86.5%. Inhibition of [^{3}H](+)-pentazocine binding to hSigma1 [g]: K_i = 4.4 µM. Comparison: haloperidol K_i = 0.94 nM; MDMA K_i = 19.4 µM; methamphetamine K_i = 3.18 µM.	Eshleman et al.[18]
Receptor binding profiles [h]: K_i (µM): 5-HT_{1A} = 10.29; 5-HT_{2A} >13; 5-HT_{2C} >13; α_{1A} >6; α_{2A} >20; D_1 >13.6; D_2 >30; D_3 >9.2; H_1 >14.4; TA_{1rat} = 7.2; TA_{1mouse} >10. Cytotoxicity: None detected under conditions used [i]. Transendothelial transport [j]: MDPV showed high membrane permeability based on permeability coefficient; indications that MDPV might undergo active transport since the apical to basolateral transport was significantly greater than the basolateral to apical transport.	Simmler et al.[19]

[a] hVMAT2: human vesicular monoamine transporter type 2 (HEK-hVMAT2); [^{3}H]DHTB (7-10 nM): (+)-alpha-dihydrotetrabenazine; reserpine K_i = 0.147 µM (inhibition of [^{3}H]DHTB binding); reserpine IC_{50} = 6.6 nM (inhibition of [^{3}H]5-HT uptake).

[b] HEK-hVMAT2 using 40 nM [^{3}H]5-HT.

[c] HEK-hVMAT2 using 125 nM [^{3}H]NE (less non-transporter-mediated leakage than 5-HT and DA).

[d] Release efficacy relative to maximum response elicited by 100 µM or 1 mM methamphetamine.

[e] HEK-h5-HT_{1A} (0.5 nM [^{3}H]8OH-DPAT); HEK-h5-HT2A (0.1 nM [^{125}I]DOI); HEK-h5-HT_{2C} (0.07 nM [^{125}I]DOI).

[f] HEK-h5-HT_{1A} stimulation of [^{35}S]GTPγS binding; agonist efficacy relative to 100 nM 5-HT; HEK-h5-HT_{2A} and HEK-h5-HT_{2C} stimulation of inositol monophosphate (IP-1) formation; tested in presence of 100 nM 5-HT and normalized to inhibitory efficacy of 10 µM ketanserin (h5-HT_{2A} receptors) or 100 nM SB-242084 (h5-HT_{2C} receptors). On average, 5-HT-(100 nM) stimulated 640 nM IP-1 in h5-HT_{2A}, 1920 nM IP-1 in h5-HT_{2C} cells.

[g] Cos-7-hSigma1 using 1.3 nM [^{3}H](+)-pentazocine.

[h] [^{3}H]-8-OH-DPAT and indatraline (5-HT_{1A}), [^{3}H]ketanserin and spiperone (5-HT_{2A}), [^{3}H]mesulergine and mianserin (5-HT_{2C}), [^{3}H]prazosin and risperidone (α1 adrenoceptor), [^{3}H]rauwolscine and phentolamine (α2 adrenergic receptor), [^{3}H]SCH 23390 and butaclamol (DA_{D1}), [^{3}H]spiperone and spiperone (DA_{D2} and DA_{D3}), [^{3}H]pyrilamine and clozapine (H_1) and [^{3}H]-RO5166017 and RO5166017 (TA_1).

[i] Cell membrane integrity tested by measurement of adenylate kinase release from damaged cells via bioluminescence detection (after 4 h of incubation at 37°C). Drug concentrations were 10 and 100 µM.

[j] Conditionally immortalized human brain capillary endothelial cells (TY09) as a human *in-vitro* blood-brain-barrier permeability model; human blood-to-brain influx and brain-to-blood efflux transporters expressed in TY09 cells; drug concentrations determined by LC-MS/MS.

In-vivo pharmacology

An increasing number of animal studies have shown that MDPV shares a range of behavioural and physiological features commonly observed for methamphetamine and cocaine (Table 3). Watterson et al.[26] have observed reinforcing effects in rats (progressive ratio schedule of reinforcement) which developed into escalation of MDPV intake (intravenous self-administration) under extended access conditions. Interestingly, MDPV intake was observed at higher rather than lower dosage levels which differed from observations made with more traditional equivalents such as methamphetamine. It was suggested, however, that this may point towards a potential for compulsive intake behaviour which may extend to humans. The fact that MDPV administration led to a reduced threshold for intracranial self-stimulation (ICSS) was also reported to be indicative of rewarding properties.[26] Bonano et al. also confirmed that MDPV was able to facilitate ICSS but also observed an extraordinarily long duration of action[27] which was consistent with *in-vitro* work carried out by the researchers where MDPV was found to be more resistant (slow dissociation from DAT) to wash out than cocaine (Table 1).[21] Table 3 also indicates that intensive psychostimulant-like locomotor activities have been reported following MDPV administration in animals. The development of hyperthermic effects was not observed under all experimental conditions and were influenced by ambient temperature and dosage levels (Table 3).[28-30]

An important approach when evaluating abuse liability may also come from drug discrimination studies in animals trained to distinguish a training drug from saline. Fantegrossi et al.[29] trained mice to discriminate MDPV (0.3 mg/kg) from saline and showed that MDPV, MDMA and methamphetamine resulted in full substitution (Table 3). Gatch et al.[31], on the other hand, found thatMDPV showed significant discriminative stimulus effects in cocaine-trained and methamphetamine-trained mice. Table 3 also shows that in cases where locomotor activity studies were carried out, MDPV produced powerful and long-lasting stimulant effects in mice (5-6 hours). In addition, these effects were not observed immediately (depressant effects for nearly an hour following administration) which might be relevant when assessing psychostimulant effects in humans. Based on the currently available data on various behavioural animal studies, it appears to be increasingly obvious that MDPV might share considerable and dose-dependent abuse liability that are also observed with psychostimulants such as cocaine and methamphetamine. Consistent with these observations, Baumann et al. were also able to confirm that MDPV was not only longer-lasting but also 10-fold more potent than cocaine in its ability to increase extracellular dopamine in nucleus accumbens using microdialysis sampling in conscious rats (Table 3).[17] Eshleman et al. also noted that MDPV showed long-lasting locomotor stimulant effects in mice (5-6 hours). In addition, these effects were not observed immediately (depressant effects for nearly an hour following administration).[18]

Table 3. MDPV *in-vivo* animal assays.

Behaviour	Neurochemistry / physiological responses	Reference
Locomotor activity: oral administration (p.o.) of MDPV (20 mg/kg), compared to methamphetamine (2 mg/kg) and MDMA (20 mg/kg); distance travelled and "number of movements" appeared similar for the first 90 min.	Microdialysis (mice): MDPV (20 mg/kg, p.o.) led to ~2-fold increase of extracellular DA in striatum at the 30 and 60 min mark with return to baseline at about 2.5 h; only 30 and 60 min levels considered significantly different from control at $p < 0.01$; MDPV observed to have a "milder" increase in DA levels compared to MDMA and methamphetamine; 5-HT levels were not affected by MDPV.	Fuwa et al.[32]
Intravenous self-administration [a]: revealed reinforcing and rewarding properties; similarities to methamphetamine and cocaine were observed, such as escalation under extended access conditions; escalation of MDPV intake occurred at higher rather than lower doses; MDPV amounts administered after 10 sessions higher than for methamphetamine; reward value MDPV vs. methamphetamine reported to be similar. Intracranial self-stimulation [b]: thresholds were lowered following MDPV administration which suggested hedonic and rewarding effects.	--	Watterson et al.[26]
Voluntary wheel running/rotations [c]: biphasic locomotor effects, increased activity at lower doses and suppressed activity at higher doses; similar effects to methamphetamine (MA) but less MDMA-like. MDPV may be more potent in decreasing wheel activity than MA but less efficacious at increasing wheel activity. Post-session stereotypy [d]: was scored as "present" at highest MDPV dose only.	--	Huang et al.[33]
Locomotor activity [e,f]: compared to saline, MDPV (3-17 mg/kg) caused significant increases in beam breaks and the 1 mg/kg dose significantly increased locomotor activity for 60 min; attenuation of stimulant action during first 10 min of session observed at 30-90 min at the 1, 3 and 17 mg/kg doses and at 20-30 and 50-90 min of session in mice treated with the 10 mg/kg dose. Rotarod test / apparatus (motor coordination) [e]: no effect in time spent on the rotarod with MDPV. Functional observational battery (FOB) [e,g]: significant increases in observational measures related to stimulant action (ranging from 1-10 mg/kg to 1-30 mg/kg).	--	Marusich et al. [34]
Locomotor activity [h,i]: similarity between MDPV and methamphetamine; activity significantly higher for MDPV than methamphetamine for the 5.6 but not for the 1.0 mg/kg dose; at lower doses both drugs increased locomotor activity but decreased at higher levels. Stereotypy [h,j]: dose-dependent induction of stimulant-type stereotypy. Intravenous self-administration [h]: consistent levels of MDPV intake and high reward-lever selectivity; MDPV showed higher reward value.	Thermoregulation [h,k]: MDPV modestly hyperthermic and less potent disruptor of thermoregulation than MDMA and methamphetamine.	Aarde et al.[28]
Locomotor activity [l]: MDPV significantly more potent than cocaine. Stereotypy [l]: MDPV significantly more potent than cocaine.	Microdialysis (nucleus accumbens) [l]: MDPV (0.1 mg/kg) 10-fold more potent than cocaine (1.0 mg/kg) regarding increase of extracellular dopamine; rise significantly longer lasting than cocaine (3.0 mg/kg MDPV vs. 10 mg/kg); Cardiovascular Parameters [l]: MDPV significantly more potent than cocaine for raising heart rate and blood pressure.	Baumann et al.[17]
Locomotor activity [m]: stimulation observed across range but biphasic dose-dependency only at elevated ambient temperatures (28°C vs. 20°C); selfinjurious behaviour at highest 30 mg/kg dose but only at elevated ambient temperature; locomotor activity was comparable to MDMA at 10 mg/kg at 20°C.	Thermoregulation [m]: effects strongly affected by temperature environment (28°C vs. 20°C); at 20°C and 10 mg/kg, hyperthermic effects with MDPV (~1.5°C) and mild hypothermic effects (~2°C) with MDMA; at 28°C and 10 mg/kg, excessive temperature increase (~6°C) with MDMA but milder increase (~2°C) with MDPV.	Fantegrossi et al.[29]

Table 3. MDPV *in-vivo* animal assays.

Behaviour	Neurochemistry / physiological responses	Reference
Drug discrimination [m]: ED_{50} for cumulative MDPV 0.03 mg/kg; cumulative doses of MDMA (ED_{50} 0.03 mg/kg) and methamphetamine (ED_{50} 0.08 mg/kg) elicited full substitution; interoceptive effects of MDPV were dose- and time dependent; potency differences observed when drug was administered cumulatively vs. single bolus administration.		
Locomotor activity [n]: Stimulant effects of 1 and 3 mg/kg MDPV within 10 min and lasted for 190 min, 250 min at 10 mg/kg MDPV; at 30 mg/kg MDPV, stimulant effects not observed for first 80 min but lasted for 300 min; locomotor activity depressed between 10 and 50 min after injection at a dose of 30 mg/kg; ED_{50} MDPV 1.26 mg/kg (doses 1, 3 and 10 mg/kg), ED_{50} methamphetamine 0.30 mg/kg (doses 0.5 and 2 mg/kg), ED_{50} cocaine 7.24 mg/kg (doses 10, 20 and 40 mg/kg); stimulant effects of MDPV observed to last longer than those of cocaine and methamphetamine; biphasic at high dosage levels. Drug discrimination [o]: full substitution in cocaine-trained rats (ED_{50} MDPV 0.68 mg/kg; ED_{50} cocaine 3.09 mg/kg) and methamphetamine-trained rats (ED_{50} MDPV 0.67 mg/kg; ED_{50} methamphetamine 0.37 mg/kg).	--	Gatch et al.[31]
Conditioned taste aversion [p]: MDPV induced weaker aversion in adolescent than adult subjects; reduction in aversive protective effects in teenagers when translated to humans?	Thermoregulation [p]: MDPV induced age-dependent changes in body temperature: generally increase in adolescents but decrease in adults.	Merluzzi et al.[30]
--	Dose-dependent 150% increase of heart rate demonstrated in *Daphnia magna*; EC_{50} for cathinones incl. MDPV = 1.9 µM; tachycardic effects alleviated with antiarrhythmic drug such as verapamil.	Pitcher et al.[35]
Intracranial self-stimulation [q]: comparison between MDPV, methcathinone, methylone and mephedrone revealed facilitation of ICSS with rank order methcathinone ≥ MDPV ≥ methylone > mephedrone; rapid onset of action for all compounds but MDPV and methylone showed longer duration of action.	--	Bonano et al.[27]

[a] Male Sprague Dawley rats; 0.05, 0.1 or 0.2 mg/kg per infusion; methamphetamine (0.05 mg/kg per infusion) as positive control.

[b] Intracranial self-stimulation thresholds determined following acute MDPV administration (0.1, 0.5, 1 and 2 mg/kg, i.p.); bipolar electrode implanted into the medial forebrain bundle.

[c] Male Wistar rats; 0.5-5.6 mg/kg, s.c. (MDPV) vs. *d*-methamphetamine (0.5-5.6 mg/kg, s.c.) and MDMA (1-7.5 mg/kg, s.c.).

[d] Repetitive sniffing, licking and/or circular head motion, lack of orienting response to finger tap on side of home cage.

[e] Male ICR mice; substances administered intraperitoneally.

[f] Beam breaks in open field activity chambers.

[g] 20 Minutes post-injection of test drug. Behavioral profile with emphasis on detection of potential safety concerns; adapted from Environmental Protection Agency. Observations included a range of behaviour, such as locomotion, ataxia, exploration, convulsions, circling, hyperactivity, salivation, stereotyped head weaving, head circling, other stereotyped compulsive movements and stimulation.

[h] Male Wistar rats; 0.05 mg/kg/infusion (i.v.) MDPV vs. methamphetamine for self-administration; 0-5.6 mg/kg (s.c) for body temperature and activity responses.

[i] Counts per minute of changes in signal strength from radiotelemetry transmitter relative to baseline 30 min pre-injection.

[j] Repetitive licking, biting or sniffing the walls/bars; scores obtained by the extend of disruption of stereotypy by tapping on cage.

[k] Obtained from radiotelemetry transmitter.

[l] Male Sprague-Dawley rats; locomotor activity: distance travelled; MDPV (0.1-3.0 mg/kg, s.c.) vs. saline vs. cocaine (3-17 mg/kg, s.c.).

[m] Male NIH Swiss mice (learned to discriminate 0.3 mg/kg MDPV from saline); locomotor counts and temperature monitored with radiotelemetry probe; motor activity and thermoregulation studied at 1-30 mg/kg MDPV (i.p.).

[n] Male Swiss Webster mice; locomotor activity counts in horizontal plane (ambulation counts); horizontal activity measured for 8 hours.

[o] Male Sprague-Dawley rats; learned to discriminate methamphetamine (1 mg/kg, i.p., ED_{50} 0.37 mg/kg) or cocaine (10 mg/kg, i.p., ED_{50} 3.09 mg/kg) from saline.

[p] Adolescent and adult male Sprague-Dawley rats; dosage levels 1.0, 1.8, or 3.2 mg/kg (i.p.); temperature measured with transponder.

[q] Male Sprague–Dawley rats; cathode stereotaxically implanted into the left medial forebrain bundle at level of lateral hypothalamus; dose-effect data obtained (i.p.) for methcathinone (0.1-1.0 mg/kg), MDPV (0.32-3.2mg/kg), methylone (1.0-10 mg/kg) and mephedrone (1.0-10 mg/kg).

4.2. Routes of administration and dosage

Some of the patents disclosed by Boehringer Ingelheim in the 1960s[5,6] describe a number of pyrovalerone-type compounds with a 3,4-(methylenedioxyphenyl) nucleus and propose their use in various peroral and parenteral products such as tablets or injectable formulations. In general, dosage levels were suggested to range between 2-40 mg but preferably between 10 and 20 mg. For example, the suggested tablet formulation with a total mass of 450 mg contained a dose of 15 mg MDPV hydrochloride although the anticipated daily dosing regime was not mentioned.[5,6]

Reports submitted to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)[1], user reports on websites and case reports (see section 6) indicate that routes of administration may include nasal (insufflation and sniffing), oral (swallowing) and rectal administration, intravenous injection and inhalation. Detailed information on common dosage levels may be difficult to obtain, especially if drug or product purities are not known, and it would appear that a particular route of administration may require varying dosage levels. However, tentative estimations pointed towards threshold levels around 1-5 mg to "strong" effects between 10-25 mg depending on route of administration[36] which seemed consistent with other estimations of about 5-20 mg for average dosage levels.[37]

4.3. Pharmacokinetics

Data obtained from systematic studies carried in humans are currently absent. Meyer et al.[10] found extensive phase I and phase II metabolism for MDPV when investigating rat and human urine samples and pooled human liver microsomes. In case of a human urine sample submitted for clinical toxicological analysis (acidic hydrolysis and acetylation), the presence of demethylenyl-MDPV, demethylenyl-methyl-MDPV, demethylenyl-oxo-MDPV, demethylenyl-methyl-oxo-MDPV, oxo-MDPV, demethylenyl-methyl-hydroxy-alkyl-MDPV, demethylenylhydroxy-alkyl-MDPV and demethyl-methyl-*N*,*N*-bisdealkyl-MDPV was revealed in addition to the parent molecule. The most abundant urinary MDPV metabolite detected in the human urine sample was demethylenyl-methyl-MDPV. Incubation of MDPV with recombinant CYP enzymes also showed that demethylenyl-MDPV formation was catalysed by CYP 2C19 (set to 100% due to highest level of contribution), CYP 2D6, CYP 1A2, CYP 3A4 and CYP 2A6, respectively.[10] The presence of the parent molecule in addition to demethylenyl-MDPV and demethylenyl-methyl-MDPV was also reported by Strano-Rossi et al. who employed an incubation with human liver microsomes and S9 cellular fractions.[11] Favretto et al. also reported the detection of MDPV in urine samples obtained from an intoxicated user. Phase I and phase II metabolites were identified as demethylenyl-MDPV, demethylenyl-methyl-MDPV, demethylenyl-methyl-oxo-MDPV, demethylenylhydroxy-alkyl-MDPV, demethylenyl-methyl-hydroxy alkyl-MDPV, demethylenyl-oxo-MDPV and the corresponding glucuronides.[38]

Further studies are needed to address a range of observations made in the clinical and pre-clinical environment. For example, frequent re-dosing appears to be reported[37] while potentially long-lasting intoxications have also been noted in cases of severe acute intoxications (see section 6 below). Studies in mice have shown that MDPV may show differences in potency, when given cumulatively, in comparison to single bolus administration which sets the scene for further research into the area of non-linear pharmacokinetics, a phenomenon that has also been observed with MDMA.[29]

5. Toxicology

The therapeutic index mentioned for MDPV in the original patent literature was 875 based on subcutaneous (s.c.) administration in mice. The dose required to exert central nervous system stimulation was given at 0.20 mg/kg (s.c., mouse) whereas the LD_{50} value was reported to be175 mg/kg (s.c., mouse), thus, leading to the index value of 875.[2,3,5] However, it was not explicitly stated whether the 0.20 mg/kg value reflected the ED_{50} value, commonly used for the calculation of the therapeutic index. In comparison, the therapeutic index given for racemic amphetamine was 42 (pyrovalerone = 231), hence, indicating a potentially less favourable safety ratio in mice following s.c. administration.[2,3,5] A recently carried out assay for cell membrane integrity measuring adenylate kinase release from damaged cells via bioluminescence detection (after 4 h of incubation at 37°C, drug concentrations 10 and 100 µM) did not reveal any indications for cytotoxicity under the conditions used[19] and further studies are warranted.

A wide range of MDPV concentrations has been reported in biofluids (e.g.[39,40] and references therein) and the presence of other substances was frequently reported as well. This poses a challenge when attempting to disentangle causal relationships, especially in the absence of detailed pharmacokinetic data obtained from human studies. Data obtained from *in-vitro* and *in-vivo* (animals) pre-clinical studies carried out so far indicate that MDPV shows properties similar to the psychostimulants cocaine and methamphetamine and it appears that MDPV may be more potent in a number of assays (Tables 1-3). The capacity of MDPV to potentially induce an excessive dopaminergic tone, in combination with inhibition of norepinephrine uptake and potentially reduced ability to provide compensatory serotonergic transmission, appears to form the basis for a variety of symptoms observed in emergency departments such as severe agitation, violent behaviour, tachycardia, psychosis, profuse diaphoresis, paranoia and anxiety.

6. Adverse reactions in humans

Representative clinically relevant observations obtained from case report literature are summarised in Table 4. It is worth noting that unambiguous identification of MDPV have not been possible in all cases. The reasons for inclusion in this table stems from an association made between the search term "MDPV" and the resulting hits in scientific databases and/or associations made between MDPV and a number of case reports. A causal link could not be established in all cases due to other confounders such as pre-existing history of poly-drug use and mental health problems. However, in cases where MDPV use was established unambiguously, neurological and cardiovascular effects consistent with extensive stimulant toxidrome have been consistently observed. In addition, a number of conspicuous features appear to include an exceptional long duration of effects and after effects (> 24 h), combative behaviour, hyperthermia and psychosis which have included examples of auditory and visual hallucinations. Rhabdomyolysis and multiple organ dysfunctions have also been frequently reported in cases where the presence of MDPV was obtained from biofluid samples.

Table 4. Case reports and adverse drug reactions associated with MDPV [a]					
Reference	**Year [b]**	**Case**	**Patient, age**	**Clinically related comments (examples)**	**Notes**
Antonowicz et al. [41]	2011	1	F, 27	Paranoid psychosis; patient described as tachycardic and diaphoretic; protracted binge of nasal insufflation; treatment with risperidone.	Analytical confirmation of product ("Powdered Rush") or biofluids not reported.
Antonowicz et al. [41]	2011	2	M, 32	Hypertension, tachycardia, protracted binge; patient described as described as disorganized and frightened.	Analytical confirmation of product ("Powdered Rush") or biofluids not reported.
Centers for Disease Control and Prevention[42]	2011	35	M & F, 20-55	Thirty ED presentations in Michigan (US) Nov 2010-Mar 2011; clinical findings consistent with stimulant intoxication.	Analytical confirmation of products or biofluids not reported. MDPV implicated but extent not reported for all cases.
Durham[43]	2011	1	--	Palpitations and chest pain; involuntary facial contortions, hallucinations, profound anxiety; treatment with sublingual glyceryl trinitrate (no effects) and intravenous diazepam.	Analytical confirmation of product ("Ivory Wave") obtained from patient or biofluids not reported. [c]
Fröhlich et al.[44]	2011	1	M, 28	Acute psychosis and hepatic failure, hyper-sympathetic stimulation; rhabdomyolysis; pre-existing bipolar affective disorder; consumption of 12 tablets.	Tablet analysis: MDPV and butylone; analysis of biofluids not reported.
Gallucci et al.[45]	2011	1	F, 26	Paranoid delusions, auditory hallucinations and panic attacks; symptoms started about six weeks earlier following consumption of "bath salts"; nasal insufflation 0.5g per week; treatment with "low dose" risperidone to resolve symptoms within 48-72 hours.	Analytical confirmation of product or biofluids not reported.
Kalapos[46, d]	2011	15	13 M, 2F 21-50	Effects of alleged MDPV resemble those of stimulants but withdrawal symptoms may be akin to those of opiates; patients typically former heroin users; clinical findings: hepatotoxicity (lowered GOT, GPT and gamma-GT), elevated urobilinogen level; intoxications (>40% of cases): agitation, decreased appetite, paranoia & delusions, pseudohallucination, aggression; withdrawal (>30% of cases): muscular pain, pallor, hypersomnia; treatment with clonazepam and, if necessary risperidone (to alleviate delusion).	Analytical confirmation of product or biofluids not reported.
Kriiku et al.[47]	2011	13	M, 20-47	Post-mortem toxicology findings out of 7105 cases in 2010; MDPV not considered sole cause of death in any of these cases.	MDPV detected in blood and urine.
Kriiku et al.[39]	2011	259	--, --	Suspected driving under the influence cases (n = 3000) tested between Aug 2009-Aug 2010; 87% of the MDPV positive drivers were male; 76% were between 25 and 44 years.	MDPV detected in blood; amphetamine and benzodiazepines also detected in majority of samples.
Kyle et al. [48]	2011	1	M, 19	Paranoia, auditory and visual hallucinations, anxiety, repeated bouts of inappropriate laughter; impaired thought processes; treatment with promethazine and risperidone; substance was smoked.	MDPV detected in urine; also caffeine, cotinine, promethazine.
Macher[49]	2011	1	--	Violent outbursts and psychosis of prison inmate following ingestion of "Ivory Wave" product; inmate committed murder under the influence.	MDPV and "marijuana" detected in blood.
Nevin[50]	2011	1	M, 22	Tachycardia, hyperthermia, violent outbursts; treatment with midazolam and ondansetron.	Analytical confirmation of product or biofluids not reported.
Penders and Gestring.[51]	2011	1	M, --	Paranoia, hyperactivity, sleeplessness, extreme distractibility, anger, fearfulness; treatment with risperidone.	Analytical confirmation of product or biofluids not reported. "White Horse" and "Cloud Nine" products

Table 4. Case reports and adverse drug reactions associated with MDPV [a]					
Reference	**Year [b]**	**Case**	**Patient, age**	**Clinically related comments (examples)**	**Notes**
					purchased by investigators afterwards.
Penders and Gestring.[51]	2011	2	F, --	Anxiety, anorexia and sleeplessness, behavioural withdrawal, paranoia; product called "White Horse"; daily nasal insufflation for 2 weeks prior to admission; treatment with risperidone.	Analytical confirmation of product or biofluids not reported. "White Horse" and "Cloud Nine" products purchased by investigators afterwards.
Penders and Gestring.[51]	2011	3	M, --	Anxiety, paranoia, auditory and visual hallucinations, sleeplessness, inattentiveness; product called "White Horse"; treatment with haloperidol.	Analytical confirmation of product or biofluids not reported. "White Horse" and "Cloud Nine" products purchased by investigators afterwards.
Spiller et al.[52,53]	2011	18	M & F, 16-64	Retrospective chart review of 236 patients reported to 2 poison centres (Aug 2010 - Feb 2011); range of neurological and cardiovascular effects consistent with extensive stimulant toxidrome; treatments included benzodiazepines, antipsychotics and propofol.	Biofluids available in 18 live cases; MDPV detection confirmed in 16 cases. MDPV also confirmed in blood and urine in one fatality, self-inflicted gunshot.
Spencer et al.[54]	2011	1	W, 32	palpitations, chest pressure, shortness of breath.	MDPV confirmed in urine.
Spencer et al.[54]	2011	2	W, 32	palpitations, chest pressure, shortness of breath, parkinsonian-type symptoms.	MDPV confirmed in urine.
Spencer et al.[54]	2011	3	M, 35	Rapid heart rate and shortness of breath after nasal insufflation.	MDPV confirmed in urine.
Spencer et al.[54]	2011	4	M, 30	Agitation; nasal insufflation; jumped from second story window; found dead.	MDPV confirmed in blood.
Striebel and Pierre[55]	2011	1	M, 22	Severe chest pain, psychosis, tachycardia, nausea with emesis, anxiety, hallucinations; pre-existing Crohn's disease; treatment with lorazepam; product smoked over 2 h (125 mg, "Cloud 9").	Analytical confirmation of product or biofluids not reported.
Wood et al.[56]	2011	1	M, 28	Sympathomimetic toxicity, tachycardia, palpitations, anxiety; total of 400 mg orally administered; treatment with diazepam.	Blood analysis revealed MDPV, mephedrone and butylone.
Borek and Holstege[57]	2012	1	M, 25	Severe agitation, hyperthermia, tachycardia, combative behaviour and multi-organ failure following substance injection; treatment included midazolam, etomidate, succinylcholine, propofol, fentanyl and cooling blankets.	Analytical confirmation of MDPV in urine.
Boshuisen et al. [58]	2012	1	M, 27	Left-sided weakness/hemiplegia following inhalation of 1g "Ivory Wave" product; middle cerebral artery infarction; pre-existing HIV seropositivity; treatment with recombinant tissue plasminogen activator (little improvement); recovery within 2 months.	Analytical confirmation of product or biofluids not reported.
Cawrse et al.[59]	2012	1	F, 21	Accidental death, drowning, multiple blunt force injuries.	MDPV, methylone, morphine detected in during post-mortem analysis.
Froberg et al.[60]	2012	--	--	Retrospective analysis of representations to emergency departments (ToxIC Network Database; 40 cases out of 126); range of sympathomimetic features encountered frequently, especially tachycardia, hypertension and agitation; treatment included benzodiazepines (majority), antipsychotics and intubation due to agitation; young men (median age 29 years) formed majority.	"57.5% of cases had confirmatory testing with MDPV identified in 78% of these cases"
Fullajtár and Ferencz[61]	2012	1	M, 34	"MDPV" reportedly used i.v. for several months; arrested due to extreme	After 48 h of drug use, MDPV was not detected by analysis of

Table 4. Case reports and adverse drug reactions associated with MDPV [a]					
Reference	Year [b]	Case	Patient, age	Clinically related comments (examples)	Notes
				aggression while intoxicated. Other symptoms 12 h later: psychosis, paranoia, delusions, dysphoria, agitation, hostility; treatment (1 week): olanzapine, clonazepam followed by risperidone. Clinical findings: elevated GPT, normal GGT and GOT. Transient withdrawal symptoms (24 h after use): perception disturbance, agitation and delirium.	urine. Furthermore, no urinary cocaine, opiates, THC or amphetamine (GC-MS).
Kadaria and Sinclair [62,63]	2012	1	M, 36	Severe agitation, violent behaviour, hypertension, tachycardia; product "Ivory Wave" or "White Ivory"; treatment with lorazepam, morphine; midazolam, broad spectrum antibiotics, acyclovir.	Analytical confirmation of product or biofluids not reported.
Kirschner et al.[64]	2012	1	M, 43	Fatality following injection of product "hookah cleaner".	MDPV detected in serum during post-mortem analysis.
Kirschner et al.[64]	2012	2	M, 37	Fatality; presumed to have injected product "Crystal Clean"; pre-existing coronary artery disease.	MDPV, tramadol and caffeine detected in blood during post-mortem analysis.
Lajoie and Rich[65]	2012	1	M, 50	Three inpatient psychiatric admissions with 15-day period; chest pain, psychosis, self-mutilation, suicidality, tachycardia; treatment with olanzapine, lorazepam; pre-existing methamphetamine dependence; self reported injection of 0.5g-1g "bath salts".	Analytical confirmation of product or biofluids not reported.
Levine and LoVecchio[66]	2012	1	M, 37	Tachycardia, tachypnea, hyperthermia, agitation, paraspinal compartment syndrome, renal failure; pre-existing history of right nephrectomy due to trauma.	MDPV, caffeine, propofol detection in urine; MDPV detection in serum 7 hours later.
Lonati et al. [67]	2012	1	--	Retrospective study of 192 presentations to emergency departments classified as "new recreational drugs of abuse".	MDPV detection confirmed; details not reported.
McClean et al. [68]	2012	1	M, 29	Psychosis, disorganised speech and behaviour; history of schizophrenia polysubstance use disorder; in attendance of outpatient clinic; treatment with olanzapine but psychotic symptoms persisted presumably due to daily smoking of "bath salts"; treatment included risperidone; return to baseline functioning within a month.	Analytical confirmation of product or biofluids not reported.
Mugele et al.[69]	2012	1	F, 41	Agitation, hallucinations, tachycardia, hyperthermia, hypertension; treatment with lorazepam, diazepam, etomidate, tracheal intubation, succinylcholine, propofol, midazolam; ingestion of product "Blue Magic"; further treatment with fentanyl and cyproheptadine; development of pneumonia and pneumothorax.	Diagnosis serotonin toxicity; MDPV and lidocaine detected in urine.
Murray et al.[70]	2012	1	M, 40	Fatality following psychosis, agitation, hyperthermia, rhabdomyolysis and anoxic brain injury; drug was thought to be taken by injection and nasal insufflation; history of bipolar disorder.	MDPV and trimethoprim detected in urine and serum.
Penders et al.[71]	2012	1	M, 31	Anxiety, hallucinations, diaphoresis, paranoia, renal failure, rhabdomyolysis; consumption of "three packets 1500 mg of "bath salts""; treatment with haloperidol.	Analytical confirmation of product or biofluids not reported.
Penders et al.[71]	2012	2	M, 30	Paranoia, agitation, violent behaviour, acute renal Failure, rhabdomyolysis, multiple organ dysfunction, including acute respiratory distress syndrome.	Analytical confirmation of product or biofluids not reported.
Penders et al.[71]	2012	3	M, 26	Anxiety, confusion, diaphoresis;	Analytical confirmation of

Table 4. Case reports and adverse drug reactions associated with MDPV [a]					
Reference	Year [b]	Case	Patient, age	Clinically related comments (examples)	Notes
				hyperthermia, tachycardia; treatment with sedatives; repetitive use "bath salts" over the 3 previous days.	product or biofluids not reported.
Thornton et al.[72]	2012	1	M, 23	Psychosis, diaphoresis, tachycardia, agitation; prior psychiatric history; treatment with lorazepam, droperidol; nasal insufflation of 1g product.	Remaining product, serum and urine analysis showed MDPV, caffeine and 4-fluoromethcathinone.
Adamowicz et al. [40]	2013	1	M, --	Fatal car accident. Products "Ivory Speed" and "Exclusive Dust" also found.	MDPV and buphedrone detected in blood.
Adamowicz et al. [40]	2013	2	M, --	Fatal intoxication following ingestion of product "Speedway"; autopsy revealed HIV, emacitation, external hydrocephalus and atherosclerosis.	MDPV, clonazepam and 7-aminoclonazepam detected in blood.
Adamowicz et al. [40]	2013	3	F, 25	Slurred speech, abnormal pupillary reflex, pale skin and wobbly lifting;	MDPV and diazepam detected in blood.
Adamowicz et al. [40]	2013	4	M, 19	Driving under the influence; routine traffic control.	MDPV, THC and metabolite, JWH-018 metabolite detected in blood.
Al-Saffar et al.[73]	2013	21	--, --	Eighty-seven urine samples obtained from "addiction treatment clinics"; in 1 urine sample detection of 4-fluoroamphetamine.	MDPV detected in urine.
Andrassy et al.[74, d]	2013	54	3M, 30M, 10F, 9M, 2F	Usually snorting but about 28% injection user of "MDPV"; compulsive use not uncommon; intoxication: tachycardia, hypertension, agitation, muscle rigidity, lack of appetite, xerostomia, bruxism, itching /skin erosion, psychosis, paranoia, hallucination, out-of-time feeling; clinical: elevated creatine kinase, one case of rhabdomyolysis; treatment (if needed): salsol, furosemide, risperidone, haloperidol, quetiapine.	Analytical confirmation of product or biofluids not reported.
Bäckberg et al.[75]	2013	86	--, --	Prospective analysis (Jan - Sep 2012) of intoxication cases in Sweden (STRIDA project); eighty-six MDPV detections out of 321 patient samples; 17 cases with poisoning severity score = 3; extreme agitation, psychosis, hyperthermia, tachycardia, hypertension, myocardial infarction, rhabdomyolysis and renal failure; MDPV intoxications considered local outbreak.	MDPV detected in urine or blood.
Imam et al.[76]	2013	5	M , 28-42	A range of sympathomimetic features were described including tachycardia; violent behaviour; pre-existing history of drug abuse and psychiatric conditions (4/5); treatment included supportive care but also lorazepam and ziprasidone and i.v. hydration; one death due to anoxic brain injury.	Analytical confirmation of products or biofluids not reported.
Kopec et al.[77]	2013	1	M, 16	Erratic behaviour, tachycardia, agitation and aggression; initial treatment with lorazepam (i.v., 2.5 mg) did not resolve violent behaviour; administration of 200 mg ketamine (i.m., 2.5 mg/kg) led to adequate sedation in 6 minutes; lorazepam (i.v., 2.5 mg) was given again after patient awoke 45 min later.	MDPV detected in urine.
Farkas et al.[78, c]	2013	5	M, 21 F, 36 F, 20 F, 32 M, 44	Summary (mostly from Table 1): three were former (multi)drug users; hepatotoxicity in 2 patients: elevated GGT, GOT, GPT; In one first-time experimental user elevated GGT and creatinine levels; general intoxication: dysphoria, paranoia, anxiety; aggression, hallucination, suicidal ideation, depersonalisation, anorexia in some	Analytical confirmation of product or biofluids not reported.

Table 4. Case reports and adverse drug reactions associated with MDPV [a]					
Reference	Year [b]	Case	Patient, age	Clinically related comments (examples)	Notes
				patients; typical treatment (for 2-7 days) included clonazepam, olanzapine, valproate and risperidone. One of the patients (M, 44 w/criminal background, multiple drug use) was a regular i.v. user of "MDPV" (30 × per day) with severe anorexia (minus 20 kg), insomnia for weeks; received valproate and zuclopenthixol; left clinic (emission) after 2 days.	
Favretto et al.[38]	2013	1	M, 27	Patient admitted to emergency department; reported agitation, delirium, hallucinations and depression all preceding week; could not remember time of MDPV use; self-treatment with benzodiazepines led to semi-conscious state; pre-existing psychiatric history and chronic drug abuse.	MDPV and benzodiazepines detected in urine.
Jolliff et al.[79]	2013	1	F, 24	Pregnant patient found unconscious after reported "bath salt" product; 34 weeks small-for-gestational-age infant delivered via emergent C-section deliver protocol; infant treated for neonatal abstinence syndrome.	MDPV detected in infant blood, urine and cord blood.
Kesha et al.[80]	2013	1	M, 39	Fatal intoxication. Agitation, ventricular tachycardia, hyperthermia; treatment included use of amiodarone, paracetamol, atropine; history of depression, back pain, drug and alcohol abuse.	Bile positive for salicylates, diphenhydramine, MDPV, promethazine, diazepam, and nordiazepam.
Kopec et al. [77]	2013	1	M, 16	Agitated delirium, tachycardia, aggressive behaviour; treatment with lorazepam with little effect; intra-muscular administration of 2.5 mg/kg ketamine led to successful sedation.	MDPV was detected in urine.
Lenz et al.[81]	2013	1	M, 22	Syncopal episode, confusion, agitation, tachycardia; nasal insufflation of ~1g "Cristalius" product; treatment with lorazepam.	Analytical confirmation of product or biofluids not reported.
Lindeman et al.[82]	2013	13	--,--	Retrospective study of medical records following a local epidemic of suspected MDPV use; three May-April slots between 2010-2012; twelve of the 13 MDPV positives considered chronic drug users; > 60% tested positive for Hepatitis C.	In 2012, MDPV positive results in 13 out of 45 cases.
Macher and Penders[15]	2013	1	M, --	Fatal intoxication; psychotomimetic and sympathomimetic toxicity, hyperthermia; false-positive PCP detection by immunoassay.	MDPV detected in blood.
Marinetti et al.[83]	2013	30	M/F, 19-53	Nine human performance cases, 21 post-mortem cases which were found to reveal MDPV but also a range of other substances.	MDPV and others detected in blood.
Murphy et al.[84]	2013	1	M, 50	Intravenous administrations of "bath salt" product; anxiety and difficulty to urinate; did not show signs of intoxication; history of aortic valve replacement, colon resection, depression, anxiety, chronic back pain, acid reflux, and substance abuse (cocaine).	Analytical confirmation of product or biofluids not reported.
Murphy et al.[84]	2013	2	M, 40	Insufflation and injection; agitation, shocked with electronic control device, hyperthermia, cardiac arrest; resuscitated but developed disseminated intravascular coagulopathy, rhabdomyolysis and brain death.	MDPV detected in serum and urine.
Murphy et al.[84]	2013	3	M, 22	Nasal insufflation of “eight ballz” for 5 days; lying in bed with choreoathetoid	MDPV detected in urine and serum.

Table 4. Case reports and adverse drug reactions associated with MDPV [a]					
Reference	Year [b]	Case	Patient, age	Clinically related comments (examples)	Notes
				movements of arms and legs and writhing movements of tongue but no fasciculations, hallucinations; treatment with lorazepam and haloperidol;	
Murphy et al.[84]	2013	4	M, 38	Fatality. Patient found with difficulty breathing; bottle of "Q bath salts" found; patient found in asystole. Death considered accidental, related to MDPV toxicity with cocaine and fluoxetine toxicity as contributing agents.	Detection of MDPV, 7-aminoclonazepam, benzyoylecgonine, Fluoxetine, norfluoxetine and tramadol.
Namera et al.[85]	2013	1	F, 35	Fatality; found unconscious but details not reported.	MDPV and α-pyrrolidinobutiophenone (α-PBP) detected in cardiac blood and hair.
Nguyen et al.[86]	2013	1	M, 21	Tachycardia, significant hyperkinesias, rhabdomyolysis with acute renal failure, psychosis; treatment with benzodiazepines and haloperidol.	MDPV detected; details not reported.
Pedersen et al.[87]	2013	3	--, --	Three out of 1335 Danish forensic traffic cases revealed the presence of MDPV.	MDPV detected in blood.
Penders et al.[88]	2013	1	F, 21	Patient referred to inpatient care; persistent hallucinations, social withdrawal; nasal insufflation of "bath salts" began 13 months before admission; prior treatment with haloperidol and risperidone was not successful; lurasidone, citalopram and trazodone also prescribed. Modified bilateral electroconvulsive therapy found beneficial for persistent psychotic and affective symptoms.	Details about cathinone used not reported.
Roman et al.[89]	2013	1	--,--	Screening of post-mortem blood samples (n = 125).	MDPV detected in one sample.
Sivagnanam et al.[90]	2013	1	M, 27	Agitation, tachycardia, hypotension, febrile, reversible cardiomyopathy; "bath salts" inhaled and injected.	Analytical confirmation of product or biofluids not reported.
Stoica and Felthous [91]	2013	1	M, 30	Psychosis following injection of "bath salt"; history of valproic acid and quetiapine prescription treatment.	Analytical confirmation of product or biofluids not reported.
Tóth et al.[92]	2013	1	M, 19	Fatal road accident; detected drug levels in blood considered low; consumption suggested to have taken place one day before accident.	MDPV, 3,4-dimethylmethcathinone and ethanol detected in blood and MDPV, THC-COOH, 4-fluoromethcathinone, 3,4-dimethylmethcathinone, ethanol and amphetamine detected in urine.
Tóth et al.[92]	2013	2	M, 22	Apparent suicide.	MDPV, codeine, amphetamine detected in blood and urine. Ethanol also detected in urine.
Troendle et al.[93]	2013	1	M, 29	Paranoia, diaphoresis, mydriasis, tachycardia, hypotension, Hyperthermia; myocardial infarction, rhabdomyolysis, hepatotoxicity, acute kidney injury; treatment included aggressive cooling, hydration, benzodiazepines, phenylephrine Infusion. Ingested product "White Girl".	MDPV detection on product; analysis of biofluids not reported.
Winder et al. [94]	2013	1	M, 33	Hypertension, psychomotor agitation, intermittent anxiety, paranoia, episodes of mood instability; history of drug use; treatment with quetiapine, lorazepam and antidepressant.	Analytical confirmation of product or biofluids not reported.
Wright et al.[95]	2013	1	M, 46	Fatality using product "Drone IV"; medical history of hospitalizations for	MDPV detected in blood and urine; metoclopramide

Table 4. Case reports and adverse drug reactions associated with MDPV [a]

Reference	Year [b]	Case	Patient, age	Clinically related comments (examples)	Notes
				uncontrolled diabetes mellitus with diabetic ketoacidosis, polysubstance abuse, myocardial infarction, anemia due to erosive esophagitis, chronic obstructive pulmonary disease, hypertension, and coronary artery disease with stent placement.	detected in blood and urine; product analysis revealed MDPV.
Wright et al.[95]	2013	2	M, 40	Fatality. History of polysubstance use; medical history included HIV, hypertension, chronic obstructive pulmonary disease, bipolar disorder, asthma.	MDPV detected in blood and urine; detection of guaifenesin and dextromethorphan.
Wyman et al.[96]	2013	1	M, 39	Fatal intoxication; history of schizophrenia, depression, drug abuse, retinitis pigmentosa.	MDPV detected in several tissues including hair; caffeine, fluoxetine, lamotrigine, risperidone, hydroxyrisperidone, ibuprofen, nicotine/cotinine, pseudoephedrine and benztropine (10 ng/mL) detected in blood; methylone detected in hair.
Young et al.[97]	2013	1	M, 20	Fatality; agitated delirium, tachycardia, hypertension, hyperthermia, disseminated intravascular coagulation.	MDPV detected in blood.
Young et al.[97]	2013	2	F, 48	Fatality; agitated delirium, tachycardia, hypertension, hyperthermia, disseminated intravascular coagulation; history of ethanol abuse, depression, hepatitis C.	MDPV detected in blood.
Zuba et al.[98]	2013	1	M, --	Fatal road traffic accident.	MDPV and buphedrone detected in blood.
Sadeg et al.[99]	2014	1	M, 47	Acute psychosis; agitation, episode of delirium, paranoia, tachycardia, nasal congestion; standard blood analysis normal; treatment with diazepam and loxapine; pre-existing history of psychotic episodes associated with psychomotor agitation; regular use of "NRG-3" product; patient described to experience craving;	Analysis of serum sample was interpreted to contain MDPV.
EMCDDA–Europol[1]	2014	107 + 99	--,--	Up to 107 non-fatal intoxications (analytically confirmed) and 99 fatalities have been reported from a number of European member states to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA); note: there may be some overlap with cases shown in this table above; in most cases, other psychoactive substances were present in biological samples; extensive display of sympathomimetic features mentioned were consistent with severe features mentioned above in this table.	MDPV and other substances detected in biofluids.

[a] Some of the cases reported in the cited literature in this table have been associated with MDPV as a representative "bath salt" constituent. Although an association has been occasionally made between MDPV and a number of case reports (linked by database search or mentioned in citation), unambiguous confirmation of MDPV in biological fluids were not always provided.
[b] Year of publication.
[c] The "Ivory Wave" product might serve as an example to illustrate the challenges encountered when dealing with brand names with changing substance composition. For example, in the UK and Ireland, "Ivory Wave" was also reported to represent desoxypipradrol (2-diphenylmethylpiperidine, 2-DPMP) rather than MDPV.[100,101]
[d] Dr István Ujváry is gratefully acknowledged for assisting with translation.

7. Dependence potential

Detailed, controlled studies on dependence potential of MDPV are currently absent from the literature but examples of withdrawal symptoms, including those reminiscent of opiates, have been reported from users in Hungary (Table 4).[46,61]

8. Abuse potential

Detailed clinical studies in humans are currently not available and most of the available information is derived from clinical observations made within the context of emergency and hospital admissions where severe acute toxicity is encountered (Table 4). It is currently unclear how the number of these cases relate to prevalence of MDPV use in the general population. Based on what has been described in the case report literature, it would appear that MDPV might show abuse liability similar to cocaine and methamphetamine, especially in experienced recreational drug users with a history of poly-drug abuse.[102] MDPV has also been reported to be consumed over extended periods of time (re-dosing and MDPV binge) (Table 4). These clinical observations appear to be consistent with currently published animal studies that indicate that MDPV might show a propensity to display rewarding properties based on self-administration studies (Table 3). A potential reason for this might be related to the ability of MDPV to show a potentability to increase extracellular dopamine levels in nucleus accumbens in conscious rats.[17]

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

Not known.

10. Listing on the WHO Model List of Essential Medicines

Not listed.

11. Marketing authorizations (as a medicine)

Not available.

12. Industrial use

Not known.

13. Non-medical use, abuse and dependence

Recreational use of MDPV has been reported by a number of UN member states.[1,103]
Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances

14. Nature and magnitude of public health problems related to misuse, abuse and dependence

Based on the available literature discussed in sections 4 to 8 it appears likely that harms associated with MDPV use will be restricted to a small section of the publication which engages in recreational drug use.

15. Licit production, consumption and international trade

Not known. Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances

16. Illicit manufacture and traffic and related information

Information provided to the EMCDDA indicated that twenty-seven Member States (all Member States with the exception of Luxembourg), Norway and Turkey have reported seizures (7) of MDPV to the EMCDDA. In excess of 5500 seizures have been reported with two countries reporting more than 1000 seizures each: the United Kingdom (1704) and Finland (1340). A further four countries reported more than 100 seizures: Hungary (599), Poland (401), Ireland (242) and Spain (176). More than 4500 individual MDPV powder cases have been reported, amounting to an excess of 200 kilograms of seized MDPV. In addition, over 500 cases involving MDPV tablets or capsules amounted to approximately 30,000 tablets in total.[1] Among the 44 synthetic cathinones reported up to 2012, MDPV represented the second most abundant compound based on reports received from UN member states.[103] MDPV appeared to have a particularly pronounced presence in the USA.[104] The Drug Enforcement Administration, after reviewing the scientific literature, 3-factor analysis, consultation of NFLIS, law enforcement, Customs and Border Protection and other sources, that MDPV appeared to be sufficiently prevalent to pose public health risk.[105]

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances

17. Current international controls and their impact

Not applicable in terms of medical use.

18. Current and past national controls

The EMCDDA received confirmation that MDPV is controlled in the following countries:[106] Belgium (20 March 2013, list of psychotropic substances), Bulgaria (amendments to National Drug Law, came into force on 09 February 2011), Croatia (amendments to the List of drugs, psychotropic substances, plants used to produce drugs and substances that can be used in the production of drugs (precursors) (OG 19/11), February 2011), Czech Republic (amendment of the Act n. 167/1998 on addictive substances; came into force on 22 April 2011), Denmark (list of controlled substances (List B) as of 13 March 2009), Estonia (regulation of Minister of Social Affairs number 73 (Annex), as of 29 November 2010), Finland (narcotics act as of 28 June 2010), France (27 July 2012), Germany (adoption of the 26th Amending Regulation on

Narcotic Drugs, i.e. 26. Betäubungsmittelrechts-Änderungsverordnung, BtMÄndV, came into force on 26 July 2012, permanently placed under schedule II (narcotics eligible for trade but not for medical prescription) of the German Narcotics Act (Betäubungsmittelgesetz, BtMG)), Hungary (Act CLXXVI of 2011 on the amendment of certain health related acts; amended Act XXV of 1998 on human pharmaceuticals and added MDPV to schedule 'A', the illegal drugs schedule), Ireland (Criminal Justice (Psychoactive Substances) Act 2010), Italy (generic definition, Decree of 29 December 2011), Latvia (listed), Lithuania (Law on the Control of Narcotic Drugs and Psychotropic Substances 2010), Poland (08 June 2011), Portugal (Portaria nº 154/2013, 17 April 2013), Romania (21 July 2010), Slovenia (via amendment of Decree on classification of illicit drugs, published on 22 July 2013 in Official Gazette of RS No. 62/2013 and entered into force 15 days afterwards), Sweden (01 February 2010), United Kingdom (generic definition, 16 April 2010). Not controlled in Cyprus and Malta. MDPV is currently controlled in the United States, Canada, Korea, Australia, Japan.

Also refer Annex 1: Report on WHO questionnaire for review of psychoactive substances

19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance

Not applicable.

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Annex 1: Report on WHO Questionnaire for Review of Psychoactive Substances for the 36th ECDD: Evaluation MDPV

Data were obtained from 72 WHO Member States (18 AFR, 13 AMR, 5 EMR, 29 EUR, 3 SEAR, 4 WPR).

A total of 65 Member States answered the questions for 3,4-methylenedioxypyrovalerone (MDPV). Of these, only 31 respondents (AMR 4, EUR 22, SEAR 1, WPR 4) had information on this substance.

LEGITIMATE USE

None reported that MDPV was currently authorized or in the process of being authorized/registered as a medical product in their country. Six respondents stated that this substance was used in medical and scientific research and as analytical standard. There was no use stated for MDPV in animal/veterinary care.

HARMFUL USE

Twenty-two respondents confirmed there was recreational/harmful use of MDPV**.** Of these two stated that the common route of administration was oral, six oral, inhaling/sniffing, four inhaling/sniffing, one oral/injection and five oral, injection, inhaling/sniffing. For such use, 15 stated this was obtained only via trafficking, two via diversion and trafficking, one via clandestine manufacturing and one via trafficking and clandestine manufacturing. Common formulations of MDPV available were reported by 13 as powder and by four as powder and tablet. When asked if MDPV was used by any special populations two respondents stated that it was used by the general population and in clubs, four only in clubs and four only among general population – general population includes people with other dependences. In 2012 4 respondents reported a total of 29 deaths either due to or related to MDPV/cathinones. For 2012, 2 respondents reported 8 emergency room visits and in 2013 another respondent reported 194 visits because of MDPV. Eleven respondents reported withdrawal, tolerance and other adverse effects or medical illnesses caused by MDPV. These include hallucinations, psychosis, self-harming, delusions, aggression, heart and CNS effects and also withdrawal symptoms. It is also reported as a substance used together with other substances; the use of such substances are increasing and also causing harm including deaths.

Additional information provided – ‘Several synthetic cathinones have resulted in emergency department visits for agitation, sympathomimetic toxicity, and death. The Center for Disease Control (CDC) published a “Morbidity and Mortality Weekly Report” summarizing overdose cases for 35 persons (including one death) who used bath salts and visited a Michigan emergency department (ED) during November 13, 2010-March 31, 2011. The symptoms (number of subjects) observed in the ED were agitation (23), tachycardia (22), delusions/hallucinations (14), seizure/tremor (10), hypertension (8), drowsiness (8), paranoia (7), and mydriasis (7). Some of the patients were violent. Subjects were 16 males and 19 females, primarily in the 20-29 age range. Routes of administration were: injection (22 subjects); snorting (9 subjects); ingestion (4 subjects); and unknown (5 subjects). Five subjects used more than one route of administration. Based on medical reports provided to the FDA, some of these cases involved a bath salt labeled “White Cloud”. This product was confiscated from a local store considered to be the source of the bath salts in some of the cases, and submitted to the Michigan Department of State Police laboratory for testing. The

"White Cloud" product consisted of powdered material found to contain MDPV. MDPV was not tested for in the individuals involved in the overdose episodes. However, toxicological analysis in the case of death revealed the presence of MDPV in the blood (>400 ng/mL). According to the 2010 Annual report of the American Association of Poison Control Centers, (AAPC) "bath salts" are an emerging drug of concern, with the center receiving a peak of approximately 40 calls per day between April and July 2011 (Bronstein et al. 2011). Another AAPC update reported receiving 6,138 calls related to bath salts in 2011 (AAPC 2012). It is unknown whether these calls were due to MDPV specifically, although MDPV has been positively identified in over-the-counter samples of "bath salts". The majority of reports documenting the behavioral effects and overdose with MDPV or its analogues are case reports and media reports. These reports have described a wide variety of effects typical of stimulant-like drugs (MMWR 2011) including hallucinations (Penders and Gestring 2011), paranoid psychosis (Antonowicz et al. 2011), delirium (Kasick et al. 2012), and death (Murray et al. 2012). Some of these case reports are based upon the consumption of "bath salts" so a direct link to MDPV cannot be made, however, MDPV has been confirmed in biological samples obtained from patients hospitalized after ingesting bath salts (Borek and Holstege 2012;Kyle et al. 2011;MMWR 2011;Mugele et al. 2012;Murray et al. 2012;Penders and Gestring 2011;Spiller et al. 2011;Wood et al. 2011).'

'Among users primarily injecting other drugs (N=819) the share of new psychoactive substances was even more dominant as compared to 2011. In 2012 the most typically injected drug was a substance reported on its street name, which was represented by an insignificant proportion in 2011. Presumably the street name refers to pentedrone, a synthetic cathinone derivative, the increasing popularity and injecting use of which was also identified in the 2012 seizure data. Pentedrone was followed by those other drugs that occurred the most frequently in 2011, such as MDPV, methadone and mephedrone.'

CONTROL

Of those with information on the substance, 29 reported that MDPV was controlled under legislation that was intended to regulate its availability. Of these, 25 was under "controlled substance act" and two each under "medicines law" and "other" laws including one narcotics related legislation. Four respondents stated that there were challenges with the implementation of this legislation. On illicit activities involving MDPV, three respondents reported clandestine manufacture and two the synthesis of the product itself. Five respondents reported processing into the consumer product, 15 countries reported trafficking, four countries diversion and 13 countries an internet market.

Details on seizures are presented below.

	2011 (number of respondents)	**2012 (number of respondents)**
Total number of seizures	4,419 (11)	4,450 (13)
Total quantity seized (kg)	132.62 (9)	111.06 (12)
Total quantity seized (L)	0.05 (1)	0.53 (1)
Total quantity seized (pills/tablets)	7,090 (3)	9,389 (4)

IMPACT OF SCHEDULING

Twenty-seven out of 31 respondents reported that if MDPV was placed under international control, they would have the laboratory capacity to identify the substance. It has no reported medical use.