1. **Comments based on the review report**

   a. **Evidence on dependence and abuse potential**

      Detailed, controlled studies on dependence potential of 3,4-Methylenedioxypyrovalerone (MDPV) are currently absent from the literature but examples of withdrawal symptoms, including those reminiscent of opiates, have been reported from users in Hungary. In addition to that, the critical review provides information referring to the psychoactive and behavioral profile of MDPV. This profile has been demonstrated not only by drug discrimination studies but also by self-administration evaluations, including significant similarities to psychomotor stimulants such as cocaine and methamphetamine. In addition to that the report indicates that micro dialysis 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 review points out that increasing research indicates that MDPV shows cocaine-like properties which means that it functions as an uptake blocker; these cocaine-like rather than amphetamine-like properties of MDPV were provided using a variety of cell-line based work. Specific studies done as voltage clamp experiments, confirmed that MDPV is more potent than cocaine as uptake inhibitor.

      The critical review quotes an increasing number of animal studies that have shown that MDPV shares a range of behavioral and physiological features commonly observed for methamphetamine and cocaine. Among those features the review mentions the reinforcing effects in rats (progressive ratio schedule of reinforcement) which developed into escalation of MDPV intake (intravenous self-administration) under extended access conditions.

      With regards to abuse liability and information derived from drug discrimination studies in animals trained to distinguish a training drug from saline, the review presents data obtained with trained mice to discriminate MDPV (0.3 mg/kg) from saline and showed that MDPV, MDMA and methamphetamine resulted in full substitution. In these aspects and based on the currently available data on various behavioral animal studies, the critical review concludes that it appears to be increasingly obvious that MDPV might share considerable and dose-dependent abuse liability that are also observed with psycho stimulants such as cocaine and methamphetamine.
Abuse potential in humans

According to the critical review, 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.

b. Risks to individual and society because of misuse

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 - as reported in the critical review - to form the basis for a variety of symptoms observed in emergency departments such as severe agitation, violent behavior, tachycardia, psychosis, profuse diaphoresis, paranoia and anxiety.

Nevertheless, analytical confirmation of MDPV concentrations has not been reported in all references cited in the review. This poses a challenge when attempting to disentangle causal relationships, especially in the absence of detailed pharmacokinetic data obtained from human studies.

From 81 case reports cited in the review, MDPV was detected in at least 45 cases in different fluids, alone or in combination with other substances including amphetamine, benzodiazepines, caffeine, cotinine and tramadol. The symptoms reported included: Paranoia, auditory and visual hallucinations, anxiety, repeated bouts of inappropriate laughter, impaired thought processes, palpitations, chest pressure, and shortness of breath, parkinsonian-type symptoms, severe agitation, hyperthermia, tachycardia, combative behavior and multi-organ failure.

In the report on WHO questionnaire for review of psychoactive substances for the 36th ECDD for 2012, 2 respondents reported 8 emergency room visits and in 2013 another respondent reported 194 visits because of MDPV.

c. Magnitude of the problem in countries (misuse, illicit production, smuggling etc)

The critical review points out that 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. Among the 44 synthetic cathinones reported up to 2012, MDPV represented the second most abundant compound based on reports received from UN member states. MDPV appeared to have
a particularly pronounced presence in the USA. 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.

Additionally in the WHO questionnaire survey, 22 respondents confirmed there was recreational/harmful use of MDPV. 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. The survey also reports on seizures as shown below

<table>
<thead>
<tr>
<th></th>
<th>2011 (number of respondents)</th>
<th>2012 (number of respondents)</th>
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</thead>
<tbody>
<tr>
<td>Total number of seizures</td>
<td>4,419 (11)</td>
<td>4,450 (13)</td>
</tr>
<tr>
<td>Total quantity seized (kg)</td>
<td>132.62 (9)</td>
<td>111.06 (12)</td>
</tr>
<tr>
<td>Total quantity seized (L)</td>
<td>0.05 (1)</td>
<td>0.53 (1)</td>
</tr>
<tr>
<td>Total quantity seized (pills/tablets)</td>
<td>7,090 (3)</td>
<td>9,389 (4)</td>
</tr>
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d. Need of the substance for medical (including veterinary) practice

The critical review does not mention medical or veterinary use. In the WHO questionnaire survey, of 35 respondents with information on this substance, 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.

e. Need of the substance for other purposes (e.g. industrial)

Not Known

f. Measures taken by countries to curb misuse

In the WHO questionnaire survey, of those 35 with information on the substance, 29 reported that MDPV was controlled under legislation that was intended to regulate its availability. Of these, 25 were 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.
g. Impact if this substance if scheduled

Twenty-seven out of 35 respondents in the WHO questionnaire survey 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.

2. Additional information to the critical review

2.a A method to detect MDPV
An updated reference describes the development of a liquid chromatography high-resolution mass spectrometry quadruple-time-of-flight (LC-HRMS-QTOF) method for the analysis of new stimulant designer drugs, including phenethylamine, amphetamine, cathinone and piperazine derivatives. The methodology applied in this study enabled the identification of metabolites of a preferred target list including methylenedioxyxpyrovalerone (MDPV). This method constitutes a very useful tool for the combined targeted and untargeted analysis of drugs of abuse in biological matrices such as urine. (Paul M, Ippisch J, Herrmann C, Guber S, Schultis W. Analysis of new designer drugs and common drugs of abuse in urine by a combined targeted and untargeted LC-HR-QTOFMS approach. Anal Bioanal Chem. 2014 May 15. [Epub ahead of print].)

2.b Fatalities and MDVP, not a rare event:
A recent study indicates that the lack of clinical studies on the effects and toxicity of recreational drugs that have entered the global market has made interpretation of toxicological findings difficult. The study provides findings in post-mortem and criminal casework where these have been detected and/or implicated. MDVP occupies the fourth position among drugs detected in life or post-mortem blood and urine in order of decreasing frequency. The case report that in fatalities, alternative causes of death (including mechanical suicide, accidental death and non-psychoactive drug overdose) accounted for the majority. Related to this was that of all fatalities involving cathinones, 41% of these were hangings or other mechanical suicides, this was a higher proportion than seen with other drugs found in such cases. (Elliott S, Evans J. A 3-year review of new psychoactive substances in casework. Forensic Sci Int. 2014 Apr 16;243C:55-60. doi: 10.1016/j.forsciint.2014.04.017. [Epub ahead of print])

3. Other comments or opinions
No additional comments

4. Expert reviewers view on scheduling with rationale
Evidence presented is consistent with the characterization of MDPV as a psycho stimulant as cocaine. There is information on its liability to abuse and to induce significant harm effects in humans, including death. Consequently it meets the criteria for inclusion in Schedule I of the 1961 Convention, but, on the other hand, its liability is not offset by substantial therapeutic advantages not possessed by substances other than drugs in Schedule IV. On the view of this, it could be placed in Schedule IV.